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1.0 TITLE PAGE

Abbreviated Title	Effects of Depth of Neuromuscular Blockade and Insufflation Pressure on Surgical Conditions
Title	Randomized, Controlled, Parallel-Group, Double-Blind Trial to Compare the Use of Deep or Standard Neuromuscular Blockade in Combination With Low or Standard Insufflation Pressures Using a 2x2 Factorial Design in Patients Undergoing Laparoscopic Cholecystectomy (Protocol No. MK-8616-076-00 also known as SCH 900616, P07982)
Sponsor	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Sponsor's Address	One Merck Drive P.O. Box 100 Whitehouse Station, NJ 08889-0100, U.S.A.
IND No.	Not Applicable
EudraCT No.	2012-001886-33
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Date of Finalization of This Current Version of the Protocol	***19 JUL 2012 – Amendment 1***
Protocol Template Approval Date	13 OCT 2011

C O N F I D E N T I A L

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SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

This protocol is being amended to adjust the definition of standard neuromuscular blockade to a targeted TOF ratio of 10% (range: TOF count 2-3 to TOF ratio of 20%). After additional discussions with the Scientific Advisory Committee, a consensus was reached that this definition is more reflective of current anesthesia practice and would allow sites to maintain the targeted depth of blockade during the trial.

Section Number	Section Title	Description of Change
7.4.1.1	Treatments Administered	*Definition of standard neuromuscular blockade has been changed to a targeted TOF ratio of 10% (range TOF count 2-3 TOF ratio 20%) per guidance of the Scientific Advisory Committee.*

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

- For neuromuscular blockade a bolus dose of 0.45 mg/kg rocuronium will be used for intubation and to induce NMB in all patients. Neuromuscular blockade will be maintained as needed using rocuronium bolus dose or infusion according to the randomly assigned treatment condition by the unblinded anesthetist.
- Based on feedback from the Scientific Advisory Committee scoring instruction on the surgical conditions questionnaire has been updated to include the following wording, "The surgeon will rate the surgical conditions according to his opinion but if a rescue maneuver has been applied, an analysis will be performed in which that individual patient will be counted with a score of zero".
- *Minor editorial comments were made throughout the protocol to make consistent with the primary changes*

Section Numbers	Section Titles	Description of Changes
7.4.1.1	Treatments Administered	*Administration of NMBA (rocuronium) has been changed to include the option of a bolus dose or infusion to maintain the appropriate level of blockade.* The treatment administration section has been updated to reflect the surgeons assessment at the time of rescue intervention and planned analysis.
7.6	*Trial Procedures*	*# 17 Administration of NMBA (rocuronium) has been changed to include the option of a bolus dose or infusion to maintain the appropriate level of blockade.* #22 The surgeon will rate the surgical conditions according to his opinion but if a rescue intervention has been applied, that individual patient will be counted with a score of zero.
8.5.1	*Primary Efficacy Analysis*	An additional sensitivity analysis will use the actual assessment score for surgical conditions before any rescue intervention (surgical conditions after establishment of the randomized NMB and insufflation pressure).
2.5	*Study Flow Chart by Assessment*	*Minor editorial changes were made, including removing 'provoked' after shoulder pain assessment and updating the changed noted within The Summary of Changes.*

2.0 SYNOPSIS

TITLE OF TRIAL: Randomized, Controlled, Parallel-Group, Double-Blind Trial to Compare the Use of Deep or Standard Neuromuscular Blockade in Combination With Low or Standard Insufflation Pressures Using a 2x2 Factorial Design in Patients Undergoing Laparoscopic Cholecystectomy (Protocol No. MK-8616-076-00 also known as SCH 900616, P07982)

ABBREVIATED TITLE: Effects of Depth of Neuromuscular Blockade and Insufflation Pressure on Surgical Conditions

OBJECTIVES:

Primary Trial Objective: The primary objective of the trial is to assess the benefit of deep neuromuscular blockade in surgical conditions when compared to standard neuromuscular blockade.

Key Secondary Objective:

The key secondary trial objective is to assess whether the use of low insufflation pressure improves the overall patient's pain score within 24 hours (average of all pain assessments at 1, 2, 4 and 24 h) as compared to standard insufflation pressure, based on a standard pain scale following a laparoscopic cholecystectomy.

Other Secondary Trial Objectives:

An additional secondary objective for this study is to evaluate the visual field during laparoscopy (as determined by the surgeon) after use of sustained deep neuromuscular blockade compared to standard neuromuscular blockade.

Other Trial Objectives:

This trial will also evaluate the following objectives:

- Overall adequacy of neuromuscular blockade during surgery (as determined by the surgeon)
- Overall adequacy of insufflation pressure during surgery (as determined by the surgeon)
- Assessment of interference of patient's movements during surgery (as determined by the surgeon)
- Assessment of patient reported post-operative pain after 48hours, as well as post-operative Day 3-8
- Assessment of post-operative analgesic consumption
- Assessment of additional clinical endpoints such as
    - rate of residual NMB,
    - recurrence of NMB,
    - gas volume needed to install pneumoperitoneum,
    - number of rescue actions performed during surgery for improving surgical conditions
    - intra-operative measurement of abdominal wall relaxation after establishment of assigned NMB (e.g. distance from umbilicus to promontorium or bowel)

Trial Design

Overview:
This is a randomized, controlled, parallel group, blinded (subject, surgeon, and safety-assessors blinded to treatment) multi site pilot trial to compare the use of deep or standard NMB in combination with low (starting at 8 mm Hg) or standard (starting at 12 mm Hg) insufflation pressure using a 2x2 factorial design in subjects of both sexes undergoing laparoscopic cholecystectomy.

Number of Trial Centers: Approximately 6 centers

Duration of Participation: Each subject will participate in the trial for approximately 14 days from the time the subject signs the Informed Consent Form (ICF) through the final assessment on Day 8. After a screening phase of up to 7 days, each patient will receive the assigned treatment. The primary period of hospital observation will be for at least 48 hours post surgical procedure. Subjects will record pain assessments and intake of analgesic and anti-emetic medications until Day 8 following hospital discharge. A follow up telephone call or visit will occur on Day 8 (Follow-Up Visit) at which time the subject has completed the trial. Female subjects will have an additional pregnancy follow up phone call at $\geq$ 30 days after study medication.

Duration of Trial: The trial will require approximately 8 months from the beginning to the end of the overall trial (first subject signing informed consent to last contact with last subject).

Key Inclusion/Exclusion Criteria:

Subjects must be: Males/Females ≥ 18 yrs; ASA (American Society of Anesthesiologists) Class 1, 2 or 3; scheduled for laparoscopic cholecystectomy (standard 4-hole) procedure under general anesthesia with total intravenous anesthesia (TIVA) using propofol and remifentanil and is expected to undergo rocuronium-induced neuromuscular blockade for endotracheal intubation and require active reversal of neuromuscular blockade.

Subjects with neuromuscular disorders that may affect neuromuscular blockade and/or assessments will be excluded from this study, in addition subjects who cannot meeting general standards for anesthesia trials (inability to intubate, renal/hepatic dysfunction, allergies to general anesthesia medications, malignant hyperthermia, interactions with toremifene/fusidic acid, pregnant patients, previous enrollment in trials or relation to staff) will also be excluded.

Investigational Medicinal Product: Sugammadex will be sourced locally as 5 mL vials containing 500 mg (i.e. 100 mg/mL). After the last dose of rocuronium, a single intravenous (IV) bolus dose of sugammadex will be administered within 10 seconds into a fast running IV infusion. A dose of either 2 mg/kg or 4 mg/kg will be administered according to current dosing guidelines in the approved label.

STATISTICAL METHODS:

Data Set(s) to be Analyzed: The primary efficacy analysis is to be performed on the Full Analysis Set, defined as all randomized patients who experienced rocuronium-induced NMB and pneumoperitoneum using low or standard insufflation pressure and did not convert to open surgery (before start of application of NMB and/or insufflation pressure). Patients will be included in the treatment group to which they are randomized.
All safety analyses including the analysis of the key secondary endpoint will be performed on the All-Patients-as-Treated (APaT) Set, defined as all randomized subjects who experienced rocuronium-induced NMB or pneumoperitoneum, according to actual treatment conditions (depth of NMB and level of insufflations pressure)

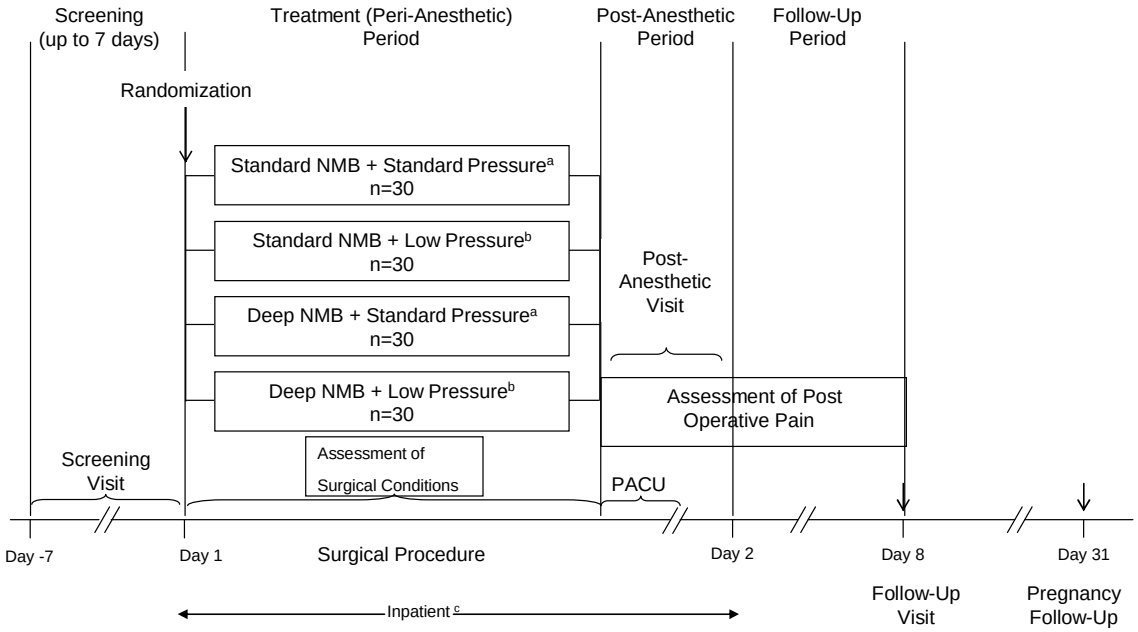
Sample Size: Approximately 120 subjects will receive randomized treatment assignment in the trial with 30 subjects assigned to each of the 4 treatment arms.

Efficacy Analysis: The primary Efficacy Endpoint(s) for the current trial is the surgeon's assessment of surgical conditions which will be analyzed by an Analysis of Variance (ANOVA) with factors depth of NMB (deep or standard), level of insufflation pressure (low or standard), and operating surgeon/surgical team. The (confirmatory) contrast of primary interest for surgical conditions will be deep NMB versus standard NMB.

Analysis of Pain Assessments: The Key Secondary Endpoint for the current trial is the patient's overall average pain score within 24 hours (average of all pain assessments at 1, 2, 4 and 24 h) and will be analyzed with an Analysis of Variance (ANOVA) with factors depth of NMB (deep or standard), level of insufflation pressure (low or standard), gender and operating surgeon/surgical team. The (confirmatory) contrast of primary interest for the average pain score will be low insufflation pressure versus standard insufflation pressure.

Interim Analysis: No formal interim analyses are planned.

2.1 Trial Design Diagram



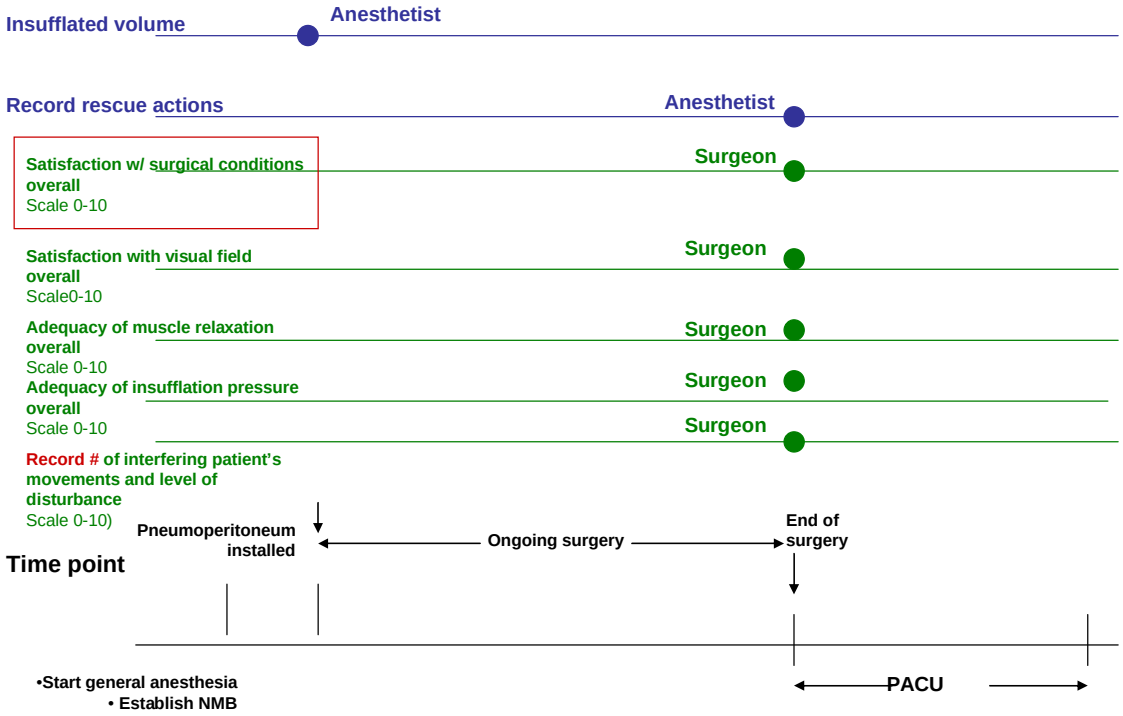
[a] Standard insufflation pressure: starting at 12 mm Hg

[b] Low insufflation pressure: starting at 8 mm Hg

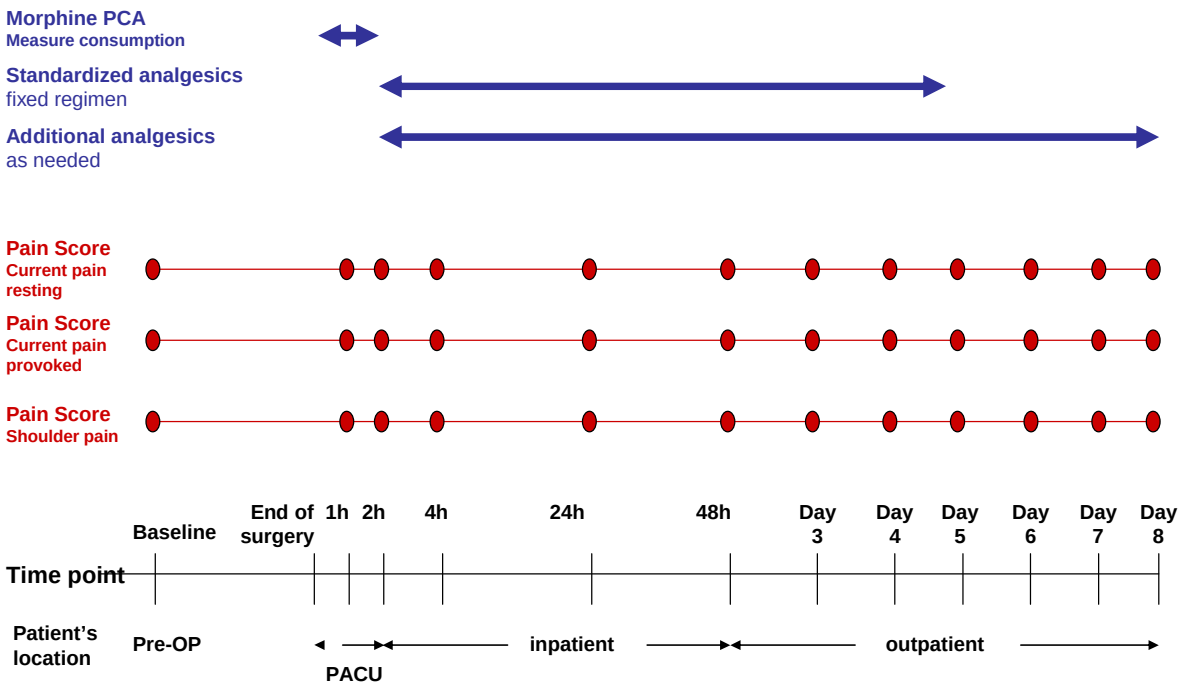
[c] Patients may be discharged from the hospital 48 hours (Day 2) following the surgical procedure

NMB=neuromuscular blockade; PACU=Post-Anesthesia Care Unit

2.2 Overview of Surgical Condition Assessments



2.3 Overview of Pain Assessment Measures



2.4 Trial Flow Chart

2.4.1 Chronological Flow Chart

Screening period Visit 1 (within 7 days prior to Randomization)		• Obtain written Informed Consent(s) (i.e., enrollment, screening number assignment) • Obtain Pharmacogenetic Consent • Issue Patient Identification Card • Obtain demographics and record medical history • Record pre-trial medication intake (within 7 days prior to entering trial) • Assess/record vital signs (heart rate [HR], respiratory rate [RR], and blood pressure [BP]) in supine position • Perform focused physical examination (including weight and height) • Perform, if applicable, a pregnancy test (within 24 hours before surgery) • Assess previous medication intake • Assess PONV Risk Factors • Assess pre-treatment Adverse Events (AEs) and Serious AEs (SAEs) • Confirm patient meets inclusion and no exclusion criteria • Obtain sample for pharmacogenetic analysis (should be obtained before first drug dose or as soon as Informed Consent and Pharmacogenetic Consent are signed
Peri-anesthetic period		• Confirm patient meets inclusion and no exclusion criteria; update medication information if any changes • Randomize to treatment with one of four treatment groups (IVRS) • Exclude routine use of preoperative pain medication (ibuprofen or paracetamol) as well as dexamethasone • Record local anesthetics used for pain management. Prior to trochar insertion local anesthetics will be injected up to a maximum of 100 mg of levobupivacaine, bupivacaine or ropivacaine as per Section 7.6.1 • Insert an intravenous (IV) cannula (s) • Induce anesthesia. All patients will receive a standard regimen for general anesthesia using Total Intravenous Anesthesia (TIVA) with propofol and remifentanil as per Section 7.6. • Assess/record vital signs (HR and BP) prior to administration of-neuromuscular blocking agent (rocuronium) • Administer intubating dose of rocuronium. A bolus dose of 0.45 mg/kg of rocuronium will be used for intubation • Intubate patient • Maintain anesthesia as per standard anesthesia regimen Section 7.6 • Assess baseline vital signs (heart rate and blood pressure) (just prior to administration of Sugammadex preferably at stable anesthesia) • Record any rescue interventions as per Section 7.6 and Appendix 3. If at any time the surgeon requests a rescue intervention, the overall assessment of surgical conditions should be rated as 0 (=poor, needed intervention). Note: The surgeon will rate the surgical conditions according to his opinion but if a rescue intervention has been applied, that individual patient will be counted with a score of zero.
Day 1	t = 0	• Assessment of depth of neuromuscular blockade Using TOF-Watch® SX by anesthetist. Surgeon should assess the adequacy of the neuromuscular blockade. Insufflation should be initiated only after the target depth of NMB has been reached. • Record insufflation pressure (continuously controlled/recorded by anesthetist keeping surgical team blinded to CO2 pressure) and surgeon should assess the adequacy of the insufflation pressure.Assessments relevant to the overall surgical conditions will be completed be the Surgeon. At the end of the remifentanil infusion, a bolus dose of 8 mg morphine will be administered prior to extubation and patient controlled analgesia (PCA) with morphine will be started. • Assess Adverse Events (AEs)/Events of Clinical Interest (ECIs)Serious AEs (SAEs) and Medical Device Reporting reportable events (MDRs) • Extubate patient • Assess/record vital signs (heart rate, respiratory rate and blood pressure) prior to administration of sugammadex • Reverse neuromuscular blockade. In all patients NMB will be reversed with 2 or 4 mg/kg of sugammadex (depending on depth of NMB) according to the approved label of sugammadex. See Section 7.6. • Collect clinical interaction data • Assess/record vital signs (heart rate, respiratory rate and blood pressure) at 2, 5, 10, and 30 minutes after administration of Sugammadex • Assess concomitant medication. Patients will receive morphine PCA for 2 hours while in the PACU. Administer pain medication (Section 7.6.1) after discharge from PACU. Pain Assessments will be recorded in all patients at 1, 2, 4 and 24 hours after the administration of Sugammadex
Post-anesthetic visit (Day 1 to Day 2)		• Assess/record vital signs (heart rate, respiratory rate and blood pressure) • Assess/record concomitant medication intake • Assess/record Nausea and Vomiting events • Assess AEs /SAEs
Follow-up Period (Day 3 to Day 8)		• Patients assess/record pain measurements on Day 3 through Day 8 using ePRO device • Patients assess/record concomitant medication intake (specifically Anti-Emeric and Analgesics) • Contact patients when applicable as a reminder to complete required pain and medication assessments • Contact subject at least 7 days after study medication (Day 8)(safety assessor by telephone or visit, when applicable) • Assess AEs and SAEs • Return Subject Identification Card and Study Material (ePRO device) per Sponsor requirements • End of trial
> 30 days after study medication		• Inquire about possible pregnancy for female patients (≥30 days post study medication)

2.5 Study Flow Chart by Assessment

Table 1 Flow Chart by Assessment

Visit Title	Timing of Evaluation and Procedures				
	Screening	Treatment (Peri-anesthetic Period)	Post-Anesthetic Period[a]	Follow-Up	Pregnancy Follow-Up ≥30 Days After Study Medication
Scheduled Day	Day -7 to Day -1	Day 1[b]	Day 1 to Day 3	Day 8	≥ Day 30
Explain Study and Obtain Informed Consent [c]	X				
Obtain Pharmacogenetic Consent [c]	X				
Subject Identification Card	X				
Medical History	X				
Prior Medication Review	X				
Physical Exam	X				
Vital Signs[d]	X	X	X		
Pregnancy Test[e]	X				
Inclusion/Exclusion Criteria	X	X			
Pharmacogenetic sample[c]	X				
Randomization		X			
Administration of NMBA (rocuronium)		X			
Neuromuscular Assessments[f]		X			
Assessment of Neuromuscular Blockade		X			
Assessment of Insufflation Pressure		X			
Physical Assessments of Abdominal Wall Relaxation		X			
Administration of Reversal Agent (sugammadex)[g]		X			
Surgeon Satisfaction with the overall Surgical Conditions [h]		X			

Visit Title	Timing of Evaluation and Procedures				
	Screening	Treatment (Peri-anesthetic Period)	Post-Anesthetic Period[a]	Follow-Up	Pregnancy Follow-Up ≥30 Days After Study Medication
Scheduled Day	Day -7 to Day -1	Day 1[b]	Day 1 to Day 3	Day 8	≥ Day 30
Surgeon assessments of surgical conditions (overall, visual field, muscle relaxation, pt movements) [h]		X			
Assessment of Post-Operative Pain prior to hospital discharge[i]					
Overall pain (at rest and provoked)		X[i]	X[i]	X	
Post-operative shoulder pain (at rest)		X[i]	X	X	
Daily Assessment of Pain After Discharge up to Day 8[j]					
Overall pain (at rest and provoked)				X	
Shoulder pain (at rest)				X	
Concomitant Medications (includes analgesics and anti-emetic medications	X	X	X	X	
Safety assessments (AE, SAE, MDR) [j]	X	X	X	X	
Pregnancy Follow-Up (females only)					X
End of Trial				X	

	Timing of Evaluation and Procedures				
Visit Title	**Screening**	**Treatment (Peri-anesthetic Period)**	**Post-Anesthetic Period[a]**	**Follow-Up**	**Pregnancy Follow-Up ≥30 Days After Study Medication**
Scheduled Day	**Day -7 to Day -1**	**Day 1[b]**	**Day 1 to Day 3**	**Day 8**	**≥ Day 30**

E=adverse event; hCG=human chorionic gonadotropin; MDR=medical device reportable event; PACU=post-anesthesia care unit; PTC=post-tetanic count; SAE=serious adverse event; (S)AE=serious or non-serious adverse event

[a] The Post-Anesthetic Period begins when the subject is discharged from the operating room to the PACU and extends up to and including the Post-Anesthesia Visit. Patients may be discharged from the hospital after discharge from the PACU and a Post-Anesthetic Visit (24 hrs post surgery)

[b] Day 1 is the day of surgery (Peri-anesthetic period) and includes administration of sugammadex.

[c] Informed consent for pharmacogenetic samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized patients only, or at a later date as soon as the informed consent is obtained.

[d] At screening, prior to administration of rocuronium, prior to administration of sugammadex, at 2, 5, 10, and 30 minutes after administration of sugammadex, and at the Post-Anesthetic Visit in the supine position.

[e] Urine or serum hCG test, within 24 hours prior to surgery.

[f] Recording of the depth of neuromuscular blockade.

[g] According to the approved sugammadex label.

[h] These assessments should be completed by the surgeon prior to leaving the operating room suite.

[i] These assessments should occur at 1, 2, 4 and 24 hours after administration of sugammadex, and daily (morning) from Day 3 to Day 8. Day 3 assessment to occur prior to discharge from the hospital. Patients will assess their level of post-operative pain using a score of 0 to 10 using an ePRO device. Pain assessment questionnaire may be administered by study staff while the subject is in the hospital.

[j] After discharge, subjects will continue to record pain assessments on a daily basis from Day 3 to Day 8 until the Follow-Up Visit. *Subjects will receive a phone call from the study staff on Day 5 as a reminder to complete the required assessments.* During the Screening Period: trial procedure related events and (S)AEs. During the Peri-Anesthetic Period: trial procedure related events, MDR reportable events, and (S)AEs. During the Post-Anesthetic Period: trial procedure related events and (S)AEs. During the Follow-Up Period: trial procedure related events and (S)AEs until 7 days after administration of sugammadex.

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4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
AE	Adverse Event
AMA	American Medical Association
AMG	Acceleromyography
ANOVA	Analysis of Variance
APaT	All Patients as Treated
ASA	American Society of Anesthesiologists
BIS	Bispectral Index
BMI	Body mass index
CFR	Code of Federal Regulations
CRF	Case Report Form
CSR	Clinical Study Report
CTD	Clinical Trial Directive
eCRF	Electronic Case Report Form
ECI	Event of Clinical Interest
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcome
EU	European Union
FBR	Future Biomedical Research is equivalent to the pharmacogenetics sub-study mentioned in this protocol.
DSM-IV TR™	Diagnostic and Statistical Manual of Mental Disorders (DSM)
Safety Data Reporting Form	The Sponsor's collection form used to report serious adverse events (SAE) or other events to Global Safety in the event that the EDC system is not functioning or able to accept SAE reports. The form is accompanied by the Safety Data Reporting Form Completion Guide and Instructions. SAE information can also be provided by means of a suitable alternative as long as it contains the equivalent information and is approved by Global Safety.
FAS	Full Analysis Set
GCP	Good Clinical Practice
GCRP	Good Clinical Research Practice
hCG	Human Chorionic Gonadotropin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product

Term	Definition
IND	Investigational New Drug Application; legal instrument in the USA that allows trial of unapproved, investigational new drugs in human subjects
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
LDA	Longitudinal Data Analysis
LMA	Laryngeal mask airway
MAR	Missing at Random
MDR	Medical Device Reporting
MedDRA	Medical Dictionary for Regulatory Affairs
MNAR	Missing Not at Random
NMB	Neuromuscular Blockade
NMBA	Neuromuscular Blocking Agent
NOMESCO	Nordic Medico Statistical Committee
OR	Operating room
PACU	Post-Anesthesia Care Unit
PCA	Patient Controlled Analgesia
PEEV	Positive End Expiratory Pressure
PGt	Pharmacogenetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PONV	Post Operative Nausea and Vomiting
PNS	Peripheral Nerve Stimulator
PTC	Post-Tetanic Count
PQC	Product Quality Complaint
RSI	Reference Safety Information
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPc	Summary of Product Characteristics
SOC	Subject Organ Class
T_1, T_2, T_3, T_4	First (T_1),second (T_2), third (T_3), or fourth (T_4) twitch in response to TOF stimulation
T_4/T_1 ratio	TOF ratio: Ratio of the height of T_4 over the height of T_1 in the recording of the response to TOF stimulation. Ratio expressed in decimals (e.g., 0.7 or 0.8 or 0.9)
TIVA	Total Intravenous Anesthesia
TOF	Train of Four Stimulation
US	United States
USP	US Pharmacopoeia

5.0 INTRODUCTION

The purpose of this pilot trial is to investigate the potential benefits of deep neuromuscular blockade for patients, surgeons, and anesthetists. The trial is designed to systematically examine the combination of "insufflation pressure" (standard pressure vs. low pressure) and "sustained depth of neuromuscular blockade" (deep NMB vs. standard NMB).

5.1 Therapeutic Rationale

Drug -induced neuromuscular blockade (NMB) is used with general anesthesia to aid intubation and to improve surgical conditions during various surgical interventions. In order to reverse drug-induced NMB at the end of surgery, anesthetists can either wait for the effects of the neuromuscular blocking agent (NMBA) to wear off or accelerate recovery from the NMBA by administering a reversal agent. Available reversal agents, such as neostigmine, can reverse shallow to moderate levels of NMB, but are not effective at reversing a deep level of NMB, which is more likely than shallow to moderate NMB to provide the most benefit for surgeons during surgical interventions. Anesthesiologists currently avoid the routine use of deep NMB throughout surgery due to the risk of residual blockade, which can prolong a patient's stay in the post-anesthesia care unit (PACU) and be associated with post -operative complications.

Sugammadex is a modified gamma-cyclodextrin that selectively binds to the NMBAs rocuronium and vecuronium. It is indicated as a selective relaxant-binding agent to reverse rocuronium- or vecuronium-induced NMB. Complexation of sugammadex with rocuronium or vecuronium prevents these NMBAs from binding to nicotinic receptors in the neuromuscular junction, thereby rapidly, predictably, and completely reversing any degree of NMB. Sugammadex is currently the only reversal agent capable of reversing deep NMB at any time during surgery. Thus, sugammadex could enable anesthetists to safely use deeper and more sustained NMB during surgery.

The frequency of laparoscopic interventions in clinical practice has sharply increased, mainly due to a number of tangible individual benefits for patients such as earlier mobilization, shorter hospitalization times, less post-operative pain, and smaller cicatrices. In order to obtain acceptable surgical conditions and a clear visual field, laparoscopic interventions are performed using a pneumoperitoneum with an insufflation of CO_2 at pressures of approximately 12 to 15 mm Hg. During laparoscopic surgery, insufflation pressure is continuously monitored and maintained at a pressure that provides a clear view of the surgical field and at least acceptable surgical conditions.

In laparoscopic surgery, a significant number of patients report post-operative pain, such as shoulder- tip pain, abdominal pain, or visceral pain. At least some of these symptoms (esp. shoulder-tip pain) appear to be adverse events associated with

laparoscopy, but not with open surgery. The pathophysiology of these types of post-operative pain is not fully understood, but likely involves pressure-induced irritations of somatic and visceral nerves (e.g., nervus phrenicus). These painful sensations are often of considerable intensity and duration (up to several days after surgery). Laparoscopic procedures with a particularly high risk of these types of post-operative pain are cholecystectomy and gynecological procedures.

A positive correlation between insufflation pressure and post-operative pain has also been reported[1]. Standard pressures of 12 to 16 mm Hg appear to have higher rates of post-operative pain than more recently introduced lower insufflation pressures. Lower insufflation pressure (e.g., 6 to 8 mm Hg) in laparoscopic cholecystectomy has been associated with significantly reduced overall post-operative pain, reduced incidence of post-operative shoulder pain, and a reduced amount of analgesic consumption. Nevertheless, the use of lower insufflation pressure is still limited in practice, as lower pressure may lead to inferior visibility for the surgeon, the potential need to increase pressures intra-operatively, or the possible necessity of conversion to open surgery.

The relationship between insufflation pressure and the depth of NMB has not been studied systematically. Based on anecdotal reports from clinical experts, it seems plausible that maintaining deep NMB throughout the entire surgical procedure will allow the application of lower insufflation pressures than current standards without compromising acceptable surgical conditions. A sustained deep NMB, which could be reversed at any time using sugammadex according to clinical needs of the surgeon, may provide a variety of possible benefits during laparoscopic procedures:

a. For patients, deep NMB may allow the use of lower insufflation pressures leading to reduced post-operative pain and/or less post-operative analgesic consumption, as well as improved mobilization and convalescence;
b. For surgeons, deep NMB
   - may lead to greater relaxation of skeletal muscles and fewer (or no) involuntary patient movements (e.g., bucking) during laparoscopy,
   - may decrease muscle tension enabling easier manipulation in the surgical (laparoscopic) field and/or facilitate closure,
   - may allow a clear visual field during laparoscopy and maximize access, and
   - may enable the use of lower insufflation pressures without compromising the visual field or surgical conditions (i.e., provide equally satisfactory surgical conditions and/or field of view at lower CO_2 insufflation pressures)
c. For anesthetists, deep NMB
   - may optimize control of all aspects of general anesthesia throughout surgery,
   - may not be associated with residual NMB after reversal with sugammadex, and
   - may not be associated with recurrence of NMB after reversal with sugammadex

The purpose of this trial is to investigate the potential benefits of deep NMB for patients, surgeons, and anesthetists using a 2x2 factorial design. The trial is designed to systematically examine the combination of "insufflation pressure" (standard pressure vs. low pressure) and "sustained depth of NMB" (deep NMB vs. standard NMB), but not to evaluate the effects of sugammadex. Because only a limited amount of empirical data for the endpoints of potential interest are available from the literature, this trial is designed as a pilot trial to explore a number of possible endpoints of interest.

5.2 Subject Population Rationale

Subjects of both sexes undergoing laparoscopic cholecystectomy will be enrolled in this trial. For this surgical intervention, the benefits of lower insufflation pressures on post-operative pain as compared to standard insufflation pressures have already been established and are expected to be replicated. The visibility of the surgical field reportedly differs depending on the insufflation pressure used during the procedure. Since this procedure is frequently performed, if the benefits of deep NMB can be established in this group of patients, they are likely to be of clinical relevance for a large number of patients.

Details about specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying **Summary of Product Characteristics (SmPC)** and the Informed Consent documents. Subjects in clinical studies generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

5.3 Dose and Administration Rationale

Sugammadex (2 or 4 mg/kg) will be administered in all patients to reverse the randomly assigned depth of NMB in accordance with current dosing guidelines as an intravenous (IV) bolus dose in an unblinded manner according to the depth of block just prior to administration of study drug.

A dose of 4 mg/kg sugammadex is recommended if neuromuscular recovery has reached at least 1-2 post-tetanic counts (PTC) following rocuronium-induced blockade (i.e., deep blockade); a dose of 2 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium-induced blockade (i.e., moderate blockade).

6.0 TRIAL OBJECTIVES

6.1 Primary Trial Objective

The primary objective of the pilot trial is to assess the benefit of deep neuromuscular blockade in surgical conditions when compared to standard neuromuscular blockade.

6.2 Key Secondary Trial Objective

The key secondary trial objective is to assess whether the use of low insufflation pressure improves the overall patient's pain score within 24 hours (average of all pain assessments at 1, 2, 4 and 24 h) as compared to standard insufflation pressure, based on a standard pain scale following a laparoscopic cholecystectomy.

6.3 Other Secondary Trial Objectives

An additional secondary objective for this study is to evaluate the visual field during laparoscopy (as determined by the surgeon) after use of sustained deep neuromuscular blockade compared to standard neuromuscular blockade.

6.4 Other Trial Objectives

This trial will also evaluate the following objectives:

- Overall adequacy of neuromuscular blockade during surgery (as determined by the surgeon)
- Overall adequacy of insufflation pressure during surgery (as determined by the surgeon)
- Assessment of interference of patient's movements during surgery (as determined by the surgeon)
- Assessment of patient reported post-operative pain up to 48 hours, as well as post-operative pain Day 3-8
- Assessment of post-operative analgesic consumption including morphine consumption via PCA
- Assessment of additional clinical endpoints such as
    - rate of residual NMB,
    - recurrence of NMB,
    - gas volume needed to install pneumoperitoneum,

- number of rescue actions performed during surgery for improving surgical conditions
- intra-operative measurement of abdominal wall relaxation after establishment of assigned NMB (e.g. distance from umbilicus to promontorium or bowel)

7.0 INVESTIGATIONAL AND ANALYSIS PLAN

7.1 Overall Trial Design

This is a randomized, controlled, parallel-group, blinded multi-site pilot trial to compare the use of deep or standard NMB in combination with low (starting at 8 mm Hg) or standard (starting at 12 mm Hg) insufflation pressure using a 2x2 factorial design in adult subjects of both sexes undergoing laparoscopic cholecystectomy. The study is to be conducted in conformance with Good Clinical Practices.

Selected trial personnel will be blinded (see **Section 7.4.1.4**)

7.2 Beginning and End of the Trial

Each subject is considered to be enrolled in the trial when the subject (or the subject's legal representative) has provided written informed consent.

Each subject is considered to have ended participation in the trial when he/she has completed the last protocol-specified contact (e.g., visits or telephone contacts) or prematurely discontinues from the study.

A subject is considered to be a completer of the trial after he/she has completed the protocol-specified end of trial Day 8 follow-up visit (by telephone contact or site visit). Data collected up to and including this visit will be included in the planned study analyses.

A subject is considered to have discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in **Section 7.3.3**.

A subject is considered to have been lost to follow-up if he/she is unable to be contacted by the investigator prior to completing all of the protocol-specified activities. The end of participation for a subject lost to follow-up is the last known contact (e.g., visit or telephone contact).

The overall trial begins when the first subject is enrolled (i.e., signs the informed consent form). The overall trial ends when the last remaining subject has ended

participation in the trial, by completing the trial, being discontinued from the trial, or being lost to follow-up.

Each subject will be monitored for the occurrence of AEs immediately after the subject has signed informed consent. Each subject will be followed for serious adverse events for up to and including 7 days after the last dose. Follow-up procedures related to pregnancy or SAEs may continue beyond the end of the clinical trial.

Once a subject has ended participation in the trial, the investigational product(s) from the trial will no longer be available to the subject and any future care will be provided according to the subject's personal physician.

Each subject will participate in the trial for approximately 14 days from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of maximally seven days, each subject will be receiving one single dose of assigned treatment (**Section 7.4.1.1**). After treatment, each subject will be followed for safety monitoring for seven days.

7.3 Trial Population

Subjects who are selected to participate in the trial are adult surgical patients of ASA Class 1, 2, or 3 who are scheduled to undergo a laparoscopic cholecystectomy under general anesthesia requiring neuromuscular relaxation with rocuronium for endotracheal intubation and active reversal of neuromuscular blockade with sugammadex. Subjects are expected to recover in the PACU and remain in the hospital for at least 48 hours following the surgical procedure. See also **Section 5.2**.

7.3.1 Subject Inclusion Criteria

A subject must meet all the criteria listed below to participate in the trial.

1. Each subject must be willing and able to provide written informed consent for the trial.
2. Male or Female, ≥ 18 years of age,
3. Categorized as American Society of Anesthesiologists (ASA) Class 1, 2, or 3.
4. Scheduled to undergo an elective in-patient laparoscopic cholecystectomy (standard 4-hole) procedure under general anesthesia with total intravenous anesthesia (TIVA) using propofol and remifentanil and is eligible to undergo rocuronium-induced NMB for endotracheal intubation and maintenance of NMB. Subjects are expected to recover in the PACU and remain in the hospital for at least 48 hours following the surgical procedure.
5. Body mass index (BMI) ≤ 35
6. An arm accessible during surgery for monitoring the NMB using the TOF Watch SX® which will be used for objective NM transmission monitoring.

7. Willing and able to adhere to visit schedules including all required study assessments on Day 3 through 8 (daily pain and medication diary entry).
8. Able to use a medically accepted method of contraception through 7 days after receiving protocol-specified medication [for sexually active female subjects of child-bearing potential]. For subjects using hormonal contraceptives, if study medication is administered on the same day an oral contraceptive is taken, the subject must follow the missed-dose advice in the package leaflet of the oral contraceptive. In the case of non-oral hormonal contraceptives, the subject must use an additional non-hormonal contraceptive method and refer to the advice in the package leaflet of the product. Postmenopausal women are not required to use contraception. Postmenopausal is defined as at least 12 consecutive months without a spontaneous menstrual period.
9. Subjects must be willing to give written informed consent for pharmacogenetic testing, and able to adhere to dose and visit schedules.
   Note: Subjects who are unwilling to sign the informed consent for pharmacogenetic testing may be included into the trial, however, pharmacogenetic samples must not be obtained.

7.3.2 Subject Exclusion Criteria

A subject meeting any of the exclusion criteria listed below must be excluded from participating in the trial:

1. Anatomical malformations that may lead to difficult intubation.
2. Neuromuscular disorders that may affect NMB and/or trial assessments.
3. A history of previous laparoscopy procedures including laparoscopic hernia repairs and laparotomies (but not a diagnostic laparoscopy).
4. A subject must not currently (within the past 6 months) meet the DSM-IV-TR™ criteria for substance abuse or dependence (excluding nicotine).
5. A history of a chronic pain condition.
6. Previously have given birth to one or more children (female subjects) or is pregnant or has the intention to become pregnant between randomization and the ≥Day 30 pregnancy follow-up contact [premenopausal female of childbearing potential].
7. Evidence of acute cholecystitis.
8. Dialysis-dependency or suspected of having severe renal insufficiency (defined as estimated creatinine clearance of < 30 mL/min).
9. Significant hepatic dysfunction that would prevent participation in the trial as determined by the investigator.
10. A history of or family history of malignant hyperthermia.
11. An allergy to trial treatments (rocuronium or sugammadex) or their excipients, to opioids/opiates, or other medication used during general anesthesia.

12. Received or is planned to receive toremifene or fusidic acid within 24 hours before or after IMP administration.
13. An expected transfer to an Intensive Care Unit after surgery.
14. Any clinically significant condition or situation, other than the reason for the cholecystectomy that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.
15. Used any investigational drugs within 30 days of randomization.
16. Participated in any other clinical trial within 30 days, inclusive, of signing the informed consent form of the current trial.
17. Been a study subject or involved a family member who is among the personnel of the investigational or Sponsor staff directly involved with this trial.

7.3.3 Subject Discontinuation Criteria

A subject may discontinue from the clinical trial at any time for any reason.

It is the right and the duty of the investigator or subinvestigator to stop treatment in any case in which emerging effects are of unacceptable risk to the individual subject. In addition, the investigator or subinvestigator is to stop treatment of any subject with unmanageable factors that may interfere significantly with the trial procedures and/or the interpretation of results.

Discontinuation is “permanent”: once a subject is discontinued, he/she shall not be allowed to enroll again.

At a minimum, collect the following information when a subject discontinues:

- The reason the subject discontinued;
- The date of the last dose of test products from the trial;
- The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate;
- (Serious) Adverse events;
- Compliance with the test product administration as specified in this protocol;
- Final Assessments.
- Every effort should be made to ensure that all procedures and evaluations scheduled for the final trial visit are performed (**Section 2.4**, Trial Flow Chart).

A subject must be discontinued from the trial for any of the following reasons:

1. The subject withdraws consent;
2. The subject is administered another muscle relaxant other than rocuronium;

3. The subject is administered another reversal agent other than sugammadex;
4. The subject is allowed to recover spontaneously.

7.3.4 Replacement of Subjects

A subject that prematurely discontinues from the trial will not be replaced (i.e., a discontinued subject will not be replaced by a subject with the same treatment assignment as the discontinued subject). Randomization will continue until the scheduled number of subjects (120) are evaluable for the primary endpoint.

7.4 Treatments

7.4.1 Trial Treatments

7.4.1.1 Treatments Administered

Treatment should be administered as close as possible to the date in which randomized treatment is assigned, preferably on the same day.

All patients will receive a standardized regimen for general anesthesia using Total Intravenous Anesthesia (TIVA) with propofol and remifentanil.

For general anesthesia an initial bolus of 1 μg/kg followed by fixed doses of remifentanil (0.25 μg/kg/min as infusion) will be used. Additional doses may be administered as clinically required by the anesthesiologist. A bolus dose of propofol (2.5 mg/kg) will be used for induction. Anesthesia will be maintained with propofol infusion with a starting infusion rate of 6 to 12 mg/kg/h (100 to 200 μg/kg/min) titrated to maintain a Bispectral Index (BIS) of 40-50 throughout the surgery. This proposed dose may be adjusted as clinically required by the anesthetists.

For neuromuscular blockade a bolus dose of 0.45 mg/kg rocuronium will be used for intubation and to induce NMB in all patients. Neuromuscular blockade will be maintained using rocuronium infusion or additional bolus doses of rocuronium as needed for the management of NMB to the targeted depth according to the randomly assigned treatment condition by the unblinded anesthetist. The anesthetist will keep the surgeon blinded to the applied depth of NMB. The depth of NMB will be controlled by the anesthetist using acceleromyography via the TOF Watch SX® including Train-of-Four (TOF) stimulation and Post-Tetanic Count (PTC). Procedures for operating the TOF Watch SX® and recording of data should follow the latest version of the Neuromuscular Monitoring Transmission guidelines. The latest version available at the start of the trial will be the version used for the duration of the trial and will be provided to all participating sites.

- Standard NMB will be maintained with a continuous infusion or bolus dosing (as needed for the management of NMB to the targeted depth) of NMBA titrated to a depth of blockade at a targeted TOF ratio of 10% (range: TOF count 2-3 to TOF ratio of 20%).

- Deep NMB will be maintained with a continuous infusion or bolus dosing (as needed for the management of NMB to the targeted depth) of NMBA titrated to a targeted depth of 1-2 PTCs (deep blockade, range 1-5 PTC).

  These definitions will be used to establish and maintain the different levels of neuromuscular blockade after intubation following the initial bolus of 0.45 mg/kg rocuronium. Insufflation should be initiated only after the target depth of NMB has been reached. Insufflation pressure for the induction of a pneumoperitoneum will also be continuously controlled by the anesthetist keeping the surgical team blinded to the applied CO2 pressure.

- For the standard-insufflation-pressure treatment groups, a starting pressure of 12 mm Hg will be used.
- For the low-insufflation-pressure treatment groups, a starting pressure of 8 mm Hg will be used.

Insufflation pressure will be monitored and maintained during the surgical procedure using appropriate devices.

In case the surgical conditions are considered unacceptable with the randomly assigned depth of NMB and insufflation pressure, the surgeon (while remaining blinded) may request a rescue intervention from the anesthetist in order to safely proceed with the surgery. The anesthetist (being unblinded for treatment conditions) may then apply a "rescue" intervention. This will be done systematically as follows:

- If the patient is on standard NMB, the preferred rescue intervention should be to increase the NMB by titrating the NMBA infusion to a depth of 1-2 PTCs. The second option should be the increase of pneumoperitoneum pressure by 4 mm Hg.

- If the patient is already on deep NMB, the preferred option should be the increase of pneumoperitoneum pressure by 4 mm Hg.

If a rescue intervention is required, the anesthetist will document the time, the reason for the requested rescue intervention as well as the new applied parameters (such as depth of NMB or new target insufflation pressure). The surgeon will rate the surgical conditions according to his opinion, but if a rescue intervention has been applied, that individual patient will be counted with a score of zero.

In all subjects, the NMB will be reversed with 2 or 4 mg/kg sugammadex (depending on the depth of NMB) according to the approved label for sugammadex.

7.4.1.2 Method of Treatment Assignment, Randomization, and/or Stratification

Randomization to one of the four treatment groups as indicated in the Trial Diagram (**Section 2.1**) will occur centrally using an interactive voice response system (IVRS). Subjects will be randomized on Day 1 in a 1:1:1:1 ratio to one of 4 treatment groups:

- Standard NMB and standard insufflation pressure starting at 12 mm Hg
- Standard NMB and low insufflation pressure starting at 8 mm Hg
- Deep NMB and standard insufflation pressure starting at 12 mm Hg, or
- Deep NMB and low insufflation pressure starting at 8 mm Hg.

Standard insufflation pressure will be initially installed at 12 mmHg.

Low insufflation pressure will be initially installed at 8mm Hg.

Randomized treatment assignment will be stratified for surgeon/surgical team (i.e. surgeon with anesthetist) at the site level.

7.4.1.3 Selection and Timing of Dose for Each Subject

7.4.1.3.1 Selecting the Dose for Each Subject

The rationale for the selection of doses to be used in this trial is presented in **Section 5.3**.

Subjects who are randomized will be administered sugammadex based upon the current dosing guidelines as noted below.

7.4.1.3.2 Determining the Timing of Dose Administration for Each Subject

After the last dose of rocuronium, a single intravenous (IV) bolus dose of 2 or 4 mg/kg sugammadex will be administered within 10 seconds into a fast running IV infusion to reverse the NMB according to the randomized treatment group.

Sugammadex (2 or 4 mg/kg) will be administered as an intravenous (IV) bolus dose in an unblinded manner as per the approved labeling. The 2mg/kg dose will be administered at reappearance of T_2 (moderate NMB) and the 4 mg/kg dose will be administered at 1-2 PTC (deep NMB).

7.4.1.4 Blinding Trial Treatments

Patients, surgeons, safety assessors and the appropriate Sponsor personnel will be blinded to the experimental conditions. It is expected that any unblinded person from the study site or Sponsor will not share information with any blinded personnel. A blinded safety assessor (assigned physician) will evaluate the safety parameters (e.g., adverse events, SAEs, pain scores and medical device reportable [MDR] events related to the TOF Watch SX®). In addition the blinded safety assessor will assess a number of relevant measures of functionality such as convalescence, time spent in PACU, and analgesic medications used by the patient until hospital discharge.

Anesthetists will not be blinded to treatment assignment because they will control the depth of NMB and will record the dose and time of administration of all medications, insufflation pressures, and changes to the insufflation pressure or NMB as requested by the surgeon.

7.4.1.5 Investigational Medicinal Product/Study Medications

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

7.4.1.5.1 Identity of Investigational Medicinal Products

The following study medications will be used in the trial:

- Sugammadex (further referred to as Investigational Medicinal Product [IMP]) – marketed product
- Rocuronium bromide injection (further referred to as Investigational Medicinal Product [IMP]) - marketed product.

7.4.1.5.2 Source

All Investigational Medicinal Product [IMP] for this trial will be sourced locally by the site.

7.4.1.5.3 Labeling

Labeling for Investigational Medicinal Product [IMP] according to the Drug Preparation Manual will comply with the regulatory requirements for the clinical sites.

7.4.1.5.4 Packaging

Sponsor will not supply packaged Investigational Medicinal Product [IMP] specifically for this study; investigational medicinal product [IMP] will be sourced locally.

7.4.1.5.5 Storage

Trial treatment supplies (Investigational Medicinal Product [IMP]) must be stored in a secure, limited-access location under the storage conditions specified on the supply label. Site storage conditions should be monitored by the site personnel for adherence to label specifications and reviewed during site visits.

7.4.1.5.6 Dispensing

The investigator or qualified designee(s) will dispense trial treatments at the designated site(s) to subjects who have provided written informed consent and have met the entry criteria. Investigational Medicinal Product [IMP] designated as study drug for the purposes of this study and any clinical supplies may not be used for any purpose other than that which is stated in this protocol.

See the Trial Flow Chart in **Section 2.4** for a schedule of when Investigational Medicinal Product (s) [IMP] are to be dispensed to the subjects.

7.4.1.5.7 Replacement of Investigational Product

The study site is responsible for the replacement of rocuronium and sugammadex as needed, as these Investigational Medicinal Products [IMP] are sourced locally.

7.4.1.5.8 Investigational Medicinal Product Accountability

Accurate and current accounting of the dispensing and return of investigational product will be maintained on an ongoing basis by a member of the trial site staff:

- Investigational medicinal product(s) purchased by each site will be recorded in a trial-specific Site Investigational Medicinal Product (IMP) Accountability Log (or equivalent document approved by the Sponsor);
- Investigational medicinal product as dispensed to each subject will be recorded in a trial-specific Subject Accountability Log (or equivalent document approved by the Sponsor).

The Site IMP Accountability Log and Subject Accountability Log will be verified by the Sponsor's trial monitor. The original Site IMP Accountability Log and Subject Accountability Log will be approved by the investigator and retained at the trial site and a copy supplied to the Sponsor when the trial is complete.

A final inventory of the total amount of Investigational Medicinal Product [IMP] procured and designated for use in the trial by the site against the amount used and returned must be recorded in the Site IMP Accountability Log. Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.

7.4.2 Non-Trial Treatments

7.4.2.1 Prior and Concomitant Medications

7.4.2.1.1 Medications, Supplements, and Other Substances Prohibited Prior to Screening, Baseline, Randomization and During the Trial

The medications, supplements, and other substances prohibited prior to randomization are listed in **Section 7.3.2** with the subject exclusion criteria.

7.4.2.1.2 Concomitant Medications, Supplements, and Other Substances Allowed During the Trial

All clinically required concomitant anesthetic agents that are not contraindicated in the enrolled patients except for the required study medications are allowed to be administered during the trial.

Note that the use of any concomitant medication may relate to the documented medical history, prophylaxis, or an adverse event of the subject. All concomitant medications taken should be recorded on the concomitant medication form.

7.4.2.2 Other Treatments

Not applicable.

7.4.3 Procedures for Monitoring Subject Compliance with Administration of Trial Treatments

At the Day 1 protocol-specified visit, the investigator or qualified designee is to record whether treatment had been administered per protocol.

7.5 Trial Schedule

The visit-by-visit schedule of trial activities is provided in the Trial Flow Chart in **Section 2.4**.

The timing of each visit is relative to Day 1, which is defined as randomization of the subject until the post-anesthetic visit (**Section 7.4.1.2**).

7.6 Trial Procedures

The Trial Flow Chart in **Section 2.4** summarizes the trial procedures to be performed at each visit. Individual trial procedures are described below.

In order to minimize variability of evaluations, it is preferred that the same individuals perform the same types of evaluations for all subjects at each trial site.

1. **Explain Trial and Obtain Written Informed Consent**

   The investigator or qualified designee will explain the trial to the subject, answer all of his/her questions, and obtain written informed consent before performing any trial-related procedure, including pharmacogenetic sampling (see item 11). A copy of the informed consent will be given to the subject (see **Section 9.1.2** for further description of the Informed Consent).
2. **Issue or Collect Patient Identification Card**

   The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent. The investigator or qualified designee will retrieve the card from the subject at the last contact (see **Section 9.1.3** for further description of the Subject Identification Card).
3. **Obtain Medical History**

   A medical history will be obtained by the investigator or qualified designee. Subject history should include information on family history and personal history.
4. **Demographic Information**

   Demographic information (i.e., date of birth, gender, race and ethnicity) and clinically relevant items from the patient's medical history and physical examination (including weight) will be recorded. The patient will be asked about his/her height. Surgical information (i.e., ASA class, date of surgery, indication for surgery, and surgical procedure) will also be recorded.
5. **Review Inclusion/Exclusion Criteria**

   The inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.
6. **Review Prior Medications**

   A record of prior medication taken by the subject within 7 days before starting the trial is to be obtained.
7. **Record Concomitant Medications**

   A record of concomitant medications taken by the subject during the trial is to be obtained.
8. **Record Adverse Events including Serious Adverse Events and Events of Clinical Interest.**

   See **Section 7.7.2.2.1**, for instructions on the assessment and reporting of (Serious) Adverse Events and **Section 7.7.2.2.2** for instructions on the reporting of (Serious) Adverse Events to the sponsor.

Recording of adverse events or events of clinical interest (hypersensitivity events and/or anaphylactic reactions/anaphylaxis) in the appropriate eCRF module should be recorded in the additional separate modules) including results of laboratory tests evaluated by a local laboratory and other procedures deemed necessary by the study doctor.

9. **Focused Physical Examination**

   If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final focused physical examination and details of the exam will depend on the clinical situation's requirement.

10. **Pregnancy Assessment: Enrollment/Randomization**

    At Enrollment/Randomization, patients will be assessed if they are pregnant using a medically acceptable test, such as a urine hCG or serum hCG test.

11. **Pharmacogenetic Sampling (PGt)**

    Informed consent specific for PGt sampling, must be obtained prior to collection. To obtain sufficient DNA for pharmacogenetic studies, a single 8.5-mL blood sample will be drawn at the specified time points indicated in **Section 2.4**, Study Flow Chart, into the appropriate tubes provided by the sponsor (see **Appendix 2** for sample acquisition, shipping and labeling instructions and for additional information.

12. **Vital Signs**

    Heart rate and blood pressure will be assessed at the following time points: Screening, prior to administration of sugammadex, at 2, 5, 10 and 30 minutes after sugammadex and at the Post-Anesthetic Visit. All assessments should be in the supine position.

13. **Patient Randomization**

    Patients will be randomized to treatment with one of the four treatment groups indicated in the Trial Diagram. Randomization will occur centrally using an interactive voice response system (IVRS). See Section 7.4.1.2 for randomization procedures.

14. **Standard Pre-operative and Peri-operative Procedures**

    Surgical procedures for both pre-operative and peri-operative periods will be standardized (See **Section 7.6.1**).

15. **Pain Management (Preoperatively and Peri-operatively)**

    Specific procedures and medications to be used for pain management are described in **Section 7.6.1**.

16. **Induction of Anesthesia**

All patients will receive a standardized regimen for general anesthesia using Total Intravenous Anesthesia (TIVA) with propofol and remifentanil.

General anesthesia will use:

- An initial bolus of 1 μg/kg followed by fixed doses of remifentanil (0.25 μg/kg/min as infusion). Additional doses may be administered as clinically required by the anesthesiologist.

- A bolus dose of propofol (2.5 mg/kg) will be used for induction. Anesthesia will be maintained with propofol infusion with a starting infusion rate of 6 to 12 mg/kg/h (100 to 200 μg/kg/min) titrated to maintain a Bispectral Index (BIS) of 40-50 throughout the surgery. This proposed dose may be adjusted as clinically required by the anesthetists.

17. **Administration of NMBA (rocuronium)**

A bolus dose of 0.45 mg/kg rocuronium will be used for intubation and to induce NMB in all patients. Neuromuscular blockade will be maintained using rocuronium infusion according to randomly assigned treatment condition by the unblinded anesthetist keeping the surgical team blinded to the applied depth of NMB. The depth of NMB (standard or deep as defined in **Section 7.4.1.1**) will be controlled by the anesthetist using acceleromyography via the TOF Watch SX® including Train-of-Four (TOF) stimulation and Post-Tetanic Count (PTC) as per the latest version of the Neuromuscular Monitoring Transmission Guidelines.

18. **Pneumoperitoneum and Insufflation Pressure**

Insufflation should be initiated only after the target depth of NMB has been reached. Insufflation pressure for the induction of a pneumoperitoneum will also be continuously controlled by the anesthetist keeping the surgical team blinded to the applied CO2 pressure as defined in **Section 7.4.1.1**.

19. **Rescue interventions**

In case the surgical conditions are considered unacceptable with the randomly assigned depth of NMB and insufflation pressure, the surgeon (while remaining blinded) may request a rescue intervention from the anesthetist in order to safely proceed with surgery.

Rescue intervention procedures will be followed as defined in **Section 7.4.1.1**.

20. **Administration of reversal medication**

Patients will be administered sugammadex (2 or 4 mg/kg) for reversal of NMB according the approved label based on depth of neuromuscular blockade. Sugammadex is to be administered intravenously after wound closure and when it is imminently acceptable for the patient to move spontaneously.

21. **Pain Management (Post-operatively)**

Specific procedures and medications will be used for pain management as described in **Section 7.6.1**

22. **Surgical Conditions Assessment**

Surgeons will be asked to assess several parameters relevant for the evaluation of surgical conditions using a numerical scale with a score from 0 to 10 (0= poor/needs intervention and 10 = excellent) as soon as possible following surgery [**Appendix 3**]:

NOTE: The surgeon will rate the surgical conditions according to his opinion but if a rescue intervention has been applied, that individual patient will be counted with a score of zero. In the case of a rescue intervention, the assessments should refer to the surgical conditions/visability/movements etc. before the rescue intervention was applied.

- Satisfaction with overall surgical conditions during surgery (assessed at the end of surgery)
- Overall visual field during surgery (assessed at the end of surgery)
- Adequacy of muscle relaxation during surgery
- Adequacy of insufflation pressure
- Interference of intra-operative movements (e.g. movement of the extremities or abdominal muscles, coughing, bucking)

In addition, the surgeon will also document the number of interfering movements as well as any conversion to open surgery if clinically required.

Anesthetists will record

- Number and parameters of rescue interventions performed during surgery in order to improve insufficient surgical conditions
- Volume of gas needed to establish the pneumoperitoneum
- Any clinical evidence of residual neuromuscular blockade
- Any clinical evidence of recurrence of NMB or post-anesthetic complication

23. **Pain Related Measures Assessment**

After the completion of surgery, subjects will record their pain intensity at rest and provoked as per the questions in **Appendix 3**. Subjects will use a numerical self-rating scale to record pain with scores from 0-10 with the following anchor points: 0 = no pain, 1 – 3 = mild pain, 4-6 = moderate pain and 7-10 = severe pain [**Appendix 3**]. Patients will rate their pain symptoms at 1, 2, 4, 24 and 48 hours post-op as well as daily in the morning on Days 3-8.

The assessments will be comprised of the:

- Level of overall pain intensity at the time of assessment (at rest and provoked, i.e. in connection with the transition from lying to sitting position)
- Post-operative shoulder pain at the time of the assessment
- Amount of pain medications and anti-emetic medications consumed after the surgery up to Day 8.

Additional symptoms such as nausea and/or vomiting (incidences per 24 hours) will also be studied.

24. **Clinical Interaction and Recovery Data**

Any clinical evidence of residual neuromuscular blockade or recurrence of neuromuscular blockade (e.g., significant change in the respiratory rate, significant decrease in SpO2 level attributed to NMB) from administration of study medication until the patient is PACU discharge ready, will be recorded on the AE CRF. Additionally, the following event times will be recorded: time of OR admission, time of intubation, time of first incision, time of last stitch, time of study medication administration, time of extubation, time of OR discharge, time of PACU arrival and time of PACU discharge ready.

25. **Post Treatment Follow-up (Day 8) End of Trial**

The trial ends with the post-treatment follow up Day 8 visit which will either be a phone call or visit to the clinic if the patient is expected to return to the hospital.

26. **Pregnancy Follow-Up (≥Day 30)**

It is the Sponsor's policy to collect data on pregnancies in female trial participants. Pregnancy follow-up will be conducted as a phone call to the patient and applies to female subjects whose pregnancy is detected during the trial or ≥ 30-day after study medication. All pregnancies must be reported as soon as practical (within 24 hours of awareness) to the Sponsor. Reporting of a pregnancy must be done by means of the Safety Data Reporting Form. The sub-Investigator completes this form (as comprehensively as possible) and sends the form and all available supporting documentation by fax directly to the Sponsor. Pregnancy in a trial female patient should be entered on the AE eCRF.

If exposure to study medication has taken place, the pregnancy must be followed up for final outcome. (S)AE Forms should be completed as appropriate to

document and/or report both maternal and fetal (S)AEs. If an adverse outcome is present that corresponds with the seriousness criteria defined for SAEs (e.g., congenital malformations, spontaneous abortion, late fetal death or an AE in the newborn/neonate), this should be reported within 24 hours of awareness. As soon as possible after the end of the pregnancy (i.e., induced/spontaneous abortion or delivery) the Pregnancy Follow-up Form must be completed and be sent with all available supporting documentation by fax directly. Pregnancy data will be entered into the safety database but is not part of the clinical trial database.

7.6.1 Protocol Specific Controlled Parameters:

- **Subject Positioning:** Subject positioning during surgery will also be standardized. After induction of the NMB and intubation, the subject will be positioned in the 20° anti-Trendelenburg position with both arms out to the side. The arm with the TOF monitoring equipment should be adequately positioned to allow for precise neuromuscular monitoring.

- **Surgical Experience:** The level of experience of the surgeon will also be standardized, with the requirement that participating surgeons should have performed at least 40 laparoscopic cholecystectomy procedures. Each site will have a maximum of 2 surgeons who will participate in this study.

- **Pre-operative and Peri-operative Procedures:** The following procedures should be standardized for the trial:

    - Emptying of the stomach should occur prior to surgery

    - Gastric tube should be inserted prior to surgery and removed prior to extubation

    - Target end tidal CO_2 concentration should be 40 mmHg (range 37-45)

    - Positive End-Expiratory Pressure (PEEP) level should be set at 5 cm H_2O

    - Total volume of iv fluids peri-operatively should not exceed 1500 ml (e.g. NaCl 0.9% or similar) unless clinically required.

- **Pain Management:**

    - Preoperatively: Preoperative pain medication (ibuprofen and/or paracetamol) as well as dexamethasone will not be dispensed routinely.

- Peri-operatively: prior to trochar insertion local anesthetics will be injected, as needed up to a maximum of 100 mg of levobupivacaine, bupivacaine or ropivacaine. At the end of the remifentanil infusion, a bolus dose of 8 mg morphine will be administered prior to extubation and patient controlled analgesia (PCA) with morphine will be started.
- Post-operatively: Patients will receive morphine PCA for 2 hours while in the PACU. After discharge from the PACU, patients will receive oral pain medication according to the following schedule:
  - 4 x 400 mg ibuprofen up to (and including) Day 5
  - 4 x 1000 mg paracetamol up to (and including) Day 5
  - Additional as-needed medication will also be available for the patient, and its use will be recorded.

All pain medications will be systematically recorded up to Day 8.

7.7 Assessments

7.7.1 Surgical Efficacy Assessments

7.7.1.1 Primary Endpoint

The Primary Endpoint for the trial is the surgeon's overall satisfaction with the surgical conditions rated at the end of the surgery using a numerical scale with scores from 0 (=poor, needed intervention) to 10 (=excellent). The Primary Efficacy Endpoint is related to the Primary Trial Objective.

7.7.1.2 Key Secondary Endpoint

The Key Secondary Endpoint for the trial is the patient's overall reported pain as measured by a numerical scale with scores from 0 (no pain) to 10 (severe) within 24 hours (average of all pain assessments at 1, 2, 4 and 24 hours).

7.7.1.3 Secondary Endpoints

This trial will also explore the following secondary endpoints:

- Surgeon's satisfaction with the visibility of the surgical field rated at the end of the surgery using a numerical scale with scores from 0 (unacceptable visibility) to 10 (excellent)

- Surgeon's overall rating of the adequacy of muscle relaxation and insufflation pressure during surgery using a numerical scale with scores from 0 (=unacceptable muscle relaxation, required intervention) to 10 (=excellent)

- Number of patient's movements that interfered with the surgical conditions during laparoscopy (includes abdominal muscle contractions, diaphragm movement, breathing/coughing against the ventilator, hiccups, patient movements)

- Surgeon's assessment on the effect that these variables had on the overall surgical procedure (using numerical scale with scores of 0-10)

- Number of rescue actions performed during surgery in order to improve insufficient surgical conditions

- Daily assessments of patient reported overall pain (resting and provoked [i.e. in connection with the transition from lying to sitting position] and shoulder pain at rest using a numerical scale with scores (0 to 10) starting on Day 2 up to and including the Follow-Up Visit (Day 8)
- Post-operative consumption of analgesic medications

7.7.1.4 Other Exploratory Endpoints

This trial will also explore the following additional parameters:

- Volume of gas needed to establish the pneumoperitoneum according to the assigned insufflation pressure

- Post-operative consumption of anti-emetic medications

- Total amount of PCA morphine use for up to at least 2 hours after surgery
- Conversion to open surgery if clinically required
- Patient Outcome Measures (e.g., number of days till convalescence, duration of hospitalization)
- Rate of residual blockade and signs and symptoms of residual blockade (e.g., significant change in the respiratory rate, significant decrease in SpO2 level as clinically determined by the investigator)
- Rate of recurrence of NMB
- Procedural measures (duration of surgery, duration of anesthesia, time from administration of sugammadex to when the subject is ready to be discharged)
- Physical measures of abdominal wall relaxation (e.g. distance from the umbilicus to a promontorium or bowel).
- O_2 flow rate and method of delivery

7.7.2 Safety Monitoring and Assessments

7.7.2.1 Safety Endpoints

7.7.2.1.1 Commonly Occurring Safety Endpoints

The Commonly Occurring Safety Endpoints include the AE preferred terms observed to be "common." For this current trial, an AE is considered "common" if it occurs in at least 10% of the subjects in any one treatment group.

7.7.2.1.2 Descriptive Safety Endpoints

Descriptive Safety Endpoints include adverse events due to a possible interaction of sugammadex with endogenous compounds or with exogenous compounds other than rocuronium and recurrence of NMB or residual NMB.

7.7.2.2 Definition of Terms

7.7.2.2.1 Adverse Event

Per the International Conference on Harmonization (ICH), an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

7.7.2.2.2 Serious Adverse Event

Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

1. Results in death;
2. Is life-threatening;
3. Requires hospitalization or prolongation of existing inpatients' hospitalization;
4. Results in persistent or significant disability or incapacity; and/or
5. Is a congenital anomaly or birth defect;
6. Is a cancer;
7. Is associated with an overdose;
8. Is an Other Important Medical Event.

Life-threatening in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. These are considered “Other Important Medical Events”.

7.7.2.2.3 Events of Clinical Interest

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 – as described in **Section 7.7.2.5.1**.

For this protocol, events of hypersensitivity: serious adverse events suggestive of hypersensitivity and/or possible events of anaphylaxis will be considered events of clinical interest.

7.7.2.2.4 Overdose

An overdose is a significant variation above the recommended/scheduled dosage for a product.

In this 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 SmPC for further information.

7.7.2.2.5 Product Quality Complaint

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

7.7.2.2.6 Planned Hospitalization

A hospitalization planned by the subject prior to signing the ICF 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.

7.7.2.2.7 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.

7.7.2.2.8 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 (e.g., if a subject reports that one of the investigational products looks like a different product, the report would be considered a potential medication error).

7.7.2.2.9 Interaction

More information on interaction of sugammadex with other drugs can be found in the approved sugammadex label.

7.7.2.2.10 Incident

An incident is any product complaint that led to or might have led to death or serious deterioration of health/serious injury/serious illness for the user of the product or any other person.

7.7.2.2.11 Medical Device Reporting Reportable Event

A device-related incident is any product (e.g., TOF-Watch® SX) complaint that led to or might have led to death or serious deterioration of health/serious injury/serious illness for the user of the product or any other person. These events are reported using the Safety Data Reporting Form.

7.7.2.3 Monitoring

7.7.2.3.1 Monitoring Adverse Events

Each subject will be monitored for the occurrence of AEs immediately after the subject has signed informed consent. The IMP causality assessment of all post-

treatment AEs will be assessed by a blinded safety assessor, who must be a licensed physician. Each subject will be followed for serious adverse events for up to and including 7 days (i.e., the Day 8 follow-up visit) after the administration of study medication as described in **Section 7.7.2.2.1**

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 adverse events 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 electronic Case Report Forms (eCRF; **Section 9.2**), 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 as clinically appropriate, until final resolution or stabilization of the event(s).

7.7.2.3.2 Monitoring Laboratory Assessments

No protocol-required laboratory assessments are planned for this trial.

Local laboratory assessments may be performed to rule out or confirm a pregnancy and in any circumstance in which the investigator or qualified designee believes additional assessments are clinically necessary (e.g., a tryptase sample in the severe cases of hypersensitivity or anaphylaxis).

Based on the clinical case at hand, the investigator can order any appropriate local laboratory assessments as needed per local practice. If laboratory assessments are conducted, the results will be documented in the study database.

7.7.2.4 Assessment of Adverse Events

7.7.2.4.1 Assessment of Severity

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

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;

7.7.2.4.2 Assessment of Causality

A medically-qualified investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product using the guidelines listed below:

- Yes, there is reasonable possibility of drug relationship. There is evidence of exposure to test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause.
- No, there is not a reasonable possibility of drug relationship. Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.7.2.4.3 Reference Safety Information (RSI) for the Assessment of Expectedness of Adverse Events

The Reference Safety Information (RSI) for assessing the expectedness of an adverse event for the investigational product (sugammadex) in this trial is to be the most recent SmPC.

7.7.2.4.4 Known Potential Toxicities of Investigational Products

Known potential toxicities of sugammadex are listed below. Refer to the approved SmPC for sugammadex for additional information on AEs related to toxicities observed to date.

Sugammadex

Adverse effects include hypersensitivity and anesthetic complications (generally indicative of the restoration of neuromuscular function, such as movement of a limb or the body, coughing, grimacing, or suckling on the endotracheal tube during the anesthetic procedure or during surgery). Hypersensitivity reactions, including anaphylaxis, have occurred in some patients and volunteers. 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 and swelling of tongue and pharynx. Severe hypersensitivity can be fatal. In a clinical trial in patients with a history of pulmonary complications, bronchospasm was reported as a possibly related adverse event in two patients, and a causal relationship could not be fully excluded. As with all patients with a history of pulmonary complications the physician should be aware of the possible occurrence of bronchospasm.

Currently defined Adverse Drug Reactions in Medical Dictionary for Regulatory Affairs (MedDRA) preferred terms can be found in the SmPC.

7.7.2.5 Reporting Safety Observations by the Investigator to the Sponsor

7.7.2.5.1 Expedited Reporting of Safety Observations by the Investigator to the Sponsor

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the sponsor's Global Safety representative or designee by entering all information relevant to the event in the appropriate eCRFs within **24 hours of learning of the event**. Adverse Event Intake Form – or a sponsored-approved equivalent form – should be used in the event that the EDC system is not functioning.

1. SAE (including SAEs associated with overdose, pregnancy, exposure during pregnancy or lactation);
2. Death;
3. Planned hospitalizations (not previously reported in the medical history);
4. Events of clinical interest;
5. Cancer;

Any occurrence of pregnancy or exposure during pregnancy or lactation NOT associated with an SAE in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the sponsor or designee by entering all information relevant to the event in the appropriate eCRFs within **24 hours of learning of the event**. Adverse Event Intake Form – or a sponsor-approved equivalent form – should be used in the event that the EDC system is not functioning.

If the investigator is unsure about when to report an observation from the lists above, the event or outcome should be reported to the sponsor or designee by entering all

information relevant to the event in the appropriate eCRFs within 24 hours of learning of the event. The Adverse Event Intake Form – or a sponsor-approved equivalent form – should be used in the event that the EDC system is not functioning.

Any observation reported to the sponsor or designee that is also an AE, is to be recorded in the eCRF (**Section 9.2**), as well as in the subject's source documentation, along with any actions taken as a result of AE and follow-up results.

If an autopsy is performed, available results should be entered into the EDC screens.

The investigator must assess causality of the event as relative to the investigational product administered in the trial as described in **Section 7.7.2.4.2**. The EDC uses 2 categories of causality as describes in **Section 7.7.2.4.2**. Adverse Event Intake Form uses 3 categories of causality. If the Adverse Event Intake Form must be used to report an event because the EDC system is not available, the investigator is to record causality according to the guidance for the form using the 3 categories. The 3 categories from the form will be mapped to the 2 categories for evaluation by the sponsor according to the guidance in **Table 2.**

Table 2 Mapping Causality for SAE from EDC to Adverse Event Intake Form

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Record the following		**Use the following criteria as guidance**
On the eCRFs	**On the Adverse Event Intake Form**	
No	Unlikely Related	No temporal association, or the cause of the event has been identified, or the drug, biological, or device cannot be implicated based on available information
Yes	Possibly Related	Temporal association, but other etiologies are likely to be the cause; however, involvement of the drug, biological, or device cannot be excluded based on available information
	Probably Related	Temporal association, other etiologies are possible, but unlikely based on available information

7.7.2.5.2 Expedited Reporting by the Sponsor to a Regulatory Health Authority

The Sponsor's Global Safety department will monitor the safety data. The Sponsor will manage the expedited reporting of relevant safety information to concerned health authorities, competent authorities, and IRBs/IECs in accordance with local laws and regulations.

7.7.2.6 Discontinuation, Treatment Interruption, and Unblinding of Blinded Treatment Due to Safety Observations

7.7.2.6.1 Discontinuation

See **Section 7.3.3** for the criteria by which a subject must be discontinued. Should a subject be discontinued from the trial, complete the visit activities as specified for discontinuation in the Trial Flow Chart in **Section 2.4**.

7.7.2.6.2 Temporary Interruption of Treatment for a Subject

The investigator is to discontinue a subject as necessary according to the criteria provided in **Section 7.3.3**.

7.7.2.6.3 Modification of Dose and/or Administration of Investigational Product for a Subject

The doses of Sugammadex (2 or 4 mg /kg) administered based upon current dosing guidelines. See **Section 5.3.**

7.7.2.6.4 Unblinding Treatment for a Subject During the Trial

To assess an occurrence of a safety observation, Global Safety may unblind the treatment of any subject for whom a safety observation was reported by the investigator to the sponsor as described in **Section 7.7.2.5.1**.

Unblinding by the request of the investigator should occur only in the event of adverse event for which it is necessary to know the trial treatment to determine an appropriate course of therapy for the subject. If the investigator must identify the treatment assignment of an individual subject, the investigator or qualified designee is to call the Central Randomization Service. Unblinding performed by the Central Randomization Center at the request of the investigator is to be reported in writing by the investigator to the sponsor, including a written explanation of the reason why the blind was broken.

7.7.3 Pharmacogenetics

7.7.3.1 Pharmacogenetics Endpoints

Exploratory pharmacogenetics (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Pharmacogenetic studies will be conducted with Biostatistics design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome will require validation in future clinical trials.

7.7.3.2 PD/PGt, PK/PGt and Safety/PGt Analysis

Pharmacogenetic interrelationships may be explored.

7.8 Criteria for Early Termination of the Trial

There are no pre-specified criteria for terminating the trial early. The study may be terminated at any point at the discretion of the Sponsor.

8.0 STATISTICAL AND ANALYTICAL PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

8.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the designee/ Clinical Biostatistics department of the SPONSOR.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

8.2 Primary and Secondary Hypotheses

Objectives of the study are stated in **Section 6**.

The primary hypothesis is:

- The use of sustained deep NMB improves the surgeon's overall satisfaction with surgical conditions as compared to standard NMB, based on the surgical conditions score (0-10).

The key secondary trial objective translates to the hypothesis:

- The use of low insufflation pressure improves the overall patient's pain score within 24 hours (average of all pain assessments at 1, 2, 4 and 24 h) as compared to standard insufflation pressure, based on the pain scale (score 0-10).

8.3 Analysis Endpoints

Efficacy and pain endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.3.1 Efficacy/Surgical Conditions and Pain Endpoints

8.3.1.1 Primary Endpoint

The Primary Endpoint for the trial is the surgeon's overall satisfaction with the surgical conditions rated at the end of the surgery using a numerical scale with scores from 0 (=poor, needs intervention) to 10 (=excellent). The Primary Endpoint is related to the Primary Trial Objective.

8.3.1.2 Other Surgical Conditions Endpoints

Other secondary and exploratory endpoints related to surgical conditions (e.g. surgeon's assessment of visibility of the surgical field, assessment of movements interfering with the surgery, adequacy of muscle relaxation etc.), as indicated in **Section 7.7.1** will be evaluated for between-treatment differences.

8.3.1.3 Key Secondary Endpoint

The Key Secondary Endpoint for the trial is the patient's overall reported pain as measured by a numerical scale with scores from 0 (no pain) to 10 (severe) within 24 hours (average of all pain assessments at 1, 2, 4 and 24 hours).

8.3.1.4 Other Clinical Exploratory Endpoints

Other secondary and exploratory endpoints as indicated in **Section 7.7** will be evaluated. These include pain assessments at 48 hours and on Days 3-8, adverse events, amount of pain medication and vital signs.

8.3.2 Derivations of Surgical Conditions Endpoints

Subjects who needed 'rescue' medication on request of the surgeon due to unacceptable surgical conditions, thus switching from the randomized treatment conditions with respect to depth of NMB and level of insufflation pressure, will be analyzed according to the initial randomized treatment conditions, i.e. as randomized, using the worst possible score of zero for the surgical conditions.

8.3.3 Derivations of Pain Endpoints

The Key Secondary Endpoint, i.e. the patient's reported overall average pain score within 24 hours will be derived as the average pain score of all of the assessments at 1, 2, 4 and 24 hours post surgery, across assessments of overall pain, provoked and at rest, and shoulder pain.

8.4 Analysis Populations

8.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of surgical conditions/efficacy data in this study but not for pain analysis. The FAS population consists of all randomized patients who:

- Experienced rocuronium-induced neuromuscular blockade and pneumoperitoneum using low or standard insufflation pressure for laparoscopic cholecystectomy,
- did not convert to open surgery (before application of NMB and/or insufflation pressure)

No Per-Protocol population will be used for the primary efficacy endpoint(s).

The final determination on protocol violations will be made prior to the unblinding of the database and will be documented in a separate memo.

Patients will be included in the treatment group to which they are randomized for the analysis of surgical conditions/efficacy data using the FAS population. Details on the approach to handling missing data are provided in **Section 8.5** Statistical Methods.

8.4.2 Safety and Pain Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data and pain assessments in this study. The APaT population consists of all randomized patients who experienced rocuronium-induced neuromuscular blockade or pneumoperitoneum using insufflation pressure or a dose of sugammadex. Patients will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety and pain data using the APaT population. For most patients this will be the treatment group to which they are randomized. Patients who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least one vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety and pain analyses are provided in **Section 8.5** Statistical Methods.

8.5 Statistical Methods

Statistical testing and inference for safety analyses are described in **Section 8.5.5**. Efficacy and pain results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in **Section 8.6**, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

8.5.1 Primary Efficacy Analysis

The primary analysis will be conducted on the Full Analysis Set, according to initial treatment conditions as randomized, counting cases of 'rescue' medication due to unacceptable surgical conditions with the worst score of zero, and excluding subjects who experience conversion to open surgery (due to non-application of insufflation pressure).

An additional sensitivity analysis will use the actual assessment score for surgical conditions before any rescue intervention (surgical conditions after establishment of the randomized NMB and insufflation pressure).

The Primary Efficacy Endpoint for the current trial is the surgeon's overall satisfaction with the surgical conditions as assessed as a surgical conditions score (0-10). The Primary Efficacy Endpoint will be analyzed with an Analysis of Variance (ANOVA) with factors depth of NMB (deep or standard), level of insufflation pressure (low or standard), and surgeon/surgical team. Contrasts between levels of treatment factors will be estimated and tested from this model, i.e., the contrast between low versus standard insufflation pressure, the contrast between deep versus standard NMB, and the contrast between deep NMB with low insufflation pressure versus standard NMB and standard insufflation pressure. The (confirmatory) contrast of primary interest for surgical conditions will be deep NMB versus standard NMB (aiming to detect an advantage for deep NMB).

The interaction between the two treatment factors (depth of NMB and insufflation pressure) will be investigated in a sensitivity analysis, adding an interaction term to the ANOVA model.

Before unblinding of the trial it will be investigated whether BMI has a significant effect ($p<0.05$) on the primary efficacy endpoint and if so, BMI will be included as additional covariate in the model.

8.5.2 Key Secondary Analysis (on pain assessment)

The key secondary analysis will be conducted on All-Patients-as-Treated (APaT) according to actual treatment conditions (depth of NMB and insufflation pressure). The Key Secondary Endpoint for the current trial is the patient's average pain score within 24 hours (average of all pain assessments at 1, 2, 4 and 24 h) as assessed on a pain assessment score (0-10).The Key Secondary Endpoint will be analyzed with an Analysis of Variance (ANOVA) with factors depth of NMB (deep or standard), level of insufflation pressure (low or standard), gender and surgeon/surgical team. Contrasts between levels of treatment factors will be estimated and tested from this model, i.e., the contrast between deep versus standard NMB, the contrast between low versus standard insufflation pressure, and the contrast between deep NMB with low insufflation pressure versus standard NMB and standard insufflation pressure. The contrast of primary interest will be low insufflation pressure versus standard insufflation pressure (aiming to detect an advantage for low pressure).

The interaction between the two treatment factors (depth of NMB and insufflation pressure) will be investigated in a sensitivity analysis, adding an interaction term to the ANOVA model.

8.5.3 Other Secondary Analyses

Other secondary efficacy parameters assessed as a score (0-10) (e.g. the surgeon's overall satisfaction with the visibility of the surgical field, the rating of the adequacy of muscle relaxation during surgery and the assessment of the effect of patient movements on the surgical procedure) as well as counts of movements/muscle contractions interfering with the surgery will be analyzed in a similar way as the primary and key secondary parameter (using an ANOVA with factors depth of NMB (deep or standard), level of insufflation pressure (low or standard) and surgeon/surgical team, after appropriate transformation for normalization, if appropriate. Interaction between the two treatment factors will be investigated in a sensitivity analysis.

The primary and secondary parameters assessed on a scale from 0 to 10 will be checked for normality of the distribution (including normal probability plots). In case of strong deviation from normality, sensitivity analyses will be performed, including a nonparametric analysis in form of a stratified Wilcoxon test comparing the two levels of one treatment factor (providing Hodges-Lehmann estimates for the median difference and associated 95% confidence interval) while using the two levels of the other treatment factor as strata. For the primary parameter the main comparison will be deep NMB versus standard NMB, for the key secondary parameter (average pain score) low pressure versus standard pressure.

These analyses should be interpreted in an exploratory sense.

For a secondary (supportive) analysis of repeated pain assessments up to 24 hours post surgery, a longitudinal data analysis (LDA) method [9], [see **Appendix 4**] will be used. This model assumes a different mean for each treatment at each of the repeated time points in the analysis. In this model, time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will adjust for depth of NMB, level of insufflation pressure, gender and surgeon/surgical team, and the interaction of time by depth of NMB and time by level of insufflation pressure. The treatment difference in terms of the mean pain score at a given time point and for the average across time points will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements.
Of note, in the event that there are no missing data, the estimated treatment difference from the above LDA model will be identical to that from a corresponding traditional ANOVA model at a given time point. However, the LDA model allows the inclusion of patients who have missing data at certain time points, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation code are given in **Appendix 4**.
If the unstructured covariance model fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance such as Toeplitz will be examined to model the correlation among repeated measurements. In this case, the empirical option will be used because the sandwich variance estimator is asymptotically unbiased while the model-based variance estimator can grossly overestimate or underestimate the true variance.

The LDA method assumes that data are missing at random (MAR). In this study, it is expected that MAR/MCAR mechanisms will underlie most of the missingness of pain assessment within the first 24 hours and the proportion of data missing not at random [MNAR], driven solely by unobserved values of the study endpoints, will be small. In particular, patient discontinuation within the first 24 hours after surgery is an unlikely reason for missing pain assessments in this in-patient period, and it is expected that missing assessments will be rare due to the controlled surgical setting. Reasons for discontinuation from the study may include residual blockade, clinical adverse experiences, relocation, withdrawal of consent, protocol violations, and/or data processing issues. Missing data caused by relocation and data processing issues, are likely to be MCAR. In general, it is unlikely that randomized treatment conditions (depth of NMB and level of insufflation pressure) have an impact on missingness of pain assessments within 24 hours. If treatment in part determines the loss of data for other reasons (such as clinical adverse experiences), the mechanism may be close to MAR since treatment assignment is an observed variable and included in the analysis model.

Table 3 summarizes the key efficacy and pain analyses.

Table 3 Analysis Strategy for Key Efficacy Variables and Pain Assessment

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method[‡]	Analysis Population	Missing Data Approach
Primary Hypothesis #1				
Surgeon's overall satisfaction with the surgical conditions	P	ANOVA with factors depth of NMB, insufflation pressure and surgeon/surgical team	FAS, as randomized	No imputation, rescue intervention counted with a score of 0.
Surgeon's overall satisfaction with the surgical conditions	S	ANOVA with factors as above, but including interaction term between depth of NMB and insufflation pressure	FAS, as randomized	No imputation, rescue intervention counted with a score of 0.
Secondary Endpoints/Hypotheses				
Secondary Hypothesis #1				
Average overall post-OP pain score up to 24 h post surgery	P	ANOVA with factors depth of NMB, insufflation pressure, gender and surgeon/surgical team	APaT, as treated, excluding subjects with conversion to open surgery	No imputation, at least one post-surgical assessment is required.
	S	ANOVA extended with interaction term between depth of NMB and insufflation pressure	APaT, as treated, excluding subjects with conversion to open surgery	No imputation, at least one post-surgical assessment is required.

Other Secondary Endpoints				
Surgeon's overall satisfaction with the visibility in the surgical field	P	ANOVA with factors depth of NMB, insufflation pressure and surgeon/surgical team	FAS, as randomized	No imputation, rescue intervention counted with a score of 0
Surgeon's overall satisfaction with the visibility in the surgical field	S	ANOVA extended with interaction term between depth of NMB and insufflation pressure	FAS, as randomized	No imputation, rescue intervention counted with a score of 0
Post-operative overall pain score at 1, 2, 4 and 24 hours post surgery (repeated assess-ments)	S	LDA model[a] over time points of assessment, with fixed factors depth of NMB, insufflation pressure, gender and surgeon/ surgical team	APaT, as treated, excluding subjects with conversion to open surgery	Model-based
Other exploratory (continuous) Secondary Endpoints				
	P	ANOVA with factors depth of NMB, insufflation pressure and surgeon/surgical team	FAS (for efficacy) or APaT (for pain related endpoints)	No imputation

ANOVA=analysis of variance; BMI=body mass index; FAS=Full Analysis Set; APaT=All-Patients-as-Treated, LDA=longitudinal data analysis; NMB=neuromuscular blockade; P=Primary approach; S=Secondary approach;

† P=Primary approach; S=Secondary approach.

‡ Statistical models are described in further detail below:

[a] Longitudinal data analysis model with fixed terms for treatment factors (NMB and pressure), gender, time, surgeon/surgical team, and interaction of time by treatment factor(s).

The strategy to address multiplicity issues with regard to multiple treatment comparisons and multiple endpoints is described in **Section 8.6**, Multiplicity.

8.5.4 Other Exploratory Analyses

The other (exploratory) efficacy endpoints as well as procedural time intervals (e.g. duration of surgery/anesthesia, time from administration of sugammadex to OR discharge readiness), physical measures of abdominal wall relaxation and patient outcome measures (e.g. duration of hospitalization, days till convalescence) will be analyzed with descriptive statistics per treatment group (mean, standard deviation, range of continuous parameters, incidences of categorical parameters (like incidence of rescue actions to improve surgical conditions, conversion to open surgery) and/or exploratory statistics to estimate mean differences or difference in event/outcome incidences or risk ratios between treatment factors. Parameters with ordinal outcome will be analyzed using the proportional odds model.

In a supportive analysis, the overall pain scores (at rest and provoked) and shoulder pain score will be analyzed over time with a longitudinal data analysis (LDA) with fixed factors depth of NMB during surgery (deep or standard of care), level of insufflation pressure (low or standard), gender, surgeon/surgical team, time point of assessment, interactions between main treatment factors, and time and random factor subject. Contrasts between levels of treatment factors at a given time point will be estimated and tested from this model, i.e., the primary contrast between low insufflation pressure versus standard insufflation pressure, the contrast between deep NMB versus standard NMB, and the contrast between deep NMB with low insufflation pressure versus standard NMB and standard insufflation pressure. Such analysis will be separately performed for shoulder pain and overall pain, at rest and provoked.

An unstructured covariance matrix will be used to model the correlation among repeated measurements. If the unstructured covariance model fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance specification will be examined.

The effect of duration of NMB or insufflation pressure (or alternatively surgery duration) on overall average pain score will be explored by including such variables as additional co-variate in exploratory ANOVA on the key secondary endpoint.

8.5.5 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), patient's pain assessments, amount of post-OP pain medication/ antiemetic medication and PCA morphine use, investigator-identified serious adverse events suggestive of hypersensitivity and/or suspected events of anaphylaxis, neuromuscular safety events (rate of residual blockade or recurrence of NMB) and vital signs.

The analysis of safety results will follow a tiered approach (**Table 4**). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

For this protocol, there are no pre-specified events of interest, which are considered Tier 1 events.

Adverse experiences (specific terms as well as system organ class terms) that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 patients in any treatment group exhibit the event; all other adverse experiences will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

For common adverse events (occurring in at least 10% of subjects in any group) the incidence and 95% confidence interval will be presented by treatment group.

All adverse events which started after administration of the first dose of rocuronium or after start of application of insufflation pressure will be included in analyses and summary tables.

Subjects who were converted to open surgery will be analyzed separately, according to actual conditions of NMB and (absence of) insufflation pressure.

Continuous measures such as amount of post-OP pain medication or changes from baseline in vital signs that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, analyses and statistics for the difference between treatment groups/factors will also be provided for amount of pain medication (factorial ANOVA), along with nominal p-values for between-group/factor differences.

For this protocol, there are no pre-specified events of interest, which are considered Tier 1 events.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of patients with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with events; these analyses will be performed using the Miettinen and Nurminen [(6)] method (1985), an unconditional, asymptotic method.

Table 4 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[†]	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Not applicable			
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Post-operative Nausea and/or Vomiting		X	X
	Specific AEs [‡] (incidence ≥4 patients in one of the 4 treatment groups)		X	X
	Investigator-identified serious AEs suggestive of hypersensitivity and/or suspected events of anaphylaxis		X	X
Tier 3	Specific AEs, SOCs [‡] (incidence <4 of patients in all of the treatment groups)			X

[†] Adverse Experience references refer to both Clinical and Laboratory AEs.

[‡] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.

Note: SOC=System Organ Class; X = results will be provided.

8.5.6 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.5.6.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of patients screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender, weight, BMI), baseline characteristics, primary and secondary diagnoses, type of surgical procedure (coded via Nordic Medico Statistical Committee [NOMESCO] classification) and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.6 Multiplicity

A hierarchical approach (closed testing) will be taken to control for multiple testing (Primary Endpoint and Key Secondary Endpoint). That is, the primary contrast for the Primary Endpoint will be tested at a level of 5%. If the null hypothesis associated with the primary contrast of the Primary Endpoint can be rejected at that level, the contrast of interest for the Key Secondary Endpoint will be tested at a level of 5%. In case the null hypothesis associated with the primary contrast for the

Primary Endpoint can not be rejected, the null hypothesis associated with the Key Secondary Endpoint will not be formally tested; in that case the 95% confidence interval will be presented only.

8.7 Sample Size and Power Calculations

8.7.1 Sample Size and Power for Efficacy Analyses

This study will randomize 30 patients into each the four treatment groups and has more than 80% power to demonstrate that deep NMB (n=60) is superior to standard NMB (n=60) at an overall two-sided 5% alpha-level, if the underlying treatment difference in the mean surgical conditions score is at least 52% of the standard deviation. This assumption is based on results from study data provided by Professor Manfred Blobner[8], comparing the surgeon's assessment of surgical conditions on a 100 mm visual analog scale during laparoscopic cholecystectomy with an application of 15 mmHg insufflation pressure of pneumoperitoneum between 25 subjects with deep NMB (mean score 93 mm, SD 15 mm) and 25 subjects without NMB (mean 56 mm, SD 38 mm).

The underlying treatment difference is regarded as a clinically relevant difference between the 2 treatments. The calculation is based on an ANOVA with factors depth of NMB, level of insufflation pressure and surgical team with 30 patients in each of 4 treatment groups expected to be included in the analysis and is carried out using SAS v9.1. The minimum criterion for success is that the lower bound of the 95% CI of difference between deep NMB (n=60) and standard NMB (n=60) is > 0. Given an assumed SD of 2.0 on the 11-digit scale of the surgical conditions score, this may occur when the observed difference between treatment groups/factors is approximately 0.73, i.e. 0.365*SD or larger. **Table 5**, below summarizes the power under various assumptions.

With respect to precision of estimates and confidence intervals of treatment contrasts (60 vs. 60 subjects), a total sample size of 120 subjects results in 95% confidence intervals of the size: estimate ± 0.36 standard deviation for the Primary and Key Secondary Endpoint.

Table 5 Power (%) Under Various Assumptions

(With 30 Patients randomized in each of the 4 Treatment Groups,
i.e. 60 for each of the two levels of each treatment factor)

Number of Subjects Compared	Underlying Mean Difference (expressed as fraction of the standard deviation [SD])					
	0.45*SD	0.5*SD	0.52*SD	0.55*SD	0.6*SD	2/3*SD
60 vs.60	68%	77%	80%	84%	90%	95%
30 vs.30	40%	47%	50%	55%	62%	71%
Note: The power is calculated based on 4 x 30 patients expected to be included in the analysis.						

For the Key Secondary Endpoint (average pain score within 24 hours), the sample size will also provide 80% conditional power (conditional on statistical success in the primary parameter) to demonstrate that low insufflation pressure is superior to standard pressure, assuming an underlying treatment difference of at least 52% of the standard deviation of the pain score (see **Table 5** above). This assumption is based on results from a Cochrane Collaboration review by Gurusamy et al. who compared low pressure vs. standard pressure pneumoperitoneum and found a mean standardized difference of about 0.45 in post-operative pain scores across all trials considered, but between 0.5 and 0.8, depending on time interval, in the by far largest trial (Barczynski, N=2x74) which was assessed bias-free and one of two trials with blinded pain assessment. The other trial with blinded pain assessment (Wallace) delivered estimates of -0.80 (4-8 hours post-OP) and -0.62 (9-24 hours). The actual power for the key secondary parameter in the hierarchical testing procedure is the product of the power for the primary parameter and the conditional power for the key secondary parameter, as presented in the following Table:

Table 6 **Power (%) for key secondary parameter in the hierarchical testing procedure under various assumptions (for comparison of 60 vs. 60 subjects)**

Assumed mean difference for primary parameter (deep NMB- standard NMB)	Underlying Mean Difference for key secondary parameter (expressed as fraction of the standard deviation [SD] (low pressure- standard pressure)					
	0.45*SD	0.5*SD	0.52*SD	0.55*SD	0.6*SD	2/3*SD
0.5*SD	52%	59%	62%	65%	69%	73%
0.55*SD	57%	65%	67%	71%	76%	80%
0.6*SD	61%	69%	72%	76%	81%	86%
2/3*SD	65%	73%	76%	80%	86%	90%
Note: The power is calculated based on 4 x 30 patients expected to be included in the analysis.						

8.7.2 Sample Size and Power for Safety Analyses

Not applicable.

8.8 Subgroup Analyses and Effect of Baseline Factors

The consistency of the treatment effect on the primary endpoint across various subgroups will be assessed descriptively via summary statistics of the surgeon's assessment of surgical conditions (score from 0 to 10) by category for the classification variables listed below, based on the FAS population (as randomized).

- Sex (female, male)
- Surgical team

In addition, a summary of the key secondary endpoint, the average pain score with 24 hours post surgery, will be provided per treatment group (as treated) for each of the subgroup factors listed above, based on the APaT population.

8.9 Interim Analyses

No interim analyses are planned for this study.

8.10 Compliance (Medication Adherence)

Drug/treatment accountability data for rocuronium, sugammadex, level of NMB and insufflation pressure will be collected during the study. Compliance will be measured by patients: (1) receiving unscheduled study agent infusions/injections, (2) missing an infusion/injection, and (3) receiving an incorrect study agent dose or (4) treated at a level of NMB or insufflation pressure deviating from the randomized level. Numbers and percentages of patients and infusion/injection visits with any deviation in these measures will be reported for the FAS population.

Subjects who received an intubating dose of rocuronium or dose of sugammadex that deviated more than 10% from the scheduled dose or experienced a level of NMB or insufflation pressure that deviated from the level/range prescribed in the protocol (according to randomization) will be listed.

8.11 Extent of Exposure

Summary statistics (at least median, minimum and maximum values) of: (1) the dose of sugammadex (in mg/kg), (2) the intubating dose of rocuronium; (3) the total maintenance dose of rocuronium and (4) the total gas volume needed to install pneumoperitoneum will be presented by subject group and within subject group by treatment group for the All Patients as Treated (APaT) Population. In addition, summary statistics will be provided on depth and duration of NMB and level and duration of insufflation pressure during the surgery.

8.12 Data Monitoring Committee

Not applicable.

9.0 ADHERENCE TO ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

The trial must be conducted in accordance with Good Clinical Practice (GCP) as outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, E6 Good Clinical Practice: Consolidated Guidance and other applicable laws and regulations. In addition, the trial must be conducted in accordance with: (i) the USA Code of Federal Regulations (CFR) if the trial is conducted under a USA IND, regardless of the country involved; (ii) the European Union (EU) Clinical Trial Directive (CTD) and local regulations if the trial is conducted in the EU; and (iii) any specific local regulations if the trial is conducted elsewhere.

9.1 Ethical Conduct of the Trial

9.1.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the trial at any site, the trial, including the protocol, informed consent, and other trial documents must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites, unless warranted to eliminate an immediate hazard. The IRB/IEC approval should be obtained in writing, clearly identifying the trial, the documents reviewed (including informed consent), and the date of the review. The trial as described in the protocol (or amendment), informed consent, and other trial documentation may be implemented only after all the necessary approvals have been obtained and the sponsor has confirmed that it is acceptable for the investigator to do so.

In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the trial described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.

In countries where the investigator submits the trial protocol and statement of informed consent to the IRB/IEC, the investigator or qualified designee will forward the approvals to the sponsor.

9.1.2 Subject Information and Consent

The details of the protocol must be provided in written format and discussed with each potential subject, and written informed consent must be obtained for all subjects before any trial-related procedure is performed. In obtaining informed consent, the information must be provided in language and terms understandable to the subject. The subject, or the subject's legal representative, must give their written consent to participate in the trial. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent form must be given to the subject. The consent form must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and local laws. In addition, the sponsor specifically requests that the consent form identify it as the sponsor and state that use of the investigational product(s) is experimental and the side effects of the investigational product(s)are not completely known. The consent form must be approved by the appropriate IRB/IEC and sponsor before trial initiation at a trial site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.

9.1.3 Patient Identification Card

A Patient Identification Card is provided to each patient to carry on his or her person (e.g., in a wallet) at all times while the patient is participating in the trial. The Patient Identification Card must be provided to the patient at screening. The card is to be shown to caregivers in the event of an emergency.

At a minimum, the card must contain the following information:

1. Protocol number;
2. The patient's protocol identification number;
3. A statement indicating the patient is participating in an anesthesia clinical research trial and will have already received a dose of sugammadex.
4. Contact information in the event of an emergency or hospitalization. The contact information on the card is to be the investigator or a designated site contact, rather than a contact from within the Sponsor.

9.1.4 Registration of the Trial

The trial will be registered by the Sponsor on a publicly accessible database. The results will be disclosed by the Sponsor on a publicly accessible database.

9.2 Reporting Trial Data to the Sponsor

9.2.1 Data Collection Forms

The Sponsor will provide the site with data collection forms, be they Case Report Forms (CRF), either in paper format or electronic Case Report Forms (eCRF); diaries; Electronic Data Capture (EDC) screens; or other appropriate data collection forms as the trial requires. The investigator is to provide subject data according to the Sponsor's instructions, in the designated data collection form, compliant with GCP practices. The Sponsor will also provide the site with instructions for assisting other parties - such as a central laboratory - to collect data. As instructed by the Sponsor, a designated central laboratory may collect data in a database and provide the completed database to sponsor. All data collection forms and the databases from the trial are the exclusive property of sponsor.

The investigator must maintain records and data during the trial in compliance with all applicable legal and regulatory requirements. Each data point must be supported by a source document at the trial site. Any records or documents used as the source of information (called the "subject source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency.

The investigator will ensure that there are sufficient time, staff, and facilities available for the duration of the trial to conduct and record the trial as described in the protocol and according to all applicable guidances, laws, and regulations.

All data collection forms (e.g., CRFs, diaries; EDC screens), electronic database entries, etc, should be completed as soon as possible after the evaluation has occurred. All dates appearing on the sponsor's subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

9.2.2 Preparing Case Report Forms for All Subjects

A CRF must be completed for all subjects who have given informed consent. The Sponsor must not collect subject names, initials, or other personal information that is beyond the scope of the trial from any subject. Subjects are not to be identified by name or initials on the CRF or any trial documents. The only acceptable identification for a subject who may appear on a CRF or trial document is the unique subject identification number. The investigator must maintain contact information for each participant so that all can be quickly contacted by the investigator, if necessary.

All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee. The investigator will acknowledge in writing that he/she has verified the accuracy of the recorded data.

9.2.3 Preparing Case Report Forms for Subjects Who Fail Screening

Data are to be collected from the time the informed consent form is signed until the subject is determined to have failed screening. A CRF with a minimum of the following information must be completed for subjects who fail screening: (1) demographics, (2) subject status, (3) reason for screen failure, and (4) serious adverse events.

9.3 Publications and Other Rights

9.3.1 Rights to Publish by the Investigator

The investigator has the right to publish or publicly present the results of the trial in accordance with this **Section 9.3** of the protocol. In the event that the protocol is a part of a multi-site trial, it is understood that it is the intent of the sponsor and the investigator to initially only publish or present the trial results together with the other sites, unless specific written permission is obtained in advance from the sponsor to publish separate results. The sponsor shall advise as to the implications of timing of any publication in the event clinical trials are still in progress at sites other than the investigator's site.

The investigator agrees not to publish or publicly present any interim results of the trial without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor 45 days prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication (including, without limitation, slides and texts of oral or other public presentations and texts of any transmission through any electronic media, e.g., any computer access system such as the Internet, World Wide Web, etc) that report any results of the trial. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts and the right to review and comment on the data analysis and presentation with regard to the following concerns:

1. Proprietary information that is protected by the provisions contained in **Section 9.3.2**;
2. The accuracy of the information contained in the publication; and
3. To ensure that the presentation is fairly balanced and in compliance with FDA regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality of the sponsor's confidential information, investigator agrees to meet with the sponsor's representatives at the clinical trial site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement.

9.3.2 Use of Proprietary or Confidential Information in a Publication

No publication or manuscript shall contain any trade secret information of the sponsor or any proprietary or confidential information of the sponsor and shall be confined to new discoveries and interpretations of scientific fact. If the sponsor believes there is patentable subject matter contained in any publication or manuscript submitted for review, the sponsor shall promptly identify such subject matter to investigator. If sponsor requests and at sponsor’s expense, investigator shall use its best efforts to assist sponsor to file a patent application covering such subject matter with the USA Patent and Trademark Office or through the Patent Cooperation Treaty prior to any publication.

9.3.3 Use of Trial Information in a Publication

Investigator is granted the right subject to the provisions of this protocol to use the results of all work provided by investigator under this protocol, including but not limited to, the results of tests and any raw data and statistical data generated for investigator's own teaching, research, and publication purposes only. Investigator/Institution agrees, on behalf of itself and its employees, officers, trustees, and agents, not to cause said results to be knowingly used for any commercial purpose whatsoever except as authorized by the Sponsor in writing.

9.3.4 Authorship of Publications

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship and must satisfy the 3 criteria that follow:

1. Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;
2. Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;
3. Authors must provide written approval of the final draft version of the publication prior to submission.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per the ICMJE guidelines for acknowledgment.

9.4 Trial Documents and Records Retention

During the trial and after termination of the trial – including after early termination of the trial – the investigator must maintain copies of all documents and records relating to the conduct of the trial. This documentation includes, but is not limited to, protocols, CRFs and other data collection forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms, investigator's curricula vitae/biosketch, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below. The sponsor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The investigator must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines, the EU Good Clinical Practices Directive, or applicable local laws, whichever is longer:

1. The ICH Guidelines specify that records must be retained for a minimum of 2 years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is discontinued.
2. The European Union (EU) Commission Directive 2003/63/EC which requires that Essential Documents (including Case Report Forms) other than subjects' medical files, are retained for at least fifteen (15) years after completion or discontinuation of the trial, as defined in the protocol.

All trial documents shall be made available if required by relevant health authorities. The investigator should consult with the sponsor prior to discarding trial and/or subject files.

Sponsor will retain all sponsor-required documentation pertaining to the trial for the lifetime of the investigational product. Archived data may be held on microfiche or electronic record, provided that a back-up exists and that a paper copy can be obtained from it, if required.

10.0 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

10.1 Sponsor

The Sponsor of this trial is indicated in **Section 1**, Title Page.

10.2 Investigators

10.2.1 Selecting Investigators

Only clinical investigators qualified by training and experience to perform a clinical investigation with sugammadex are selected. The sponsor will contact and select all investigators (i.e., the legally responsible party[ies] at each trial site), who, in turn, will select their staff.

10.2.2 Financial Disclosure Requirement

In connection with the clinical trial described in the protocol, the investigator certifies that, if asked, the investigator will read and answer the Certification/Disclosure Form or equivalent document truthfully and to the best of investigator's ability. Investigator also certifies that, if asked, the investigator will have any other applicable party(ies) (e.g., sub investigators) read and answer the Certification/Disclosure Form as a condition of their participation in the trial.

If the financial interests reported on the Certification/Disclosure Form change during the course of the trial or within 1 year after the last subject has completed the trial as specified in the protocol, the investigator and the other applicable party(ies) are obligated to inform the sponsor of such financial change.

10.2.3 Clinical Study Report Coordinator Investigator

A Clinical Study Report (CSR) will be prepared by the sponsor or its qualified designee to describe the results of the trial. One of the investigators shall be selected by the Sponsor to review the CSR and provide approval of the final CSR in writing. The investigator chosen to review and approve the CSR is to be called the CSR Coordinating Investigator. A second investigator shall be selected as the

Alternate CSR Coordinating Investigator. The Alternate CSR Coordinating Investigator is to review and approve the CSR should the first CSR Coordinating Investigator be unable to do so. The Sponsor is to select the CSR Coordinating Investigator and Alternate CSR Coordinating Investigator from the investigators using the following criteria:

1. Must be the Principal Investigator at a trial site actively enrolling subjects and participating in the trial;
2. Must be willing and capable of completing the necessary reviews and providing approval of the CSR in writing.

10.3 Central Organizations

Not applicable.

10.3.1 Scientific Advisory Committee

This pilot trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

11.0 REFERENCES

1. Gurusamy KS, Samraj K, Davidson BR. Low pressure versus standard pressure pneumoperitoneum in laparoscopic cholecystectomy. Cochrane Database Syst Rev 2009 Apr 15; (2):CD006930.

2. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand 2007 Aug; 51(7):789-808.

3. King M, Sujirattanawimol N, Danielson DR, Hall BA, Schroeder DR, Warner DO. Requirements for muscle relaxants during radical retropubic prostatectomy. Anesthesiology 2000 Dec; 93(6):1392-1397.

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5. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for the prediction of postoperative nausea and vomiting. Anesthesiology 1999, 91(3): 693-700.

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8. Personal Communication, Professor Manfred Blobner, Technische Universität München, Munich, Germany, 2012

9. Liang K., Zeger S. (2000) Longitudinal Data Analysis of Continuous and Discrete Responses for Pre-Post Designs. Sankhyā: The Indian Journal of Statistics, 62 (Series B), 134-148.

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Appendix 1 Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these studies in compliance with the highest ethical and scientific standards. Protection of patient safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical studies will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to studies which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated studies (e.g., Medical School Grant Program), which are not under the control of Merck.

II. Scientific Issues

A. Study Conduct

1. Study Design

Except for pilot or estimation studies, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, studies to assess or validate various endpoint measures, or studies to determine patient preferences, etc.

The design (i.e., patient population, duration, statistical power) must be adequate to address the specific purpose of the study. Research subjects must meet protocol entry criteria to be enrolled in the study.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate patients, adequacy of facilities and staff, previous performance in Merck studies, as well as budgetary considerations. Prior to study initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Study sites are monitored to assess compliance with the study protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified

versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

D. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of studies it conducts. Some early phase or pilot studies are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the study, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the study results and conclusions. Merck funding of a study will be acknowledged in publications.

III. Patient Protection

A. IRB/ERC Review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect patient safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck's Consent Form Review department (U.S. studies) or Clinical Research Director (non-U.S. studies) will approve the patient informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that patient welfare is of primary importance. Potential patients will be informed of the risks and benefits of, as well as alternatives to, study participation. At a minimum, study designs will take into account the local standard of care. Patients are never denied access to appropriate medical care based on participation in a Merck clinical study.

All participation in Merck clinical trials is voluntary. Patients are enrolled only after providing informed consent for participation. Patients may withdraw from a Merck study at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding patient confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. DNA Research

DNA sequence analyses, including use of archival specimens collected as part of a clinical trial, will only be performed with the specific informed consent of the subject. With IRB approval, an exception to this restriction on use of archival specimens may be possible (for instance, if specimens are de-identified and are not referable to a specific subject).

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck studies. Merck does not pay incentives to enroll patients in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for patient referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible patients.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the study. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck studies will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an attachment to the study protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

Appendix 2 DNA Sampling and Pharmacogenetic Analysis Procedures

1. **Definitions**
   a. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug response.
   b. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug response.
   c. Genomic Biomarkers: A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions.
   d. DNA: Deoxyribonucleic acid.
   e. RNA: Ribonucleic acid.
2. **Summary of Procedures for Pharmacogenetics**
   a. Patients for Enrollment: All patients enrolled in the current clinical trials will be considered for enrollment.
   b. Consent

      Informed consent for biosamples (i.e., DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all patients or legal guardians, at an outpatient visit, or during an inpatient stay by the investigator or his or her designate.

      Patients are not required to participate in the pharmacogenetic sub-study in order to participate in the main trial.
3. **Scope of Pharmacogenetic Study**

   The DNA sample(s) collected in the current trial will be used to study various genetic causes for how patients may respond to a drug. The DNA sample(s) will be stored to provide a resource for future studies conducted by Merck focused on the study of genes responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease. All samples will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.
4. **Techniques to Collect Samples**

   Blood samples will generally be obtained for all study participants. Blood samples for both DNA and RNA isolation will usually be obtained at a time when the patient is having blood drawn for other study purposes.
5. **Confidential Patient Information for Pharmacogenetic Analysis**

   Samples will be collected and sent to the laboratory designated for the trial where they will be processed (i.e., DNA or RNA extraction, etc) following the Merck approved policies and procedures for sample handling and preparation.

To maintain privacy of information collected from samples obtained for storage and future analysis, Merck has developed secure policies and procedures to maintain patient privacy. At the clinical site, a unique Code will be placed on the blood sample for transfer to the storage facility. The Code is a random number used only to identify the biosample of each patient. No other personal identifiers will appear on the sample tube. The first Code will be replaced with a Sample Code (e.g., Genetic Sample Code for DNA sample, Serum Sample code for serum sample) at the Central Laboratory or at the Merck designated facility. This sample is now a single coded sample. The Sample Code is stored separately from all previous sample identifiers. A secure code, hereinafter referred to as a "first coding key", will be utilized to match the Sample Code to the original blood code and patient number to allow clinical information collected during the course of the study to be associated with the biosample. This "first coding key" will be transferred by the central laboratory or Merck designated facility under secure procedures to the Merck group designated as the entrusted keyholder to maintain confidentiality of the biosamples. The Sample Code will be logged into the primary biorepository database, and in this database this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, laboratory values) associated with it. The sample will be stored in a designated repository site with secure policies and procedures for sample storage and usage.

For DNA samples, a Storage Code will replace the Sample Code at the Merck designated facility. The DNA sample is now a double coded sample. This storage code will be stored separately from all previous sample identifiers. The second secure key referred to as a "second coding key" file will be transferred by the Merck designated facility under secure procedures to the Merck entrusted keyholder. Samples with the second code are sometimes referred to as de-identified samples. The use of the second code provides additional confidentiality and privacy protection for patients over the use of a single code. Access to both coding keys is needed to link any data or samples back to a patient identifier.

The "keys" could be utilized to reconstruct the link between genetic information and identifiable clinical information, at the time of analysis. This linkage would not be possible for the investigator conducting the analysis, but may only be done by the Merck entrusted keyholder under strict security policies and procedures. The Merck entrusted keyholder will link the information, conduct the analysis, then issue an anonymized data summary on the initially single or double coded samples to the investigator conducting the genetic analysis. The only circumstance by which genetic information would be linked to clinical information would be those situations mandated by health authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the health authority. Once the link between patient's identifiers and the unique codes is deleted, it is no longer possible to trace the data and samples back to individual patients through the coding keys. Anonymization is intended to prevent patient re-identification.

6. **Biorepository Sample Usage**

Samples obtained for the Merck Biorepository will be used for analyses using good scientific practices. Exploratory analyses will not be conducted under highly validated conditions. The scope of research performed on these samples is limited to the investigation of the variability in inherited biomarkers that may correlate with a clinical phenotype in patients.

Genetic analysis utilizing the DNA samples may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will be provided with a double (single) coded sample. Reassociation of analysis results with corresponding clinical data will only be conducted by the Merck entrusted keyholder. Any contracted third party genetic analysis will conform to the specific genetic analysis outlined in the clinical protocol. DNA sample remaining with the third party vendor after genetic analysis will be returned to the Sponsor or destroyed and documentation of destruction will be reported to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Consent form signed by the patient will be kept under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any samples, test results, or medical information once the specimens have been rendered de-identified. Laboratory personnel performing the genetic testing will not have access to the informed consent document, nor will they be able to identify patients from the double (single) coded specimens. Specimens will be identified to the laboratory only by the Sample double (single) code. Patients who decline to sign the informed consent document for the sub-study will not have the sample collected or stored, nor will they be discontinued from the main study unless the pharmacogenetics sample is specifically required for study enrollment.

A template of each site's informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate sample permissions. The tracking number on this document will be used to assign sample permissions for each sample in the entrusted keyholder's Sample Database.

7. **Withdrawal From the Biorepository and Pharmacogenetic Database**

Patients may withdraw their consent to store the blood sample or the DNA or RNA derived from it. Patients can also request that their sample be destroyed at any time. If samples can be identified in any way (i.e., are not anonymized samples), patients may withdraw consent for banking samples at any time by contacting the investigator responsible for administering their initial informed consent. At that time, patient samples will be removed from the biorepository. Any DNA, RNA, or other biologic samples will be destroyed, destruction will be documented, and sample database information deleted. However, any analyses performed or data obtained from the samples prior to the patient withdrawing consent will not be deleted.

8. **Retention of Data and Biosamples**

   It is anticipated that data generated from processed samples collected during the course this study will be retained for an indefinite period. DNA specimens will be maintained for potential analysis for 20 years from the acquisition. Samples will be destroyed according to Merck policies and procedures and this destruction will be documented in the repository database.

9. **Data Security**

   Pharmacogenetic and other research databases are accessible only to authorized Sponsor and study administrator research personnel and/or designated collaborators and are only stored and accessible as anonymized data. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc entrusted key holder maintains control over access to all sample data. These data are collected for pharmacogenetic research purposes only as specified in the clinical protocol and will not be used for any other purpose without explicit consent from the research patient.

10. **Reporting of Data to Patients**

    There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to study participant. Some guidelines advocate a proactive return of data in certain instances.

    No information obtained from exploratory laboratory studies will be reported to the patient or family, and this information will not be entered into the clinical database maintained by Merck on patients. Principle reasons not to inform or return results to the patient include: lack of relevance of data, limitations of predictive capability of research data, concerns of misinterpretation of data, absence of good clinical practices standards in exploratory research.

    If any exploratory results are definitively associated with clinical significance for patients while the Merck clinical trial is still ongoing, investigators will be contacted with information as to how to offer genetic testing (paid for by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc) to patients enrolled and will be advised that genetic counseling should be made available for all who choose to participate.

    If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific patient information, inform all sites who participated in the Merck clinical trial, and post the anonymized results on our website or other accredited website(s) that allow for public access (e.g., Disease-societies who have primary interest in the results) in order that physicians and patients may pursue genetic testing if they wish to do so.

11. **Gender, Ethnicity, and Minorities**

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all patients diagnosed and treated on Merck clinical trials for pharmacogenetic sampling. When studies with samples are conducted and patients identified to serve as controls, every effort will be made to group samples from patients and controls to represent the ethnic and gender population representative of the disease under current investigation.

12. **Risks Versus Benefits of Pharmacogenetic Testing**

For pharmacogenetic testing, risks to the patient have been minimized. Risks include those associated with venipuncture to obtain the whole blood sample. This sample will be obtained at the time of routine blood samples drawn for clinical reasons.

Data privacy concerns of the patient have been strictly protected against with Merck security, policies and procedures. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for patient-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc) to be reassociated to double (single) coded samples at the time of data analysis. These patient data will be kept in a separate, secure Merck database, and all samples will be stripped of patient identifiers. No information concerning results obtained from genotyping or biomarker studies conducted with samples from the biorepository will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual patient.

13. **Self-Reported Ethnicity**

Patients who participate in pharmacogenetic study will be asked to provide self-reported ethnicity. Patients who do not wish to provide this data may still participate in the pharmacogenetic study.

14. **Questions**

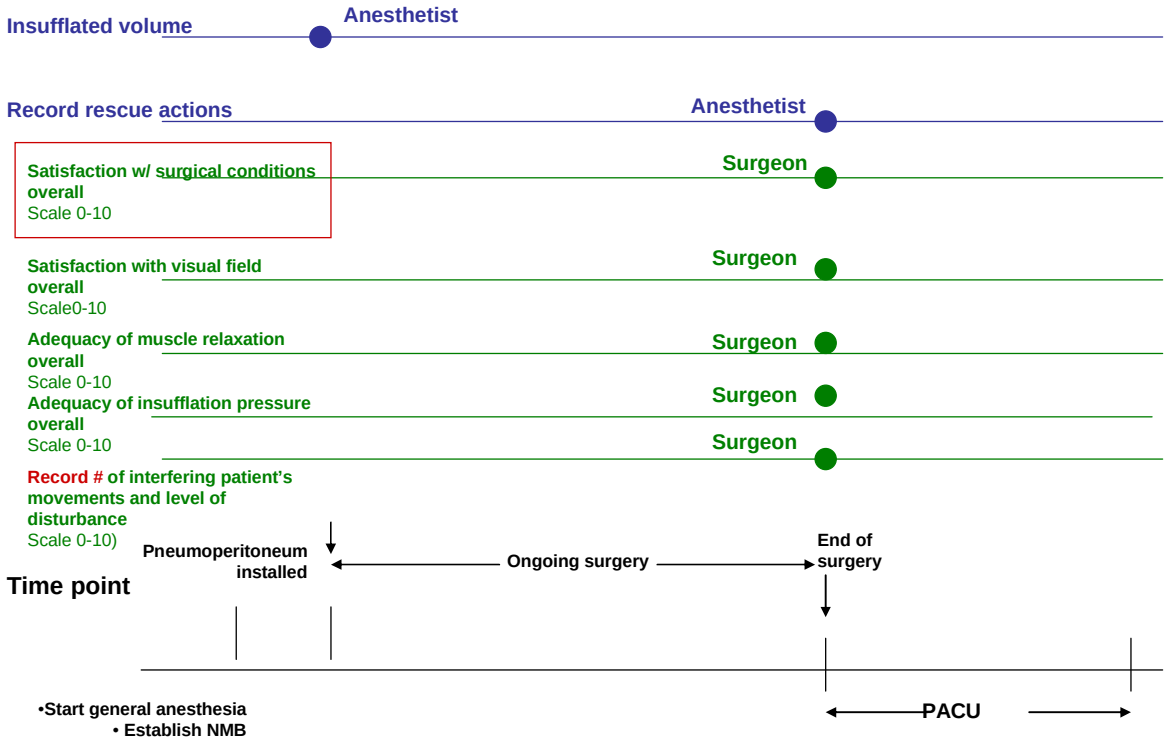
Any questions related to the genetic informed consent, genetic sampling, genetic sample handling, or genetic sample storage should be e-mailed directly to clinical.specimen.management@merck.com.

Appendix 3 Assessments of Surgical Conditions and Pain

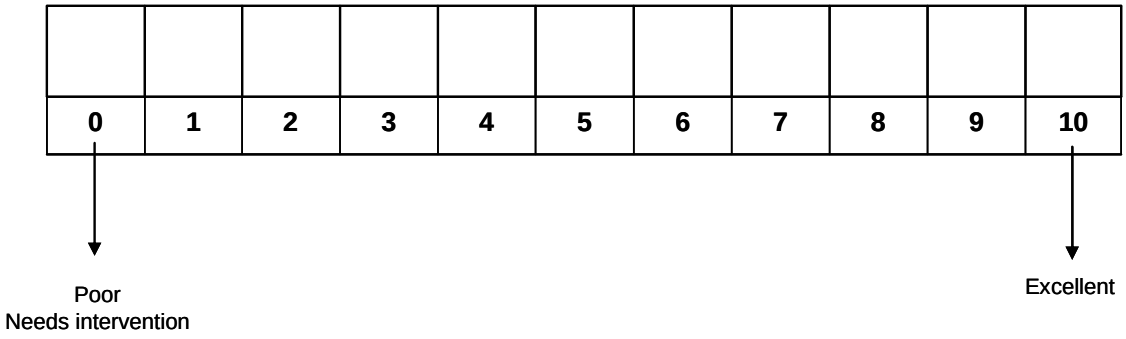
The following numerical scales will be used to assess the surgical conditions of each case and the pain assessment from each patient after the procedure.

1. Overview of surgical condition assessments

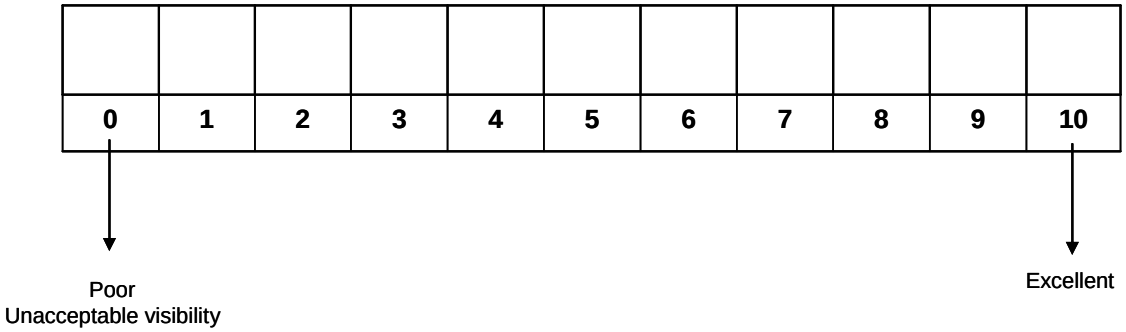
The surgeon's ratings will be recorded via a numeric scale directly after the end of surgery as follows:



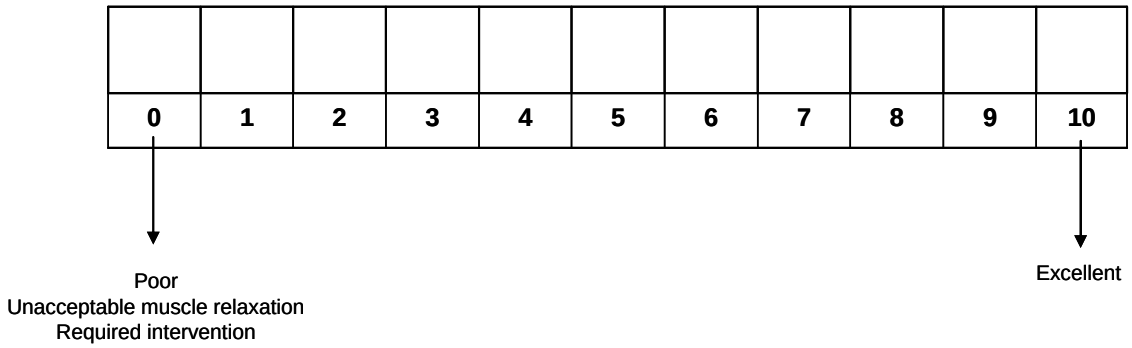
Question 1.a.:
How satisfied were you **overall** with the **surgical conditions** related to anesthesia and pneumoperitoneum during the surgery you just performed?



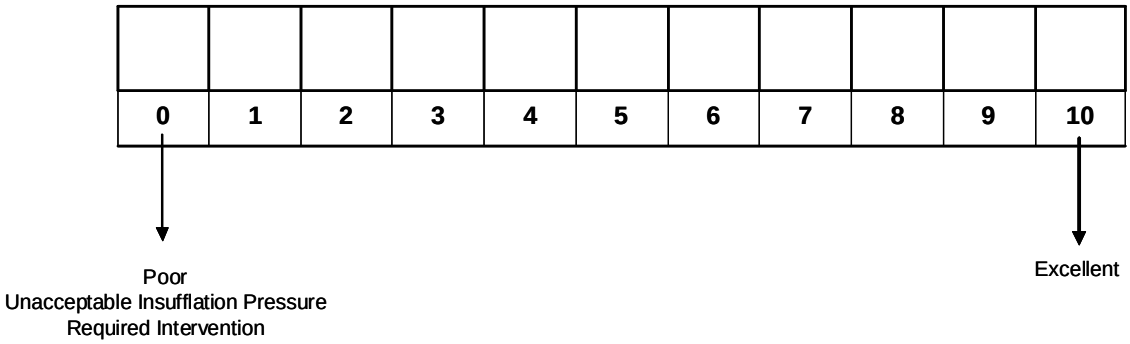
Question 1.b.:
How satisfied were you **overall** with the **visual field** during the surgery you just performed?



Question 1.c.:
How do you rate the **overall adequacy of muscle relaxation** during the surgery you just performed?



Question 1.d.:
How do you rate the **overall adequacy of insufflation pressure** during the surgery you just performed?

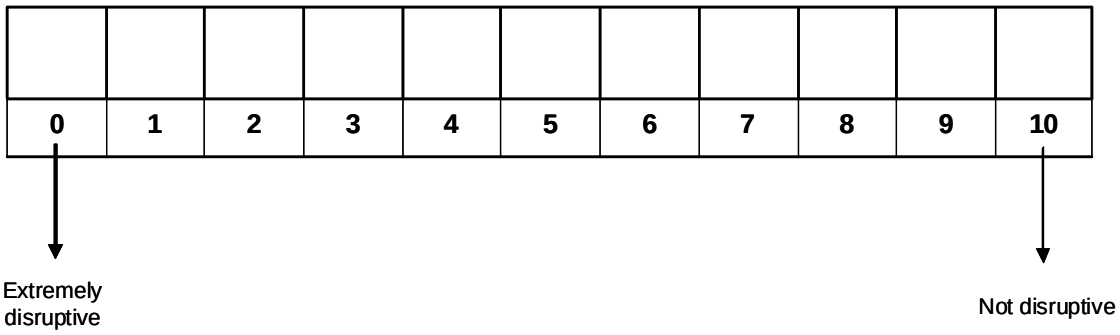


Question 1.e.:
How many times did patient's movements (coughing, bucking, hiccup) or increased muscle tone (resistance, difficulty to close fasciae or skin) interfere with your surgery?

Please insert number: __ __

Question 1.f.:

How did the patient movements described above disrupt your surgical performance?



Question 2:

Was this laparoscopic surgery converted to an open surgery? ___YES __NO

If so, why? _____

To be recorded by the anesthetist

Question 3.a.:

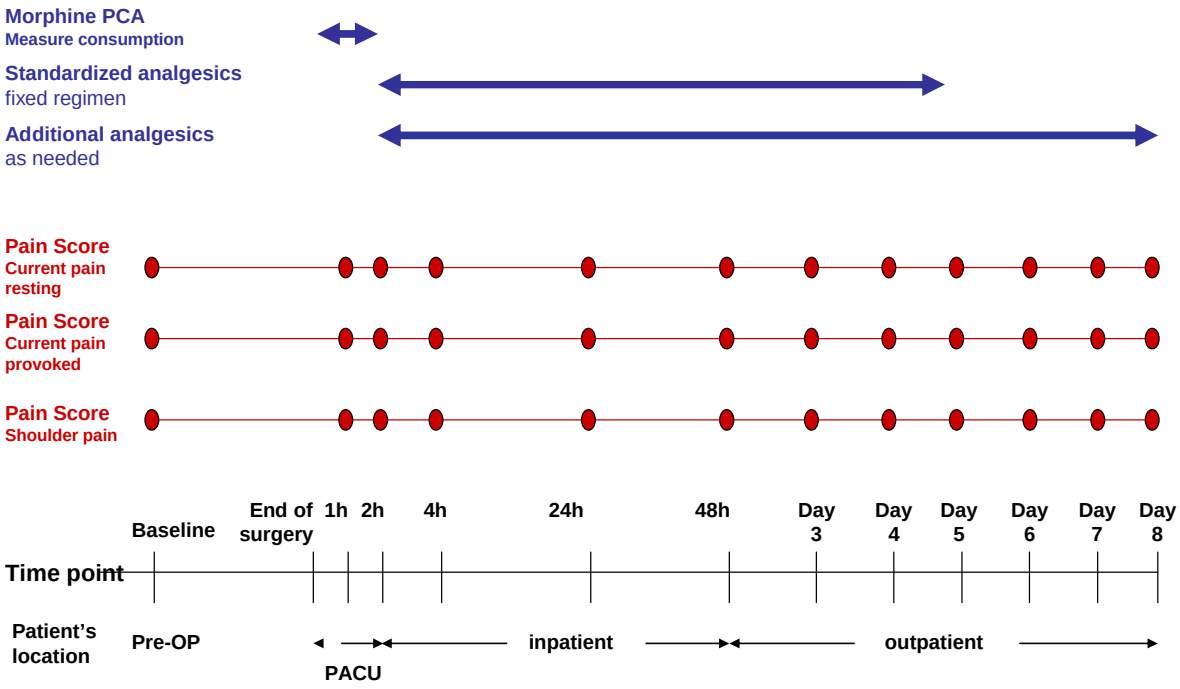
What is the volume of gas needed to establish the pneumoperitoneum according to the assigned insufflation pressure? _____

To be recorded by the anesthetist

Question 3.b.:

What is the number of rescue actions performed during surgery in order to improve insufficient surgical conditions? Please record the number, intervention and rationale: _____

Overview of pain assessment measures



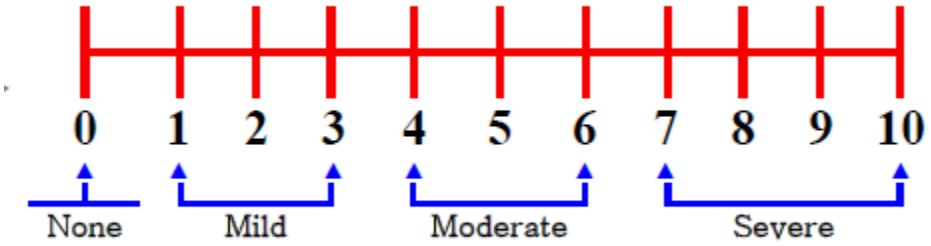
The following subjective pain intensity measures will be assessed using a numeric scale measured at various time points[7]:

- Overall pain intensity, resting, at the time of assessment
- Overall pain intensity, provoked (in connection with the transition from lying to sitting position), at the time of assessment
- Shoulder pain intensity at the time of assessment

It is planned to provide a method (ePRO) for the patient to record their score for each assessment time point.

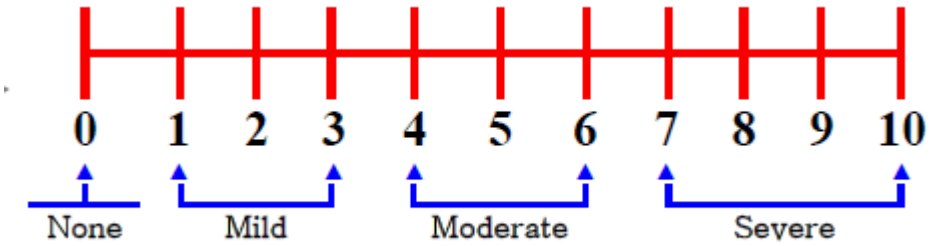
Question 2.a.:

Please rate your overall pain **while resting** by marking the number that describes best your **pain right now**:



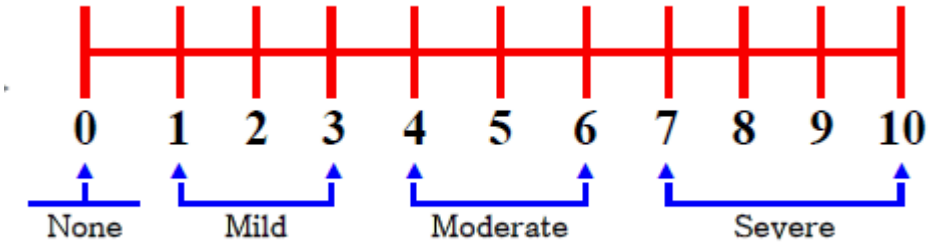
Question 2.b.:

Please rate your overall pain **when provoked** (transition from lying to sitting position) by marking the number that describes best your **pain right now**:



Question 2.c.:

Please rate your **shoulder** pain **while resting** by marking the number that describes best your **pain right now**:



The time points of assessment will be:

- pre-op (baseline)
- post- op after 1h, 2h, 4h, 24, 48 h and in the morning of Days 3-8

Question 3:

Please record any medication you have taken in the in the last 24 hours.

Appendix 4 Statistical Analysis – Technical Details

Statistical Analysis Appendix-- Technical Details

Longitudinal Data Analysis (LDA) Method (without Adjustment for Baseline Values) – Technical Details for Model Specifications, Assumptions, and SAS Implementation Codes

Model

Let Y_{ijt} be the response for subject *i,* with treatment assignment *j*, at time *t*. The marginal mean responses of the full likelihood LDA model is modeled as

$$E(Y_{ijt}) = \gamma_{jt}, \quad j = 0,1, \quad t = 1,2,.....,T,$$

The LDA model assumes that repeated measurements follow a multivariate normal distribution. An unstructured covariance matrix can be specified in the mixed model to account for within subject correlation.

The treatment difference at time point *t,* $t = 1,2,...,T$ is defined as:

$$\eta_t = \gamma_{1t} - \gamma_{0t}.$$

For $t = 1,2,...,T$, the mean response (LSMEANS) for test drug and control are γ_{1t} and γ_{0t}, respectively, as defined in the LDA model above.

This longitudinal model provides valid statistical inference in the presence of possible missing data if the missing data mechanism is ignorable (or more specifically, missing at random [MAR] or missing completely at random [MCAR]). This missing data mechanism requires that the probability of a data point being missing does not depend the missing data after adjusting for the observed data.
In this study, it is expected that MAR/MCAR mechanisms will underlie most of the missingness of pain assessment within the first 24 hours and the proportion of data missing not at random [MNAR], driven solely by unobserved values of the study endpoints, will be small. In particular, patient discontinuation within the first 24 hours after surgery is an unlikely reason for missing pain assessments in this in-patient period, and it is expected that missing assessments will be rare due to the controlled surgical setting. Reasons for discontinuation from the study may include residual blockade, clinical adverse experiences, relocation, withdrawal of consent, protocol violations, and/or data processing issues. Missing data caused by relocation and data processing issues, are likely to be MCAR. In general, it is unlikely that randomized treatment conditions (depth of NMB and level of insufflation pressure) have an impact on missingness of pain assessments within 24 hours. If treatment in part determines the loss of data for other reasons (such as clinical adverse experiences), the mechanism may be close to MAR since treatment assignment is an observed variable and included in the analysis model [9]**.**

Reference:

Liang K., Zeger S. (2000) Longitudinal Data Analysis of Continuous and Discrete Responses for Pre-Post Designs. *Sankhyā: The Indian Journal of Statistics,* 62 (Series B), 134-148.

SAS Codes

SAS codes for fitting the full likelihood LDA model are provided below.

```
**********************************************************************;
** Fitting the LDA model using SAS PROC MIXED
** (here: 4 time points, comparing a newt treatment (N) to a standard treatment (S));
**********************************************************************;
PROC MIXED DATA=long;
CLASS subj trt time;  ** subj is the patient id number, trt is the treatment variable, time is the time points for repeated measures **;
MODEL y=trt time trt*time / noint;
REPEATED time / SUBJECT=subj TYPE=UN;
ESTIMATE 'T1 Diff (N-S)' trt -1 1 trt*time -1 0 0 0  1 0 0 0 ;
ESTIMATE 'T2 Diff (N-S)' trt -1 1 trt*time  0 -1 0 0  0 1 0 0 ;
ESTIMATE 'T3 Diff (N-S)' trt -1 1 trt*time  0 0 -1 0  0 0 1 0 ;
ESTIMATE 'T4 Diff (N-S)' trt -1 1 trt*time  0 0 0 -1  0 0 0 1 ;
ESTIMATE 'T1 Standard LSM' trt 1 0 time 1 0 0 0 trt*time 1 0 0 0  0 0 0 0;
ESTIMATE 'T2 Standard LSM' trt 1 0 time 0 1 0 0 trt*time 0 1 0 0  0 0 0 0;
ESTIMATE 'T3 Standard LSM' trt 1 0 time 0 0 1 0 trt*time 0 0 1 0  0 0 0 0;
ESTIMATE 'T4 Standard LSM' trt 1 0 time 0 0 0 1 trt*time 0 0 0 1  0 0 0 0;
ESTIMATE 'T1 New trt. LSM' trt 0 1 time 1 0 0 0 trt*time 0 0 0 0  1 0 0 0;
ESTIMATE 'T2 New trt. LSM' trt 0 1 time 0 1 0 0 trt*time 0 0 0 0  0 1 0 0;
ESTIMATE 'T3 New trt. LSM' trt 0 1 time 0 0 1 0 trt*time 0 0 0 0  0 0 1 0;
ESTIMATE 'T4 New trt. LSM' trt 0 1 time 0 0 0 1 trt*time 0 0 0 0  0 0 0 1;
ODS OUTPUT Estimates=outm1;
RUN;
```