

Merck Investigator Studies Program (MISP) Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	A phase IV Investigation of Sugammadex in outpatient urological procedures
Request Date:	May 18, 2015
Institution Name	The University of Texas MD Anderson Cancer Center
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A phase IV Investigation of Sugammadex in outpatient urological procedures 2015-1007

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Section #2- Core Protocol

<p>2.1 Objectives & Hypotheses</p>	<p>2.1. List Objectives</p> <p>2.1.1 Primary: To determine if Sugammadex can improve muscle recovery time, measured by time from administration of neuromuscular blockade reversal to train-of-four ratio of 0.9, for outpatient bladder procedures.</p> <p>2.1.2 Secondary: To determine if Sugammadex can improve post-operative complications for outpatient bladder procedures; such as bladder perforation, nausea, vomiting, post-operative intubation and hospital admittance secondary to respiratory complications.</p> <p>To determine if Sugammadex can improve overall recovery time, measured by time from end of surgery to train-of-four of 0.9, for outpatient bladder procedures.</p> <p>2.1.3 List the clinical hypotheses. Using Sugammadex in conjunction with a standard paralytic agent during bladder surgeries improves anesthesia conditions and recovery time.</p>
<p>2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data</p>	<p>Background: Bladder cancer is the 8th most common cancer in the US affecting 563,000 men and women annually. There are approximately 72,000 new cases diagnosed each year and roughly 16,000 patients die each year as a result of bladder cancer [1]. Many of these patients are diagnosed with the cancer confined to the bladder. These patients often come to the operating room for an initial screening, biopsy(s), and/or resection(s). They require frequent tumor resections which may have invaded the bladder muscle wall. This would require a deep level of anesthesia with muscle relaxation for safe and adequate tumor resection. This study will evaluate the use of a unique muscle relaxation reversal agent and its effect on the surgical condition, anesthetic provided, decrease of provider variability, as well as hospital utilization.</p> <p>Sugammadex, a selective relaxant binding agent, is used to speed up recovery of muscles after anesthesia. During some operations, your muscles must be completely relaxed. This is often required by the surgeon in order to perform the operation. Muscle relaxation medications cause the muscles to relax; the general anesthetic includes muscle relaxants such as Esmeron and Norcuron. Since respiratory muscles also become relaxed, artificial ventilation is required. Sugammadex reverses the effect of the muscle relaxation medications. After the operation spontaneous breathing is achieved [2].</p> <p>This study will involve the use of Sugammadex which was recently approved by the FDA. Sugammadex has been used in Europe as Bridion since 2008 and the specific drug information has been attached as an appendix item. [3]</p> <p>Rationale for this Study Bladder cancer affects about 72,000 patients each year and the first step for the diagnosis and treatment involves a transurethral resection of the bladder (TURB) tumor. This is a highly skilled procedure due to the complexity of resecting a tumor from within the lumen of a thin, hollow organ: the bladder [4].</p> <p>Subclinical perforation of the bladder with extravasation of urine has been reported in</p>

as many as 58% of cases, when evaluation with immediate post TURB cystogram is used [5]. Clinically detected perforation of the bladder has been reported in up to 10% of cases and this can be a serious complication resulting in leakage and systemic absorption of irrigation fluid and by bleeding, vascular or bowel injury [6].

While extraperitoneal perforations can often be managed conservatively, large, intraperitoneal bladder perforations may require immediate treatment to prevent complications. In addition, perforations have been linked to reports suggesting that extravescical growth of tumor can occur in some patients when this happens [7].

There are approximately 1050 surgical cases of cystoscopy performed per year at the UT MD Anderson Cancer Center operating rooms. These procedures are performed on patients who have a history of bladder cancer or other type of abdominal cancer which has affected the bladder. Due to a large number of anesthesia providers, there is a large variability of intra-operative management of these patients. The surgeon will often ask for a short period of complete muscle relaxation when electro cautery is used, in order to decrease spontaneous movement. Because of the long duration of reversal with neostigmine/glycopyrrolate, patients are usually given lower doses of muscle relaxant, which increases the risk for bladder perforation. By using Sugammadex, the anesthesiologist expects to improve the surgical condition by providing a deeper level of muscle relaxation with a standardized dose of muscle relaxant. A more predictable reversal of muscle relaxation will be provided, while minimizing post-operative side effects. Neostigmine/glycopyrrolate usually is not administered immediately after the end of surgery and, for a profound block, takes a considerable amount of time for reversal. Sugammadex may be administered much earlier and is expected to complete the reversal in several minutes. There has not been a study which provides an outcome in outpatient surgical or urological patients. Due to the high comorbidity of this population, maintenance of patient safety needs to be studied. Therefore, this study will focus on the use of Sugammadex as a reversal agent for muscle relaxation during bladder surgery to improve the patient's ease of recovery [8,9].

Rationale for Endpoints

Patients who receive muscle relaxation reversal by use of neostigmine/glycopyrrolate experience more post-operative nausea and vomiting than patients who don't receive neostigmine. Patients also experience oral secretion and salivation, bradycardia, and tachycardia. These anesthetic complications may prolong PACU stay, prolong recovery, or result in hospital admission; effecting and increasing hospital utilization [10]. Variability of response to Rocuronium as measured by quality and duration of muscle relaxation has resulted in a variability of doses given during outpatient surgery. By use of a standard dose of Rocuronium, an improved recovery should be expected by use of Sugammadex.

Train of Four

An Acceleromyograph (e.g. TOF-Watch SX) is a neuromuscular monitoring device which can objectively measure neuromuscular blockade reversal. Electrodes are placed over the ulnar nerve near the wrist, and a transducer is placed on the thumb. The ulnar nerve is stimulated and the response of the adductor pollicis muscle is recorded.

The train-of-four (TOF) is a method that assesses the depth of neuromuscular blockade. In 15-second cycles, with a 10-second gap between cycles, the ulnar nerve is stimulated four times within two seconds and the twitch responses (T1-T4)

are recorded. The height of T4 relative to T1 is known as the TOF ratio (TOFR). After administration of neuromuscular blockade, there is a fade in the latter twitch responses. As the blockade deepens, the nerve stimulation will stop producing responses, starting with T4. The loss of T4, T3, T2, and T1 represents a blockade of 80%, 85%, 90%, and 100% respectively. Once there are no twitch responses, the device switches to post-tetanic count (PTC) mode automatically. Once in PTC mode, the nerve is stimulated at 1 Hz over fifteen seconds. If there are no responses, there is five seconds of tetanic stimulation at 50 Hz. After a pause of three seconds, there are stimulations at 1 Hz over fifteen seconds. The number of responses during this fifteen second cycle constitutes the PTC. After reversal of neuromuscular blockade, the PTC will gradually increase. Once there are more than five consecutive responses, the device automatically goes back to TOF mode [11]. Once TOFR reaches 0.9, the patient has recovered from the neuromuscular blockade and may be extubated. TOFR of 0.9 is considered the standard for neuromuscular blockade reversal, greatly reducing the risk of residual blockade [12].

2.3 Study Design

This is a Phase IV, single center, open-label, randomized, parallel study in patients scheduled for outpatient bladder surgery at The University of Texas MD Anderson Cancer Center - Mays Clinic (ACB). Patients will be treated with Sugammadex administered intravenously at 4 mg/kg for deep muscle relaxation or Neostigmine/Glycopyrrolate, which will be administered intravenously at 70 mcg/kg of neostigmine with 14 mcg/kg glycopyrrolate following Rocuronium induced blockade as per manufacturer package insert.

Patients who have been scheduled for cystoscopy with suspected diagnosis of bladder tumor. In this Phase IV study, up to approximately 50 eligible patients will be enrolled. It is anticipated that full accrual to this study will take approximately 10 months.

Inclusion Criteria

- Is scheduled to undergo cystoscopy with bladder tumor resection procedure under general anesthesia requiring neuromuscular relaxation using Rocuronium bromide to secure airway and requiring neuromuscular reversal at The University of Texas MD Anderson Cancer Center – Mays Clinic (ACB-outpatient)
- Male or Females who are \geq 18 years of age
- Classified by the American Society of Anesthesiologists (ASA) as Class I-IV
- Candidate for use of laryngeal mask airway (LMA)
- Able to give consent

Exclusion Criteria

- severe renal impairment as measured by eGFR less than 30 per institutional laboratory.
- Females who are pregnant or might be pregnant or are breast-feeding
- Females who have been diagnosed with breast cancer and currently taking Toremifene
- is known or suspected to have significant hepatic dysfunction, with AST & ALT 3 times above UNL per institutional laboratory.
- is known or suspected to have a (family) history of malignant hyperthermia
- is known or suspected to have an allergy to opioids, muscle relaxants or other medications used during general anesthesia
- is known or suspected to have neuromuscular disorders (ex: myasthenia gravis).

Subject Recruitment Plans and Consent Process

Recruitment Plans:

All patients who are scheduled to have an outpatient cystoscopy procedure including transurethral resection of the bladder (TURB) at the outpatient Mays Clinic Surgical Center in Houston Texas will be pre-screened to see if they meet the enrollment criteria. If so, the patient will be approached by a member of the research study team.

Informed Consent:

Patients who are eligible to participate in the study will be approached by a member of the study team and informed about the trial. Patients will be encouraged to discuss participation in the study with their family and given the opportunity to have any questions answered before written informed consent is sought.

Randomization Assignments and Results will be mailed out to the subjects after publication.

Randomization Method

Once eligibility criteria have been confirmed patients will be randomized (1:1) to one of two groups using an automated on-line randomization scheme. After assignment to one of the two treatment groups, a unique study number will be assigned. Only one unique study number will be assigned per patient.

This will be a double-blind study in that the Surgeon and patient will be blinded to the randomization. Note: The Anesthesiologist and study personnel will not be blinded.

Risks and Benefits

The risks to participating in this study are minimal. The patient may experience increased bradycardia. Adequate safety measures, vigilance, and awareness will be taken by the anesthesia team. By participating in this study the patient is not exposed to any additional risks than they would otherwise experience under the standard practice for this procedure.

The benefits to utilizing Sugammadex as a reversal agent for a neuromuscular blockade may include improved quality of recovery and decreased time for recovery when compared to the current (Neostigmine/Glycopyrrolate).

Duration of Study or Criteria for Terminating Participation in the Study

Patients will be removed from study if the patient elects to withdraw from the study prior to general anesthesia. The reason for study removal and the date the patient was removed must be documented in the Case Report Form. Additionally, if there is a change in the patient's health status or if the patient requires an alternative anesthesia plan that would contradict the use of muscle relaxation, such as regional anesthesia or sedation.

Data Collection and Follow-up for Withdrawn Subjects

Data that has already been collected prior to notifying the PI of the patient's wish to withdraw from the study will remain in the study database. No additional information will be collected past this time point.

STUDY DRUG

Rationale for Dose Regimen

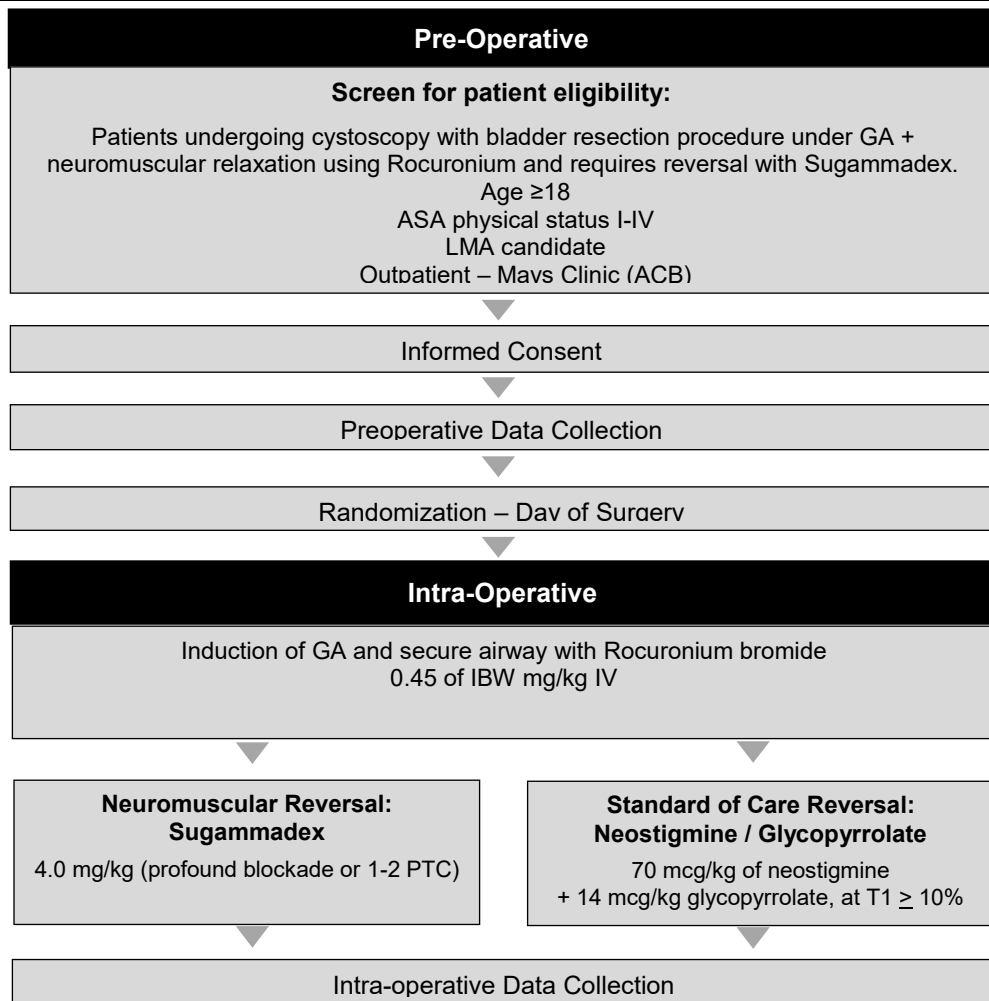
The dose used for the following medications are the standard doses from the manufacturers: Sugammadex, Rocuronium, Neostigmine/Glycopyrrolate.



Typical Dosing:

Rocuronium will be used to induce the neuromuscular blockade and will be given in a rapid sequence for endotracheal intubation at a dose of 0.45 mg/kg of Ideal Body Weight. If maintenance is needed for continued relaxation then a dose of 0.15 mg/kg of Ideal Body Weight will be repeated as necessary.

- Treatment Group: **Sugammadex** will be administered as a single bolus, intravenous injection. The amount used is based on the patient's weight. A dose of 4 mg/kg will be used if recovery has reached at least 1-2 post-tetanic counts (PTC) following Rocuronium induced blockade.
- Standard of Care: **Neostigmine/Glycopyrrolate** will be administered as a single bolus, intravenous injection. The amount used is based on the patient's weight. Once T1 is at 10% or greater, a dose of 70mcg/kg of neostigmine with 14 mcg/kg glycopyrrolate will be administered simultaneously over a period of one minute up to 5 mg.

2.4 Study Flowchart



	<div style="text-align: center;">  <div style="background-color: black; color: white; padding: 5px; margin: 5px auto; width: 80%;">Post-Operative</div> <div style="background-color: #e0e0e0; padding: 10px; margin: 5px auto; width: 80%;"> <p>PACU Data Collection:</p> <p>Ease of Recovery Postoperative Complications</p> </div>  <div style="background-color: black; color: white; padding: 5px; margin: 5px auto; width: 80%;">Follow-Up</div> <div style="background-color: #e0e0e0; padding: 10px; margin: 5px auto; width: 80%;"> <p>Follow-Up Data Collection</p> <p>Short-term follow up on Day 1 Phone follow up on Day 7 (1 week)</p> </div> </div>
<p>2.5 Study Procedures</p>	<p>Screening Period</p> <p>Screening period will be defined as the time up until consent has been signed. Confirmation of diagnosis of cancer or abdominal disease either in the electronic medical records or prior to scheduling of surgery and enrollment into the study. Inclusion/Exclusion criteria will be confirmed.</p> <p>Baseline Period (Perioperative)</p> <p>Baseline will be defined as the period after consent has been received and will include the perioperative period prior to surgery. Randomization will occur during this time frame.</p> <p><u>Recordings:</u></p> <ul style="list-style-type: none"> • Patient demographics and medical history • Height, Weight, BMI, Age, and Temperature • ASA Classification <p>Treatment Period (Intraoperative)</p> <p>This will be a parallel study. Anesthesia will be provided as standard routine practice for cystoscopy with bladder tumor resection. Patient will receive General Anesthesia; they will be induced with intravenous Propofol and Fentanyl, Rocuronium will be administered as relaxant agent during Induction. They will be maintained with volatile agents and Fentanyl. Neuromuscular blockage will be monitored with an Acceleromyograph. Neuromuscular reversal will be performed using either treatment group; Sugammadex or Neostigmine/Glycopyrrolate at the conclusion of surgery. Patient will be extubated after recovery from General Anesthesia and a TOFR of 0.9 has been reached.</p> <p>Treatment will be defined as the intra-operative period until the conclusion of the surgical procedure or prior to patient being moved to PACU.</p> <p><u>Recordings:</u></p> <ul style="list-style-type: none"> • Duration of Reversal (administration of reversal agent to TOFR 0.9) • Time of extubation • Duration of surgery • Doses for neuromuscular block and reversal (Rocuronium, Sugammadex, and Neostigmine/Glycopyrrolate)

	<p>Recovery Period - PACU</p> <p>Recovery will be defined as the time the patient is sent to PACU until he/she is discharged.</p> <p><u>Recordings:</u></p> <ul style="list-style-type: none"> • Whether anti-nausea meds were given as a parameter of ease of recovery • Length of Time for patient to meet PACU discharge criteria • Post-op complications will be documented based on event occurrence <p>Follow Up Period</p> <p>Patients will be followed for 1 day post discharge from PACU or until death, whichever occurs first. Follow up will be face-to-face if the patient is still in the hospital; otherwise it will be conducted via telephone after the patient has been discharged. Upon discharge from the hospital, the patient will be sent home with diagrams necessary to complete the assessments over the phone. A final Phone Follow-Up will be conducted a week post procedure, on Day 7.</p> <p><u>Recordings:</u></p> <ul style="list-style-type: none"> • Post-op complications such as bladder perforation, nausea, vomiting, post-operative intubation and hospital admittance secondary to respiratory complications, will be documented based on event occurrence. • Patient re-admission within one week post procedure for any other cause.
<p>2.6 Study Duration</p>	<p>Patients will be followed for 1 day post discharge from PACU or until death, whichever occurs first, then on Day 7 for a final follow up. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.</p>
<p>2.7 Statistical Analysis and Sample Size Justification</p>	<p><i>Sample Size Justification</i></p> <p>This is a randomized, double-blinded trial designed to evaluate the reversal effect of the muscle relaxation medications using Sugammadex comparing to the standard of care (SOC) using Neostigmine/Glycopyrrolate on patients undergoing cystoscopy with bladder tumor resection procedure. The primary objective is to determine if Sugammadex can improve muscle recovery comparing to the SOC, measured by time from administration of neuromuscular blockade reversal to train-of-four ratio of 0.9. Fifty-six patients will be randomized with a 1:1 ratio to receive either Sugammadex or Neostigmine/Glycopyrrolate.</p> <p>With a sample size of 25 in each group, the trial will have 80% power to detect an effect size of 0.809 in mean of the time from administration of neuromuscular blockade reversal to train-of-four ratio of 0.9 between the Neostigmine/Glycopyrrolate arm and Sugammadex arm. The two-sided Type I error rate was 0.05, and the test statistic used was the two group t-test (nQuery Advisor 7.0) Considering that 10% of the enrolled patients will be inevaluable, the trial need to enroll a total of 56 patients. Patients are considered to be inevaluable if they have protocol violations or do not have the measurement on the primary endpoint.</p> <p>Patients will be randomized through CORE at MDACC. There will not be any stratification factors.</p>

	<p><i>Analysis Plans</i></p> <p>The analysis will be performed on evaluable patients. Patients are considered to be evaluable if they don't have any protocol violations and have the measurement on the primary endpoint. Patients' demographic information at baseline will be analyzed, with data summarized in tables listing the number of subjects per treatment arm in order to assess comparability. We will summarize the distribution of time from administration of neuromuscular blockade reversal to train-of-four ratio of 0.9 and overall recovery time by each treatment. We will use the student t-test or the Wilcoxon rank sum test to compare continuous variables between two different patient groups. The Fisher's exact test will be applied to assess the association between two categorical variables. Linear regression may be utilized to assess the effects of patient prognostic factors on time from administration of neuromuscular blockade reversal to train-of-four ratio of 0.9.</p> <p>Toxicity data will be summarized by frequency tables. The association between the types and severity of toxicity and the treatment groups will be evaluated. No formal statistical testing will be performed on these summary data.</p> <p>The dosage of Rocuronium has been reduced from 0.6 mg/kg to 0.45mg/kg after enrolling two patients (one on each treatment arm). The Rocuronium dosage may impact the evaluation of the primary endpoint which is the time of recovery from neuromuscular block. We will perform a sensitivity analysis to evaluate the impact of including these two patients in the analysis.</p>
<p>2.8 Specific Drug Supply Requirements</p>	<p>Patient or insurance provider is responsible for all costs of surgery, including anesthesia and hospitalization. This includes all drugs involved in the study including Rocuronium, which is used as a neuromuscular blocking agent.</p> <p>The study/treatment drugs Sugammadex, Neostigmine and Glycopyrrolate will be covered by the Sponsor and not billed to the patient. Other drugs utilized in this study will be used as per standard routine care. The site institution's research pharmacy department will maintain study supplies and record documentation. Additionally, they will also be responsible for the destruction of the supplies at the end of the study as per ICH/GCP guidelines, local regulations, and institutional policies. Supply should be shipped in marked vials to allow for non-blinded administration by the anesthesiologist.</p> <p>Note: At conclusion of the study or upon drug expiration, the Merck GRS will be responsible for issuing a Drug Disposition Letter to the investigator for US based studies.</p>
<p>2.9 Adverse Experience Reporting</p>	<p>We will follow specific requirements outlined in the study agreement for adverse experience reporting. For clinical protocols, specific adverse experience reporting requirements must be identified in the protocol if the Model Study Agreement is not used (in general, this would apply to non-US. studies whose local requirements may prohibit the use of the agreement).</p>

2.10 Itemized Study Budget

This is a preliminary study budget that represents an initial cost estimate based on the proposed protocol and cannot be finalized until a final protocol has been submitted to the IRB. This is based on an anticipated enrollment of 50 patients. We have budgeted on the high side. However, when the statistical plan has been completed and the sample size confirmed, the budget will be adjusted accordingly.

Please note there are fixed costs that MD Anderson charges for all prospective studies and these cannot be negotiated. A description of these costs is listed in the justification below.

	<u>Direct</u>	<u>Indirect (25%)</u>
IRB Fee: Fixed Cost	\$ 5,000	n/a
Translation of Informed Consent Document	\$ 1,000	n/a
Investigational Pharmacy Admin Fee: Fixed Cost	\$ 1,500	n/a
Department Administration Fee	\$ 3,000	n/a
CORE/PDMS User Fee: Fixed rate \$250/patient	\$ 12,500	\$ 3,125
Investigational Pharmacy Fee: Fixed rate \$150/patient	\$ 7,500	\$ 1,875
Data Manager (3% effort)	\$ 2,184	\$ 546
Study Coordinators (1 @ 50% effort each)	\$ 30,913	\$ 7,728
Statistician (3% effort)	\$ 3,450	\$ 863
Principal Investigator (1% effort)	\$ 4,278	\$ 1,070
Fringe (28%)	\$ 11,431	\$ 2,858
SOC drug cost: Neostigmine/Glycopyrrolate	\$ 2,665	n/a
Office Supplies	\$ 500	\$ 125
Subtotal	\$ 85,921	\$ 18,189
Total Project	\$ 104,110	
Per Patient Cost	\$ 2,082.21	

Budget Justification

IRB Fee: This is a fixed cost for the submission of the protocol to the IRB. This fee also includes the initial translation of the informed consent document into any language. Depending on the complexity of the ICD, an additional charge may be required but is not anticipated. There will not be any additional IRB fees for amendments or protocol revisions.

Investigational Pharmacy Administration Fee: This is a required institutional fee for the start-up of investigational pharmacy. This is a fixed rate at \$1,500 per study. An additional per patient fee is required and described below.

Department Administration Fee: This is reimbursement for the protocol review, entry, and management of the study prior to study activation. This is not a fixed rate.

PDMS/CORE User Fee: Required institutional fee for patient registration in the Protocol Data Management System (PDMS), which is a computer-based information

	<p>management system that maintains and processes patient information through data collection and management, tracking mechanisms and analysis; IRB mandates the use of PDMS for regulatory compliance issues, and since the PDMS system is supported by our NCI core grant. This is a fixed rate of \$250 per patient registration. <u>Investigational Pharmacy Fee:</u> This is a required institutional fee for each patient enrolled in the study. Investigational Pharmacy will be responsible for randomizing each patient to the treatment arm and maintain all compliance documentation required per federal guidelines regarding shipping, disposal, returning of study drug to sponsor, etc. This is a fixed rate of \$150 per patient.</p>
<p>2.11 References</p>	<ol style="list-style-type: none"> 1. American Society of Cancer. What are the key statistics about bladder cancer? <i>Bladder Cancer</i> 2015; http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics, 2015. 2. Merck Sharp & Dohme Limited. Bridion 100 mg/ml solution for injection. <i>European Medicines Agency</i> 2014; https://www.medicines.org.uk/emc/print-document?documentId=21299. 3. Merck Sharp & Dohme (Australia) Pty Limited. Bridion <i>Product Compound</i> 2008; Available at: http://secure.healthlinks.net.au/content/msd/pi.cfm?product=mkpbridi. 4. Golan S, Baniel J, Lask D, Livne PM, Yossepowitch O. Transurethral resection of bladder tumour complicated by perforation requiring open surgical repair - clinical characteristics and oncological outcomes. <i>BJU Int.</i> 2011;107(7):1065-1068. 5. Balbay MD, Cimentepe E, Unsal A, Bayrak O, Koc A, Akbulut Z. The actual incidence of bladder perforation following transurethral bladder surgery. <i>J Urol.</i> 2005;174(6):2260-2262, discussion 2262-2263. 6. Collado A, Chechile GE, Salvador J, Vicente J. Early complications of endoscopic treatment for superficial bladder tumors. <i>J Urol.</i> 2000;164(5):1529-1532. 7. Herkommer K, Hofer C, Gschwend JE, Kron M, Treiber U. Gender and body mass index as risk factors for bladder perforation during primary transurethral resection of bladder tumors. <i>J Urol.</i> 2012;187(5):1566-1570. 8. Castro DS, Jr., Leao P, Borges S, Gomes L, Pacheco M, Figueiredo P. Sugammadex reduces postoperative pain after laparoscopic bariatric surgery: a randomized trial. <i>Surgical laparoscopy, endoscopy & percutaneous techniques.</i> 2014;24(5):420-423. 9. Caldwell J. Reversal of residual neuromuscular block with neostigmine at one to four hours after a single intubating dose of vecuronium. <i>Anesthesia and analgesia.</i> 1995;80(6):1168-1174. 10. an TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. <i>Anesthesia and analgesia.</i> 2014;118(1):85-113. 11. Organon (Ireland) Ltd., Drynam Road, Swords, Co. Dublin, Ireland, <i>TOF-Watch Operator Manual</i>, http://www.mainlinemedical.com/mm/manuals/bluestar_tof_watch_instruction_manual.pdf 12. Fuchs-Buder, T., Claudius, C., Skovgaard, L. T., Eriksson, L. I., Mirakhur, R. K. and Viby-Mogensen, J. (2007), Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. <i>Acta Anaesthesiologica Scandinavica</i>, 51: 789–808. doi: 10.1111/j.1399-6576.2007.01352.x 13. Royse CF, Newman S, Chung F, et al. Development and feasibility of a scale to assess postoperative recovery: the post-operative quality recovery scale. <i>Anesthesiology.</i> 2010;113(4):892-905.

2.12 Publication Plan	<p>Generally, a publication plan is discussed between the investigator and Merck /MSD during time when the protocol is under development. Details of the publication and the obligations to Merck/MSD are outlined in the study agreement.</p> <p>There are plans to publish data and findings.</p> <p>Additionally, the PI will present the data at one of the following conferences: ASA, SAMBA, Texas Society of Anesthesiology.</p>
2.13 Curriculum Vitae	<p>Investigator should provide curriculum vitae in English and a listing of references to Merck/MSD.</p>
2.14 Protocol Submission for Investigator-Initiated Studies	<p>U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiiisp.com</p> <p>Non U.S. protocols should be submitted to the MSD office by the investigators.</p>