PROTOCOL SYNOPSIS

TITLE	A Double-Blind, Randomized, Crossover Design Study To Compare The Rocuronium Reversal By Sugammadex To Succinylcholine For Electroconvulsive Therapy (ECT)
SPONSOR	Chanhung Lee
FUNDING ORGANIZATION	Merck & Co, Inc.
NUMBER OF SITES	1
RATIONALE	The purpose of this study is to find out if a novel drug, sugammadex, can be used to reverse the muscle relaxation during the Electroconvulsive Therapy (ECT). ECT exerts its therapeutic effect by inducing generalized seizures. To protect the patients from harmful seizure injury, neuromuscular blockade is used to control excessive muscle movement during the treatment. Since the optimal length of therapeutic seizure effects is brief, fast recovery of the neuromuscular function after the treatment is desirable. Succinylcholine has been traditionally used in ECT for muscle relaxation because of its fast recovery after the procedure, but with obvious limitations and side-effects. Rocuronium is a different muscle relaxant providing excellent blocking conditions and has been commonly used in surgery, but not in ECT because of its long duration of action. Sugammadex is a novel reversal drug for rocuronium, which has recently been approved by the FDA. Sugammadex can reverse the action of rocuronium on neuromuscular blockade. Researchers want to learn whether sugammadex can be used in combination with rocuronium to provide a timely recovery of neuromuscular function after the ECT treatment.
STUDY DESIGN	This is a randomized, double-blind, placebo-controlled phase 2 study.
PRIMARY OBJECTIVE	The primary objective is to further explore the pharmacology of sugammadex in electroconvulsive therapy (ECT) by measuring neuromuscular recovery time from sugammadex reversal of rocuronium, compared to traditionally used succinylcholine.
SECONDARY OBJECTIVES	Secondary aims are to document the safety and tolerability (adverse event rates) of rocuronium/sugammadex compared to succinylcholine in ECT patients, and to exploer perioperative efficacy and efficiency of sugammadex reversal of rocuronium in ECT procedures.

NUMBER OF SUBJECTS	50
SUBJECT SELECTION CRITERIA	Inclusion Criteria: • Age ≥ 18 years • Eligible and scheduled for ECT • Has the capacity to consent for the study Exclusion Criteria: • Any acute major organ failure in the last 30 days • Any known or suspected neuromuscular disorders • Any history of allergic reaction or intolerance to sugammadex, rocuronium, or succinylcholine • Any conditions with severe renal impairment, including those requiring dialysis • Anyone currently taking hormonal contraceptives • Anyone taking anti-coagulants, including vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban, and dabigatran
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Sugammadex at 4 mg/kg, IV (after rocuronium is administered for ECT)
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Succinylcholine at 1 mg/kg IV + normal saline IV
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to two treatments **Screening:** up to 7 days **Treatment:** standard procedure time (about 2 hours) **Follow-up:** 24 hours by phone The total duration of the study is expected to be one month for subject recruitment and for final subject follow-up.

CONCOMMITANT MEDICATIONS	Allowed: Standard therapy for patients' medical diseases is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below. Prohibited: • hormonal contraceptives • anti-coagulants, including vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban, and dabigatran
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• Neuromuscular recovery time from sugammadex reversal of rocuronium, compared to traditionally used succinylcholine.
SECONDARY ENDPOINTS	• Explore perioperative efficacy and efficiency of sugammadex reversal of rocuronium in ECT procedures.
OTHER EVALUATIONS	
SAFETY EVALUATIONS	• Safety and tolerability (adverse event rates)
PLANNED INTERIM ANALYSES	An interim analysis is planned after approximately 30% of the patients have been enrolled and completed follow-up to assess safety and provide estimates of within and between patient variability in the recovery time of muscle relaxants. The interim analysis for safety will be conducted by the study team. Serious adverse events will be monitored by the investigators on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	This is a two-period, two-treatment, 2x2 cross-over study. Although it is highly likely that the washout period is adequate for eliminating the first order carry-over effects since all repeated procedures are scheduled at least 48 hours apart, which exceeds the duration for all the involved medications, we will exam the period and carryover effects using a term for time period and an interaction term between the treatment group and time period. Intent-to treat analyses will be used for primary and secondary outcomes. For the primary outcome, the comparison of recovery time of T1 to 90% baseline, a continuous variable, between the groups of rocuronium /sugammadex and the

	succinylcholine /saline placebo, will be analyzed using the two sample t test.
Rationale for Number of Subjects	Based on the study by Lee, et al,[8] comparing high dosage of rocuronium 1.2 mg/kg in combination with high dosage reversal of sugammadex 16mg/kg with succinylcholine 1mg/kg, the recovery time T1 to 90% in succinylcholine was 10.9 ± 2.4 minutes. The reported T1 to 90% 4mg/kg sugammadex reversed recovery counted from time of rocuronium 0.6 mg/kg (the same proposed dosage as in our study) administration ranged from 6 to 9.3 minutes.[5, 10] With our estimation of two-tailed α=0.05, β=0.2, the reported minimum mean difference of 1.6 (10.9 minus 9.3) minutes, SD of succinylcholine of 2.4 minutes, the calculated sample size for a cross-over trial would be 35. At UCSF, there are usually 60 ECT patients each year. With a conservative estimate of 75% consent rate, we will have at least 45 patients to participate in the study. Even conservatively allowing a 20% drop-off rate, we feel that our enrollment up to 50 will provide sufficient power for the study.