# A PHASE 1, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF INTRAMUSCULAR ADMINISTRATION OF SCOPOLAMINE HYDROBROMIDE TRIHYDRATE, INJECTION

| | |
|---|---|
| Sponsor | The Surgeon General, Department of the Army |
| **Sponsor's Representative** | [redacted] |
| **Medical Monitor** | [redacted] |
| **Research Monitor** | [redacted] |
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| | |
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| **Funding Source** | [redacted] |

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## INVESTIGATOR'S AGREEMENT

# A PHASE 1, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF INTRAMUSCULAR ADMINISTRATION OF SCOPOLAMINE HYDROBROMIDE TRIHYDRATE, INJECTION

"I have read this protocol and agree to conduct the study as outlined herein in accordance with International Council for Harmonisation Good Clinical Practice Guideline and FDA, DoD, and United States Army Regulations."

Paolo DePetrillo, MD
Principal Investigator
Pharmaron

09 MAR 2021
Date

# EMERGENCY CONTACT INFORMATION

**Table 1: Emergency Contact Information**

| Role in Study | Name | Address and Telephone Number |
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| Role in Study | Name | Address and Telephone Number |
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# 2. SYNOPSIS

**Name of Sponsor:**
The Surgeon General, Department of the Army

**Name of Investigational Product:**
Scopolamine Hydrobromide Trihydrate, Injection

**Name of Active Ingredient:**
Scopolamine Hydrobromide Trihydrate, USP

**Title of Study:**
A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Intramuscular Administration of Scopolamine Hydrobromide Trihydrate, Injection

**Study Center:**
Pharmaron

**Principal Investigator:**
Paolo DePetrillo, MD

| **Study Period (years):** 1<br>Estimated date first subject enrolled: June 2020<br>Estimated date last subject completed: June 2021 | **Phase of Development:** 1 |
|---|---|

**Objectives:**
The primary objectives of this study are:

- To characterize the safety and tolerability profile of ascending doses of scopolamine hydrobromide trihydrate (Scopolamine HBT) administered by intramuscular (IM) injection
- To characterize the pharmacokinetics (PK) of ascending doses of Scopolamine HBT administered by IM injection

**Methodology:**

This is a double-blinded, randomized, placebo-controlled, in-clinic, Phase 1, single-dose, IM, sequential dose-escalation study in healthy adults aged 18-55. Healthy volunteers will be assigned to 1 of 5 cohorts of Scopolamine HBT dosage groups: 0.005, 0.007, 0.011, 0.014, or 0.021 mg/kg, or will receive the placebo administered by IM injection to the anterior thigh. In each cohort, 6 to 9 subjects will receive active drug and 2 to 3 subjects will receive placebo. Each cohort will have at least 3 male and 3 female subjects enrolled among the first 8 subjects in the dosing group to ensure that at least 1 male subject and 1 female subject in each dosing group receive active drug. If nonextreme dose-limiting toxicities are observed in any of the cohorts, 4 additional subjects, 3 active and 1 placebo, may be added to each cohort. In addition, to assure study population diversity in an 8-subject cohort, no more than 5 subjects may be enrolled from any one of these single racial and ethnic groups: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Hispanic/Latino, or Other. If the cohort is expanded to 12 subjects, no more than 8 subjects (2/3 of the subjects) may be enrolled from any one of the above racial and ethnic groups.

On the first day of dosing for each cohort, 2 subjects will be dosed (1 active and 1 placebo). Upon review of the adverse event (AE) data for both subjects at 24 hours post dose (± 1 hour), the principal investigator (PI) and the medical monitor will determine if it is safe to proceed with dosing the remaining 6 of the first 8 subjects.

New subjects will not be enrolled into the next higher dosage group until at least 8 subjects in the previous cohort have completed the Day 8 follow-up visit without the occurrence of dose-limiting toxicities, predefined as requiring termination of the study; the Data Safety Monitoring Board has reviewed data and made a dose-escalation recommendation to the sponsor; and the sponsor concurs with the recommendation. The sponsor must approve dose escalation. Dose escalation cannot occur until after sponsor approval of recommendations and notification of the investigator(s), not at the time of the recommendation.

**Estimated Number of Subjects Screened:**

240

**Maximum Number of Subjects Enrolled:**

60 (12 per group)

**Criteria for Inclusion/Exclusion:**

**Inclusion Criteria:**

1. Male or female, 18 to 55 years of age, inclusive, at the time of drug administration
2. Without clinically significant abnormities on physical examination at screening or prior to drug administration
3. Generally healthy, as determined by medical history review, physical examination, and laboratory testing at screening and prior to drug administration
4. Must have a body mass index (BMI) of ≥ 19.0 and ≤ 30.0, and weight range of 55.0 to 85.0 kg at screening or prior to drug administration
5. Must have adequate venous access and sufficient upper leg muscle tissue for drug administration
6. If female, the subject must be nonpregnant and nonbreastfeeding, and have a negative serum pregnancy test at screening and prior to drug administration
7. If female of childbearing potential, the subject must have been using adequate contraception (as defined in Section 5.3.1.5) for at least 3 months prior to drug administration and must agree to use an adequate method of contraception for at least 30 days following drug administration
8. Females of nonchildbearing potential are also eligible, defined as a subject who is postmenopausal (continuous amenorrhea for 24 months) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or total hysterectomy)
9. A male with a female partner of childbearing potential must agree to use a barrier method of contraception (defined as condoms with spermicide) for at least 30 days following drug administration
10. If male, must not have past diagnoses of benign prostatic hypertrophy or urinary tract obstruction and must not have on screening history/review of systems symptoms suggestive of urinary tract obstruction (eg, urinary hesitancy, urgency, frequency, or nocturia)
11. Nonsmoker/tobacco/nicotine product (including e-cigarettes) user within 3 months of first dosing and must have a total lifetime exposure to cigarettes of < 15 pack-years
12. No evidence of significant neuropsychiatric disorders based on the Brief Psychiatric Rating Scale (BPRS) at screening and prior to drug administration, which is defined as having a global score of ≤ 25 with no score higher than 2 on any one item, with the exception of a score of 1 (ie, Not Present) to disorientation, hallucinatory behavior, and suspiciousness (ie, paranoia)

13. No evidence of suicidal ideation or behavior at screening and prior to drug administration, which is defined as having a global score of 0 on the Columbia-Suicide Severity Rating Scale (C-SSRS)
14. Ability to read, speak, and comprehend English and a willingness to sign informed consent

**Exclusion Criteria:**

A subject meeting any of the following criteria will be excluded from the study:

1. Received any other investigational drug within 30 days prior to drug administration
2. Known allergies to any component of the study drug, other belladonna alkaloids, or the recovery medications (physostigmine, atropine, or benzodiazepines [diazepam or lorazepam])
3. History of migraine headaches or seizures
4. History of psychosis or psychotic episodes
5. Clinically relevant abnormal physical findings (including vital signs) as determined by the investigator at screening or prior to drug administration that could interfere with the objectives of the study or the safety of the subject
6. Has ongoing drug abuse/dependence (including alcohol), recent history (over the past 5 years) of treatment for alcohol or drug abuse, or a current positive alcohol breathalyzer test or current positive urine test for drugs of abuse (as defined in Section 11.1.9.5) at screening or prior to drug administration
7. Has consumed Seville orange (bitter orange), grapefruit, grapefruit juice, other grapefruit-containing products, or starfruit within 7 days prior to dosing
8. Has consumed caffeine or other xanthine-containing products within 7 days prior to dosing
9. Has any specified laboratory values (eg, hematology, serum chemistry, and urinalysis) outside of the normal range for age and sex and deemed clinically significant by the investigator within 30 days before drug administration
10. Has positive (reactive) test results for hepatitis B surface antigen, hepatitis C, syphilis, HIV-1, or HIV-2
11. Has narrow-angle glaucoma or high intraocular pressures in either or both eyes
12. Has pyloric obstruction or urinary bladder neck obstruction
13. Has impaired liver or kidney functions
14. Clinically relevant electrocardiogram (ECG) abnormalities on any 12-lead ECG obtained at screening or prior to dosing
15. ECG with a PR interval $\geq$ 200 msec at screening or prior to dosing
16. ECG with QRS duration > 120 msec at screening or prior to dosing
17. ECG RR interval > 1500 msec at screening or prior to dosing
18. ECG with a QTc interval > 450 msec for males or 470 msec for females (QT interval corrected with Fridericia correction [QTcF]) at screening or prior to dosing
19. Systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg at screening or prior to dosing
20. Systolic blood pressure < 90 mm Hg and/or diastolic blood pressure < 50 mm Hg at screening or prior to dosing
21. Currently taking or has taken other antimuscarinic drugs such as phenothiazines, tricyclic antidepressants, antihistamines (including meclizine), meperidine, or other anticholinergics that have weak antimuscarinic activity or that cause drowsiness, including antidepressants, benzodiazepines, alcohol, sedatives (used to treat insomnia), pain relievers, anxiety medicines, and muscle relaxants within 72 hours prior to dosing
22. Has taken, within 14 days of planned dosing, any prescription or nonprescription medication (including home remedies, herbal supplements, or nutritional supplements) unless the PI/subinvestigator, in consultation with the medical monitor, provides a statement justifying

that the medication taken will not impact the results of this study (with rare exceptions taking prescriptions drugs will be grounds for exclusion)

23. History of major DSM-5 Axis I or II disorder, or evidence of such disorder at Day -1 as determined via the Structured Clinical Interview for DSM-5, customized Clinical Trials version (SCID-5-CT)
24. Has any skin condition, scars, or tattoos that would interfere with injection of study drug
25. Donated > 480 mL of blood within 8 weeks of drug administration
26. Any other reason, in the opinion of the investigator, the subject should not participate in the study

**Investigational Product Dosage, Schedule, and Mode of Administration:**

Single dose, IM either 0.005, 0.007, 0.011, 0.014, or 0.021 mg/kg Scopolamine HBT or placebo

**Duration of Participation:**

Four-day and 3-night, in-clinic stay; telephone follow-up on Day 4; and follow-up visit on Day 8. Total duration of subject participation in the study, including the screening period and 30-day post-dose telephone follow-up, may be up to 9 weeks.

**Criteria for Evaluation:**

**Pharmacokinetics:**

Blood samples will be obtained for PK assessments prior to dosing and at 2, 5, 10, 15, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 36, and 48 hours post dose. Scopolamine HBT PK assessments will include determination of the following parameters: observed maximum concentration ($C_{max}$) and time to reach $C_{max}$ ($T_{max}$), apparent volume of distribution ($V_d\_F$), half-life or elimination time ($t_{½}$), apparent clearance (Cl_F), $AUC_{last}$, $AUC_{\infty}$, $C_{max}$/Dose, MRT (mean residence time), and $AUC_{\infty}$/Dose. Plasma concentration time profiles for each subject tested will be evaluated using semi-log plots and characterized using noncompartmental analysis (WinNonlin). PK and safety endpoints will undergo pharmacodynamic analysis and evaluation.

**Safety:**

All subjects participating in the study will be monitored closely throughout the in-clinic phase of the study. The PI and/or physician designee will be in the treatment room during dosing and for 4 hours post dose. A crash cart will be in the immediate area where subjects are residents. A specific rescue medication to treat Scopolamine HBT effects (physostigmine) will be immediately accessible, as well as atropine and a benzodiazepine (diazepam or lorazepam).

Continuous cardiovascular monitoring of ECG (3-lead) and vital signs (systolic and diastolic blood pressure (at 5-15 minute intervals), heart rate, respiration rate, and pulse oximetry) will be performed from 1 hour prior to and for 24 hours following Scopolamine HBT or placebo administration. During the first 24 hours and through 48 hours post dose, vital sign monitoring (including body temperature), 12-lead ECG, clinical assessment of neuropsychiatric status (using the BPRS, C-SSRS, and Richmond Agitation and Sedation Scale), and injection site reaction assessments will be performed and documented at specified times. The Digit Symbol Substitution Test will be administered prior to dosing and at 48 hours post dose and Day 8 to detect any persistent cognitive effects. Standard serum chemistry, hematology, and urinalysis testing will be performed at baseline (Day-1), at 24 and 48 hours post dose, and at Day 8. Subjects will be monitored for AEs continuously while in clinic, and AEs will be documented as they are reported. Follow-up for AEs will be conducted via telephone on Days 4 and 30, and via an in-clinic visit on Day 8 unless otherwise reported by the subject. In the event of a potential AE, additional

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| assessments/testing may be performed if, in the judgment of the investigator or designee, they are warranted for the safety of the subject. AEs will be followed until resolution/stabilization. |
| **Statistical Methods:**<br>Results of safety assessments will be summarized across dosing levels and compared to the placebo group. AEs will be listed by treatment group and body system using MedDRA terms. Confidence intervals for the probability of dose-limiting toxicities and severe adverse events will be estimated based on the number of observed events in each dosing cohort. Scores for injection site assessments, and changes in cognitive and neuropsychiatric scales will be compared for each dosage level relative to placebo. Plasma concentration curves will be fit using noncompartmental analysis to obtain PK parameters for each dosing cohort prior to dosage escalation. PK parameters will be summarized by dosage level, and the parameters $C_{max}$ and $AUC_{\infty}$ will be tested statistically for dose proportionality. |

# 3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

## LIST OF TABLES



## LIST OF FIGURES

# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

**Table 2: Abbreviations**

| Abbreviation | Explanation |
|---|---|
| µmol | micromolar |
| 2-PAM | pralidoxime chloride |
| 5x | 5 times |
| ACh | acetylcholine |
| AChE | acetylcholinesterase |
| ACLS | Advanced Cardiovascular Life Support |
| AE | adverse event |
| ATNAA | antidote treatment nerve agent, auto-injector |
| AUC | area under the curve |
| BMI | body mass index |
| BPRS | Brief Psychiatric Rating Scale |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CANA | Convulsant Antidote for Nerve Agent |
| CFR | Code of Federal Regulations |
| Cl_F | apparent clearance |
| CLIA | Clinical Laboratory Improvement Amendments |
| cm | centimeter(s) |
| $C_{max}$ | maximum concentration |
| CNS | central nervous system |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | dose-limiting toxicity(ies) |
| DoD | Department of Defense |
| DSMB | Data Safety Monitoring Board |
| DSST | Digit Symbol Substitution Test |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| $ED_{50}$ | effective dose for 50% of the population |
| EENT | eyes, ears, nose, and throat |
| dL | deciliter |
| FDA | US Food and Drug Administration |

| Abbreviation | Explanation |
|---|---|
| g | gram |
| GB | sarin |
| GD | soman |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IM | intramuscular(ly) |
| IND | Investigational New Drug (application) |
| IRB | Institutional Review Board |
| IV | intravenous(ly) |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| kg | kilogram(s) |
| L | liter(s) |
| $LD_{50}$ | lethal dose of a compound resulting in 50% mortality |
| mEq | milliequivalent |
| mg | milligram(s) |
| mL | milliliter(s) |
| mm | millimeter(s) |
| mm Hg | millimeter of mercury |
| mM | millimolar |
| MRT | mean residence time |
| msec | millisecond(s) |
| ng | nanograms(s) |
| NOAEL | no-observed-adverse-effect level |
| OP | organophosphorus |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| PB | pyridostigmine bromide |

| Abbreviation | Explanation |
|---|---|
| PD | pharmacodynamic(s) |
| PI | principal investigator |
| PK | pharmacokinetic(s) |
| [redacted] | [redacted] |
| PVG | pharmacovigilance |
| qEEG | quantitative electroencephalogram |
| QTcF | QT interval corrected with Fridericia correction |
| RASS | Richmond Agitation and Sedation Scale |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SCID-5-CT | Structured Clinical Interview for DSM-5, Clinical Trials Version |
| Scopolamine HBT | scopolamine hydrobromide trihydrate |
| SOP | standard operating procedure |
| $t_{½}$ | half-life or elimination time |
| TK | toxicokinetic |
| $T_{max}$ | time to reach $C_{max}$ |
| TSG-DA | The Surgeon General, Department of the Army |
| US | United States |
| [redacted] | [redacted] |
| USP | United States Pharmacopeia |
| VAS | visual analog scales |
| $V_d$_F | apparent volume of distribution |

# 5. INTRODUCTION

[redacted] is developing scopolamine hydrobromide trihydrate (Scopolamine HBT) as a centrally and peripherally acting injectable therapeutic that would be administered in conjunction with the ATNAA (antidote treatment nerve agent, auto-injector) upon exposure to nerve agents and also as an adjunctive therapy along with atropine. Scopolamine HBT is being developed as a liquid intramuscular (IM) injectable product in vials to treat muscarinic effects. Future plans are to develop the product in an autoinjector and file it (the final drug-device combination product) as an IM injectable therapeutic the post-exposure management of muscarinic effects in warfighters exposed to organophosphorus (OP) nerve agents.

Chemical and biological threats are real, dynamic, and ever changing. The rapid advancement and global proliferation of chemical and biological capabilities greatly extend the spectrum of plausible actors, agents, concepts of use, and targets. Specific threats may include the use of traditional chemical weapons (eg, mustard, sarin [GB], or G-series nerve agents; VX or V series nerve agents; or other newly developed nerve agents) as well as the use of nontraditional chemical agents such as pharmaceutical-based OP agents, employed in either tactical/operational military settings or as terrorist attacks. The identity of threat agents may be initially uncertain; however, broadly based response capabilities must be rapidly available.

As part of the Department of Defense's (DoD) continued search for better and more readily available treatment options, [redacted] has identified Scopolamine HBT (formulated in 1 mM citrate buffer; 150 mM sodium chloride, pH 3.0 ± 0.1) as having the mechanism of action (anticholinergic properties) to prevent the effect of excess acetylcholine (ACh) by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, cardiac muscle, and gland cells; in peripheral ganglia; and in the central nervous system (CNS).

Nonclinical data generated support the utility of scopolamine in addition to the currently fielded standard-of-care treatment regimen (medical countermeasure), which consists of PB pretreatment followed by ATNAA and CANA (Convulsant Antidote for Nerve Agent) administrations by self or buddy aid, and in some cases may provide the warfighter with the best chance of survival in the event of chemical nerve agent exposure in combat or terrorist situations.

The current, accepted understanding of the toxic effects of nerve agents in humans is primarily due to the inhibition of the acetylcholinesterase (AChE) enzyme within nerve synapses, resulting in uncontrolled accumulation of the neurotransmitter ACh. The cholinergic system is the only neurotransmitter system known in which the action of the neurotransmitter ACh is terminated by the enzyme, AChE. Although there are several types of choline esters, the neurotransmitter of the cholinergic portion of the nervous system is most relevant to nerve agent activity. This classic explanation of nerve agent poisoning holds that the intoxicating effects are due to inhibition of AChE leading to excess endogenous ACh, which produces cholinergic over-activity or cholinergic crisis (Sidell et al, 2008). Some early signs of exposure by sublethal quantities of nerve agent are miosis, rhinorrhea, and airway constriction. Without medical intervention, higher levels of exposure (experienced through greater concentrations or longer durations) to these nerve agents will cause loss of consciousness, seizures, convulsions, cessation of respiration and cardiac activity, and death. Effects occur within minutes of exposure via inhalation, and after a

high level of exposure, death occurs in 10 to 15 minutes (Schultheiss, 2013). Exposure is typically via inhalation, dermal, or ingestion.

The anticholinergic drug, scopolamine, has been approved by the FDA as a transdermal therapeutic to relieve nausea, vomiting, and dizziness associated with motion sickness and recovery from anesthesia after surgical procedures since 1979 (Novartis NDA 17-874). Scopolamine is dermally delivered by a transdermal patch (containing 1.5 mg scopolamine base) worn behind the ear that delivers scopolamine over the course of 3 days. Scopolamine can rapidly cross the blood–brain barrier and thus is centrally acting. In addition to peripheral effects, it is this antimuscarinic activity in the CNS that gives scopolamine its potential for use to treat muscarinic symptoms as part of nerve agent treatment options (Koplovitz and Schulz, 2010).

As scopolamine base and scopolamine hydrobromide have been used in humans for various therapeutic indications for more than 100 years, the proposed use of Scopolamine HBT is as a stand-alone therapeutic to manage muscarinic symptoms or as an adjunct to the current and future OP nerve agent treatment regimen of PB pretreatment and atropine plus pralidoxime chloride (2-PAM) plus an anticonvulsant as post-exposure therapeutics.

Like atropine, scopolamine prevents the effect of excess ACh levels by antagonizing or blocking its binding to cholinergic muscarinic receptors at neuroeffector sites. Scopolamine is more potent (approximately 8 times) in the CNS since it enters the brain more rapidly than atropine, but atropine is approximately 10 times more potent in the periphery than scopolamine (Ketchum et al, 1973). When scopolamine was administered with atropine (0.5 mg/kg), 2-PAM (25 mg/kg), and diazepam (0.72 mg/kg), guinea pig survival after challenge with 5 times (5x) or 10 times (10x) the lethal dose that kills 50% of those exposed (2x $LD_{50}$) of GB or VX was significantly increased compared to medical countermeasure treatment without scopolamine (Koplovitz et al, 2015).

Exposure to toxic nerve agents or OP insecticides may cause severe reactions rapidly leading to significant morbidity or mortality. The underlying, primary mechanism in these pathological toxidromes is mediated by an inhibition of the ubiquitous enzyme AChE, which catalyzes the breakdown of the primary neurotransmitter ACh at neuromuscular junctions (Adeyinka and Kondamudi, 2018). Over-stimulation of the muscarinic receptors due to excess ACh results in cholinergic crisis characterized by the "SLUDGEM" Syndrome (salivation, lacrimation, urination, diarrhea, gastrointestinal upset, emesis, and miosis). The symptoms of this muscarinic syndrome may also be characterized by another mnemonic "DUMBELS" (diaphoresis and diarrhea; urination; miosis; bradycardia, bronchospasm, bronchorrhea; emesis; excess lacrimation; and salivation). There are 5 types of muscarinic receptors ($M_1$ to $M_5$) with differential tissue distributions that are involved in the cholinergic crisis toxidrome.

Early management of cholinergic crisis is both supportive and through utilization of antimuscarinic agents. Treatment of the major symptoms of cholinergic crisis is initially targeted at the copious oral and nasal secretions, bronchorrhea, and bronchospasm as these can be life threatening (Wiercinski and Jackson, 2018). These issues can lead to airway compromise, loss of patency, and breathing difficulties. Excess cholinergic stimulation causes both glandular and mucus secretion in the airways (Rogers, 2001). Anticholinergics, such as atropine and scopolamine, are effective treatments for control of secretions (Hockstein et al, 2004; Wildiers et al, 2009). The parasympatholytic scopolamine, structurally very similar to atropine, is used in

conditions requiring decreased parasympathetic activity in salivary and bronchial secretory glands (Renner et al, 2005).

## Military Relevance

Scopolamine exerts few effects on the actions of ACh at nicotinic receptor sites such as autonomic ganglia. Like atropine, scopolamine is a tertiary amine and a competitive antagonist to ACh, and nonselectively binds all muscarinic receptor types ($M_1$-$M_5$). However, scopolamine binds to muscarinic receptors with higher potency (~ 8 times more potent) than atropine in the CNS. Since scopolamine has a greater solubility in lipids and rapidly crosses the blood-brain barrier, the high receptor potency and lipid solubility of scopolamine in the CNS results in fast inhibition of ACh activity at centrally acting muscarinic receptors. Scopolamine's high muscarinic receptor potency and ability to cross the blood-brain barrier makes it an ideal candidate for addition to the current treatment regimen by providing a centrally acting nerve agent medical countermeasure to improve the overall effectiveness for treatment of nerve agent intoxication. The symptoms elicited during the cholinergic crisis in OP nerve agent or pesticide exposure are receptor mediated via overstimulation of muscarinic receptors ($M_1$-$M_5$) within the parasympathetic nervous system. These muscarinic receptors, with differential distributions in central and peripheral tissues, are involved in the cholinergic crisis toxidrome. Early medical management of cholinergic crisis is both supportive and through utilization of anti-muscarinic agents. Treatment of the major symptoms of cholinergic crisis is initially targeted at the copious oral and nasal secretions, bronchorrhea, and bronchospasm, as these can be life threatening. Thus, an important therapeutic strategy is the targeted management of secretions.

## Rationale for Study

The goal of the Phase 1 clinical investigation is to evaluate the safety, tolerability, and PK (including dose exposure proportionality) of Scopolamine HBT in 5 cohorts, with 8 to 12 subjects in each cohort. The doses of Scopolamine HBT chosen for this study are: 0.005, 0.007, 0.011, 0.014, and 0.021 mg/kg. These doses were chosen as they have been used previously in clinical studies (Kanto et al, 1989, Ketchum et al, 1973, Liem-Moolenaar et al, 2011), and the safety of the starting dose is supported by Good Laboratory Practice, single-dose, IM toxicology studies in rats (Battelle Study Numbers 0740002 and 0740098) and monkeys (Battelle Study Number 0740001). This Phase 1 clinical study will support development by providing a human safety and PK profile.

## 5.1. Name and Description of the Investigational Product

Scopolamine HBT injection is formulated in 1 mM citrate buffer; 150 mM sodium chloride at 2 concentrations for use in the clinical study, 0.8 and 2.0 mg/mL, and is adjusted to pH 3.0 ± 0.1 with hydrochloric acid and/or sodium hydroxide. Refer to Section 7.4 for additional information.

## 5.2. Summary of Nonclinical and Clinical Trials

### 5.2.1. Nonclinical Proof-of-Concept Studies

Nonclinical proof-of-concept studies were conducted in guinea pigs to demonstrate the potential efficacy of scopolamine as an adjunct treatment after challenge with nerve agents.

Koplovitz and Schulz (2010) evaluated the effect of atropine dose, PB pretreatment, and oxime selection on the efficacy of scopolamine as an adjunct treatment to enhance survival following lethal nerve agent exposure in guinea pigs. Results showed that the use of an effective oxime and/or PB pretreatment was a critical factor in determining the efficacy of scopolamine. Scopolamine was also found to reduce the dose of atropine required for survival against lethal nerve agent intoxication.

When scopolamine was administered with atropine (0.5 mg/kg), 2-PAM (25 mg/kg), and diazepam (0.72 mg/kg), guinea pig survival was increased compared to treatment without scopolamine after challenge with 5 times (5x) or 10 times the lethal dose that kills 50% of animals exposed ($LD_{50}$) to GB or VX (Koplovitz et al, 2015).

In a pilot study (Battelle Study Report 04600), guinea pigs pretreated with PB or saline were challenged with GB or soman (GD) and 1 minute later treated with atropine, 2-PAM, and midazolam. Scopolamine was administered at 1, 30, 60, or 120 minutes following challenge. For challenge at the 5x $LD_{50}$ GB level, animals receiving scopolamine at any time point and pretreated with PB did not show increased survival at 8 or 24 hours post challenge compared to those that did not receive PB. For animals challenged with 3.5x $LD_{50}$ GD, an increase in survival at 8 and 24 hours was observed in animals receiving both scopolamine and PB when administered with the current nerve agent treatment. This observed increase in survival was not dependent on the timing of scopolamine administration provided that it occurred ≤ 60 minutes post challenge. This highlights the potential benefit of rapid scopolamine administration in combination with PB pretreatment, specifically if the exposure is to a nerve agent that is more difficult to treat (ie, GD).

JPM-CBRN Medical has tested the timing of scopolamine in conjunction with the current nerve agent treatment regimen (atropine + 2-PAM followed by an anticonvulsant) with and without PB pretreatment. The results of this guinea pig challenge study demonstrated scopolamine with PB increased survival and quality of life of animals when scopolamine was administered within 1 hour of agent exposure (Battelle Study Report 08100).

### 5.2.2. Nonclinical Studies to Support Safety

The safety of Scopolamine HBT was examined in single-dose studies using Sprague-Dawley rats and rhesus macaques. In Battelle Study 100077148-0740001, Scopolamine HBT was administered as a single IM administration to adult male and female rhesus macaques at doses of 0, 0.016, 0.128, and 1.02 mg/kg with a cohort humanely terminated on Day 2 to examine acute effects and the remaining animals observed for a 14-day recovery period before humane termination. There were no test-article-related effects or changes observed in body weights, instances of redness or swelling at the site of injection, and clinical pathology (ie, coagulation, hematology, serum chemistry, and urinalysis). In addition, there were no apparent test-article-related organ weight differences or microscopic findings when high-dose-treated animals were compared to respective control animals. Lethargy was observed in 4 out of 10 high-dose (1.02 mg/kg) animals on Day 1 following dosing; however, this was resolved by Day 2. High-dose administration of Scopolamine HBT also resulted in slight decreases in food consumption. Functional observational battery assessments revealed scopolamine-induced mydriasis and loss of pupillary constriction in response to a light stimulus observed in all animals dosed at 0.128 and 1.02 mg/kg (mid and high doses, respectively). These findings were observed at

approximately 30 minutes post dose on Day 1 and persisted through Day 2. There was no evidence of continued pupil dilation during the recovery period beginning on Day 3.

Evaluation of the toxicokinetic (TK) parameters and systemic exposure suggested that there was no sex effect on the TK parameters for Scopolamine HBT as all group mean values were within 2-fold when comparing males and females with the exception of apparent clearance and apparent Vd_F for Group 2. However, these 2 parameters were artificially high due to the low concentrations at all time points for one animal. In addition, systemic exposure, as measured by both $C_{max}$ and AUC, increased in a dose-proportional manner as the dose increased and mean $T_{max}$ remained constant between the 3 dose groups (approximately 8 to 16 minutes). The mean (± SE) elimination half-life, Cl_F, and apparent Vd_F were similar for all animals with values of 1.14 ± 0.05 hr, 2370 ± 510 mL/hr/kg, and 3640 ± 580 mL/kg, respectively. Based on data generated during this study, the IM administration of Scopolamine HBT at dose levels up to 1.02 mg/kg to male and female monkeys is associated with expected pharmacological effects, such as pupillary dilation, but there were no obvious adverse effects. Under the conditions of this study, the no observed adverse effect level (NOAEL) was the highest dose evaluated, 1.02 mg/kg, as a single IM administration, which corresponds to a mean $C_{max}$ value of 413 ng/mL in males and 476 ng/mL in females and AUC values of 551 hr*ng/mL in males and 669 hr*ng/mL in females.

In Battelle Study 100077148-0740002, Scopolamine HBT was administered to adult male and female Sprague-Dawley rats via a single IM injection at doses of 0, 0.12, 1.2, and 12 mg/kg. This study was to determine the toxicity and TK of Scopolamine HBT when administered to male and female Sprague-Dawley rats via a single IM injection. A cohort of rats was humanely terminated on Day 2 to examine acute effects, and the remaining animals were observed for a 14-day recovery period before humane termination. There were no treatment-related effects noted for body weights, food consumption, clinical pathology, organ weights, or macroscopic or microscopic findings. Scopolamine HBT primarily induced mydriasis and loss of the pupillary constriction response after dosing at all levels tested. Pupil size and reactivity returned to normal by 24 hours post dose for animals at 0.12 and 1.2 mg/kg and returned to normal by Day 3 (Day 2 of recovery) for animals at 12 mg/kg. At 12 mg/kg, all animals had normal pupil reactivity when examined in the recovery period, indicating a complete recovery of all treatment-related pupillary effects. Gasping and/or labored breathing was seen for 2 rats at 0.12 mg/kg, 2 rats at 1.2 mg/kg, and 3 rats at 12 mg/kg during clinical observations or functional battery testing. This was considered treatment related. A single animal at 0.12 mg/kg was found dead after the motor activity test, and one TK animal each in the 1.2 and 12 mg/kg groups died following anesthesia and the second TK blood collection. Gasping was noted for each of these animals prior to death, and ultimately a potential effect of respiratory abnormalities could not be excluded. Scopolamine HBT treatment increased multiple measures of locomotor activity for both sexes at all dose levels on Day 1 only. This was considered to be a pharmacological effect and not adverse. No relevant findings were noted on Day 2 or when tested during the recovery period, indicating a complete reversal of the observed motor activity effects. Evaluation of the TK parameters and systemic exposure suggested that there was no sex effect on the TK parameters for scopolamine as group mean TK parameters were typically within 2-fold, for a given dose, when comparing males and females. When comparing the 3 dose groups, there were no apparent dose effects on the TK parameters. In addition, systemic exposure, as measured by both $C_{max}$ and AUC, increased in a dose-proportional manner as the dose increased, suggesting no dose effects on scopolamine typical of nonlinear kinetics. $T_{max}$ remained between approximately 2 and 8 minutes

for the 3 dose groups. The mean (± SE) elimination half-life, Cl_F, and apparent Vd_F for all groups were 0.599 ± 0.056 hr, 3770 ± 410 mL/hr/kg, and 3170 ± 350 mL/kg, respectively. In summary, a single IM administration of Scopolamine HBT resulted principally in pharmacological effects including mydriasis and loss of pupil constriction in response to light at all dose levels examined. These were completely resolved by Day 2 for animals at 0.12 and 1.2 mg/kg and within a 14-day recovery period for animals at 12 mg/kg. Pupil diameter returned to normal by Day 3 (Day 2 of recovery) for animals at 12 mg/kg, and pupillary constriction was normal during the functional observational battery testing when examined within the 14-day recovery period for animals at 12 mg/kg. Gasping and/or labored breathing was noted post dose in a few animals from all treated groups. This was considered a serious adverse effect due to its likely contribution to morbidity for individual animals at all dose levels. Morbidity was observed at each dose level, characterized by gasping/respiratory distress and subsequent mortality, and these effects were considered test article related; therefore, a NOAEL could not be determined in this study.

Since a NOAEL could not be established due to mortality, a follow-on repeat study was conducted using an increased number of animals (35 animals/sex/group) to provide adequate statistical power to determine whether the previously observed morbidity and mortality at 0.12 mg/kg was incidental or test article related. In the repeat study, Battelle Study Number 100077148-0740098, rats were administered 0, 0.10, 0.12, 1.2, and 12 mg/kg Scopolamine HBT via a single IM injection and observed for acute effects over 24 hours and recovery for 14 days. There were 3 unscheduled deaths, 1 at 1.2 mg/kg and 2 at 12 mg/kg. Two animals died after respiratory abnormalities and seizures were observed, and the third was euthanized for gasping sustained for several hours. Seizures and respiratory abnormalities were seen for a few animals at 1.2 and 12 mg/kg only and most of the animals recovered completely. The majority of findings seen after Scopolamine HBT administration were pharmacological effects and were also seen in the previous study (Battelle Study Number: 0740002). Findings were primarily mydriasis and no pupil constriction in response to light after dosing at all levels tested (0.10, 0.12, 1.2, and 12 mg/kg). This was observable from approximately 15 minutes until 1 hour post dose. Thereafter, pupil dilation and impaired constriction to light remained partially recovered at 3 hours post dose for animals at 0.10 and 0.12 mg/kg, and at 6 hours for animals at 1.2 mg/kg. Animals at 12 mg/kg still showed full pupil dilation and impaired constriction at 6 hours post dose but recovered completely by 24 hours after treatment. In summary, a single IM administration of Scopolamine HBT principally resulted in mydriasis and loss of pupil constriction in response to light at all dose levels examined. Mortality/moribundity occurred at 1.2 and 12 mg/kg. Gasping and/or noisy/audible breathing and seizures were noted post dose in a few animals from 1.2 and 12 mg/kg only, including for the animals with premature deaths. Based on the mortality, seizures, and respiratory abnormalities observed at 1.2 and 12 mg/kg, a NOAEL of 0.12 mg/kg was established in the study under the conditions of the study; however, due to inconsistencies observed at the 0.12 mg/kg dose level across several studies, the overall NOAEL for Scopolamine HBT was considered to be 0.10 mg/kg.

The rat was determined to be the most sensitive species. Exposure parameters measured at the 0.12 mg/kg dose level included maximum plasma concentrations of 87.1 and 52.9 ng/mL and AUCs of 45.8 and 47.4 ng·h/mL in males and females, respectively. Since the PK of scopolamine was linear in rats from 0.12 to 12 mg/kg; the extrapolated $C_{max}$ and AUC values for a 0.10 mg/kg dose (based on the 0.12 mg/kg TK data) are 72.6 and 44.1 ng/mL for $C_{max}$ and 38.2

and 39.5 h·ng/mL for AUC in males and females, respectively. Thus the two lowest exposure parameters are 44.1 ng/mL and 38.2 h·ng/mL. Based on clinical PK data from healthy volunteers across several studies, an IM dose of 0.005 mg/kg (0.35 mg in a 70 kg subject) is estimated to result in a mean $C_{max}$ of 0.68 ± 0.45 ng/mL and AUC of 0.94 ± 0.52 h·ng/mL based on 99% CI. Assuming exposures on the high end of the confidence interval (1.13 ng/mL and 1.46 h·ng/mL) the exposures estimates are 39.0-fold (44.1 ng/mL / 1.13 ng/mL) and 26.2-fold (38.2 h·ng/mL / 1.46 h·ng/mL) lower than exposures supported based on the NOAEL in rats; both well in excess of a 10-fold safety margin.

#### 5.2.2.1. Bioequivalence of Vital and Phytex Scopolamine HBT

For the initial development studies, the API, Scopolamine HBT USP, was obtained from Vital Laboratories Private Limited. However, on April 6, 2017, FDA investigators audited the Vital Vapi, India facility and manufacturing findings were noted. Inspectional observations (FDA 483) were issued and agency reservations conveyed on October 10, 2017. The Ology Bioservices Quality Review Board performed a risk assessment on November 2, 2017, recommending that the API procured from Vital not be used in upcoming current good manufacturing practice lots. As a direct consequence of this occurrence, a new API supplier was identified as Phytex Australia Pty Ltd of Peakhurst, Australia. Scopolamine HBT USP was obtained from Phytex for subsequent development.

Side-by-side comparison of the physical characteristics and bioequivalence of the Phytex API with the reference Vital API was performed to determine comparability. Data from these studies showed that the two batches of API (1) were considered to be chemically equivalent, (2) were pharmacokinetically equivalent in rats, and (3) initiated comparable pharmacological responses in rats. Based on these data, it can be assumed there would be no differences in the resulting pathophysiology between the two formulations; thus, the safety studies conducted using the reference API from Vital do not need to be repeated using the new API from Phytex. A full report (K05193) of the study has been submitted with the IND.

### 5.2.3. Clinical Studies

Much is known about how scopolamine is metabolized and excreted as well as the drug's effects in different CNS domains. Scopolamine pharmacodynamics (PD) include dilated pupils, flushed skin, tachycardia, hypertension, and ECG abnormalities, which are reversible and transient, decreasing with decreased exposure levels. The literature also reports a number of previous studies conducted with scopolamine in humans for neurological and PK assessments. Scopolamine is used for the prevention of motion sickness, in various gastrointestinal disorders, and as premedication before anesthesia. As previously mentioned, in the published literature from the 1940s to 1970s physicians routinely used scopolamine to treat patients at doses of 0.07-0.7 mg/kg and, in some cases, went as high as 2.86 mg/kg (200 mg total) without causing death (Eger, 1962; Elkin et al, 1965; Wangeman and Hawk, 1942).

### 5.2.4. HMR 11-013 Clinical Study

The United Kingdom's Defence Science & Technology Laboratory sponsored a randomized, double-blind, placebo-controlled, crossover, dose-escalation study to assess the safety, tolerability, PK, and PD of physostigmine salicylate and hyoscine (scopolamine) hydrobromide by continuous, IV infusion in healthy volunteers conducted by Hammersmith Medicines

Research (HMR, 2016). Data relevant to scopolamine safety from this study are described as follows. The clinical investigation demonstrated a tolerable safety profile of scopolamine in healthy volunteers up to a total dose of 797.5 µg given over 4 hours of continuous IV infusion. Doses of 1200 µg given over 10 hours were associated with psychiatric treatment emergent adverse effects in 2 subjects and lead to withdrawal (disorientation in 1 subject, and hallucinations and confusional state in the other). The 6 male volunteers administered 797.5 µg over 4 hours resulted in an average $C_{max}$ of 1.4373 ng/mL and an average $AUC_{\infty}$ of 6.749 hr*ng/mL. All 6 volunteers (100%) displayed treatment emergent adverse effects of somnolence, dizziness, and dry mouth, 5/6 blurry vision, 4/6 headache, 3/6 mood, and 1/6 coordination abnormality.

Though not a perfect comparison, HMR IV infusion data were compared to the IM injection data presented in the report by Ketchum and colleagues (1973), patients tended to exhibit the same pattern of symptoms although the IM injections were more tolerable. In the HMR study, 50% of subjects in the group receiving 0.5945 mg over 4 hours had blurred vision, whereas the $ED_{50}$ for blurred vision in the Ketchum study was a single IM dose of 0.7 mg. Also in the HMR study, reports of a confusional state were observed in 50% of the combined subjects who received either 1.0 mg or 1.2 mg over 10 hours, whereas the $ED_{50}$ for general confusion in the Ketchum report was a single IM dose of 1.4 mg. In both cases, the dose in the HMR (IV) study is about 85% of the dose in the Ketchum (IM) study. The PK of scopolamine when administered as a single IM injection of 6 µg/kg into the deltoids of 6 healthy volunteers was found to support this hypothesis. A 90% confidence interval for the $C_{max}$ and AUC was determined based on this dose and scaled proportionally to estimate the exposures in the Ketchum report. From this, similar exposure estimates can be correlated to similar symptoms as the IV groups.

In HMR study, the frequency of dry mouth increased with dose: after 300 µg administered over 10 hours and 232 µg administered over 4 hours, half of the subjects experienced dry mouth; after intermediate doses (600 µg over 10 hours), most subjects experienced dry mouth; and, after the highest doses (≥ 1000 µg over 10 hours and 797.5 µg over 4 hours), all subjects experienced dry mouth. All instances of dry mouth began during the infusion and most persisted for many hours. This report does not have a time to effect of dry mouth after starting scopolamine infusion. The effect also reversed once scopolamine infusion ended. Plasma concentrations lower than 0.4 ng/mL (232 µg over 4 hours) reduced mean salivary weight from 1.40 g at pre dose to 0.52 g at 2.5 hours. This study confirms the clinical literature on the antisialagogue property of scopolamine in humans.

Liem-Moolenaar and colleagues (2011) evaluated the PK-PD relationships of CNS effects of 0.5 mg scopolamine administered IV to 90 healthy male subjects. Results indicated that most PD responses following scopolamine administration in 85 subjects differed significantly from the placebo. As PD measures lagged behind the plasma PK profile, PK-PD relationships were modeled using an effect compartment and arbitrarily categorized according to their equilibration $t_{1/2}k_{eo}$, hysteresis measure. The $t_{1/2}k_{eo}$ for heart rate was 17 minutes; saccadic eye movements and adaptive tracking were 1 to 1.5 hours; body sway, smooth pursuit, visual analog scales, alertness, and psychedelic effects were 2.5 to 3.5 hours; and pupil size, finger tapping, and visual analog scales for feeling high were more than 8 hours. It was concluded that scopolamine affected different CNS functions in a concentration-dependent manner, which based on their distinct PK-PD characteristics seemed to reflect multiple distinct functional pathways of the cholinergic system.

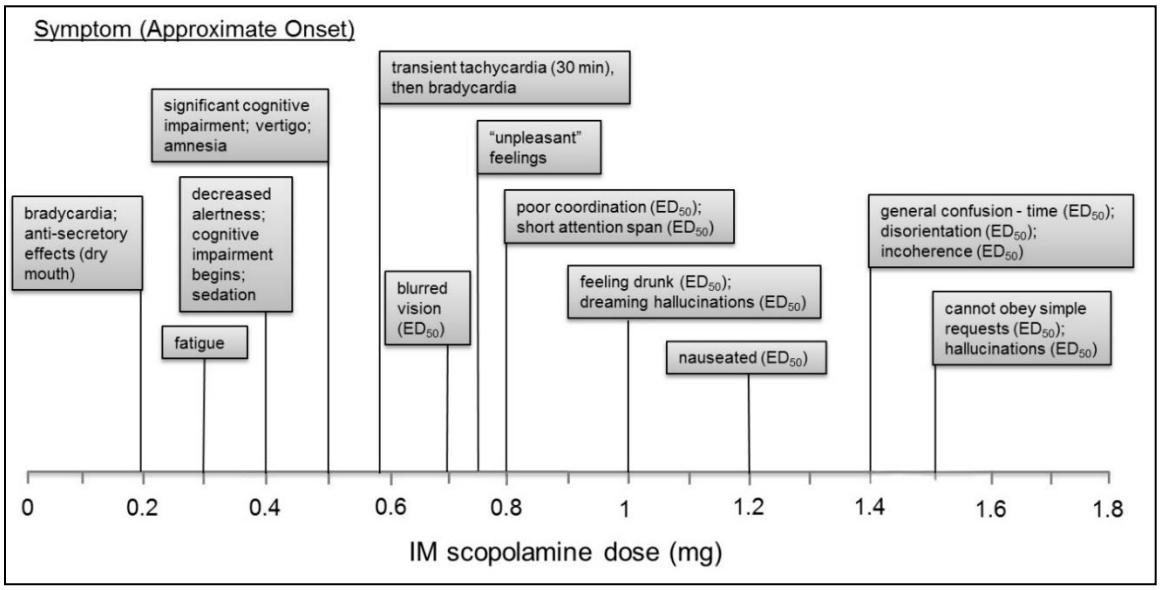
Ebert and colleagues (1998) evaluated effects of SC administered scopolamine on quantitative electroencephalogram (qEEG) and cognitive performance and correlated them with PK parameters in a randomized, double-blind, placebo-controlled, crossover study in 10 healthy male volunteers (72-88 kg). Subcutaneous administration of scopolamine produced time-dependent impairments of attention and memory, a time-dependent increase in delta power (1.25-4.5 Hz), and a decrease in fast alpha power (9.75-4.5 Hz) on qEEG compared with placebo. Maximum serum concentration of scopolamine occurred 10 to 30 minutes after drug administration. Mean peak serum concentrations (free base) were 3.27, 8.99, and 18.81 ng/mL after administration of 0.4, 0.6, and 0.8 mg scopolamine, respectively. Elimination half-life was approximately 220 minutes. These findings indicate temporary changes in qEEG and psychometric tests, and support the possible use of this testing model for impaired cognitive functions such as age-related memory disturbances.

Sannita and colleagues (1987) studied the effects of scopolamine (0.25-0.75 mg, IM) on qEEG and the neuropsychological status of healthy volunteers (63-80 kg). At a dose of 0.75 mg, subjects complained about subjective symptoms that were definitely unpleasant. The effects of this dose on the EEG and neuropsychological status did not differ significantly from those observed after a dose of 0.50 mg. Regarding dose and tolerance, 0.50 mg of scopolamine IM administered appears to be a tolerable dose for pharmaco-EEG studies.

Ghoneim and Mewaldt (1975) administered 1 mg (0.014 mg/kg) of scopolamine IM to healthy volunteers resulting in marked disorientation, confusion, and motor incoordination in addition to physical incapacitation. In a follow-up study, 70 volunteers were administered diazepam (0.3 mg/kg) and scopolamine (0.008 mg/kg) IM followed 70 minutes later by another injection of physostigmine, physostigmine plus methscopolamine, or placebo (Ghoneim and Mewaldt, 1977). The investigators found that diazepam and scopolamine did not affect recall of information that had been learned prior to drug injection; however, both drugs impaired the learning or acquisition of new information. In addition, they found that high doses of physostigmine reversed the memory deficits produced by scopolamine but not by diazepam, suggesting that scopolamine acts centrally through an anticholinergic mechanism while diazepam may act through a different system, possibly through facilitation of GABA-ergic transmission.

In a study conducted by Ketchum and colleagues (1973), healthy adult males were administered Scopolamine HBT IM from 0.005-0.024 mg/kg and evaluated for pharmacological effects and drug-drug interactions. At the highest dose, other than CNS-related pharmacological effects (ie, excitement, restlessness, irritability, hallucinations, and delirium), which are similar to the effects of other anticholinergic drugs such as atropine, no other scopolamine-related toxicities were reported. This study provided a unique dataset of the CNS effects of Scopolamine HBT, reported as effective dose for 50% of the population ($ED_{50}$) for observer ratings and subjective assessments of adverse symptoms, in a relatively large number of patients (n = 36, IM; Figure 1).

**Figure 1: Scopolamine HBT CNS Effects by Dosage (Ketchum et al, 1973)**




## 5.3. Known and Potential Risks and Benefits to Human Subjects

### 5.3.1. Risks/Discomfort to Subjects and Precautions to Minimize Risk

The following are anticipated and unexpected adverse reactions and a brief description of procedures to ameliorate risks and symptoms. All known risks and precautions described are explained in detail in the informed consent.

#### 5.3.1.1. Local Reactions

Potential risks associated with the administration of Scopolamine HBT, Injection or placebo with a syringe may include the following local effects at the site of injection:

- pain (possibly severe) and tenderness
- pruritus
- rashes
- tingling or numbness
- hematoma
- induration
- redness
- muscle stiffness
- swelling or feeling of burning
- warmth or coldness

#### 5.3.1.2. Systemic Reactions

Scopolamine HBT is more potent than atropine and has a stronger action on the iris, ciliary body, and certain secretory glands such as salivary, bronchial, and sweat (APP Pharmaceuticals, 2012). Scopolamine HBT at 0.005-0.007 mg/kg normally causes drowsiness/fatigue, dizziness, euphoria, amnesia, impairment of memory and concentration, disorientation or mental confusion, and dreamless sleep with a reduction in rapid eye movement sleep. However, the same doses occasionally cause excitement, restlessness, insomnia, delirium, hallucinations, and/or paranoia, especially in the presence of severe pain. Headaches, loss of consciousness, psychosis, seizures, and neuroleptic malignant syndrome can also occur.

Typically, dry mouth is the first notable reaction followed by dry skin. Thirst and difficulty in swallowing occur when the mouth and esophagus become sufficiently dry; chronic dry mouth also fosters dental caries. Suppression of sweating causes reflexive flushing and heat intolerance and can result in heat exhaustion or heat stroke in a hot environment; it also contributes to the hyperthermia seen in intoxication. Mydriasis frequently occurs with Scopolamine HBT, and photophobia and blurring of vision are consequences of mydriasis. Cycloplegia (which exacerbates blurred vision) occurs approximately concomitantly with mydriasis but usually higher doses are required. In susceptible persons, especially the elderly, cycloplegia may contribute to an elevation of intraocular pressure. Difficulty in urination and urinary retention may occur. Tachycardia is a common side effect. Bradycardia (at low doses), initial tachycardia followed by bradycardia (at higher doses), hypotension, and arrhythmia can occur.

Constipation, bowel stasis, nausea and vomiting may occur. In higher doses (ie, 0.011 mg/kg and above), Scopolamine HBT may cause dizziness, restlessness, tremors, fatigue, and locomotor difficulties.

Scopolamine HBT reduces salivary secretion, gastric secretion (both the volume and acid content), and also inhibits the motor activity of the stomach, duodenum, jejunum, ileum, and colon, characterized by a decrease in tone, amplitude, and frequency of peristaltic contractions.

#### 5.3.1.3. Pregnancy

Scopolamine HBT is a Category C investigational product. Risks to unborn babies are unknown at this time; pregnant females will be excluded from this study. Female subjects should not become pregnant for at least 30 days after dose administration.

#### 5.3.1.4. Lactation

Risks to nursing infants are unknown at this time; breastfeeding females will be excluded from this study.

#### 5.3.1.5. Reproductive Health

The effects of Scopolamine HBT on the reproductive health of men and women are unknown. Appropriate contraceptive measures will be required for females of childbearing potential and men whose female partners are of childbearing potential.

Females of childbearing potential must have been using adequate contraception for at least 3 months prior to drug administration and must agree to use an adequate method of contraception for at least 30 days following drug administration.

For this study, adequate contraception for females of childbearing potential is defined as a male partner using condoms with spermicide or the use of one of the following methods:

- Cervical cap or diaphragm with spermicidal gel, cream or foam,
- Hormonal contraceptives (oral, implant, injection, patch, or vaginal ring), or
- Intrauterine devices.

Females of nonchildbearing potential are also eligible, defined as a subject who is postmenopausal (continuous amenorrhea for 24 months) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or total hysterectomy). There are no contraceptive requirements for females of nonchildbearing potential.

Males with female partners of childbearing potential must agree to use adequate contraception from screening, throughout the study period, and for 30 days after drug administration. Adequate male contraception is defined as male condoms with spermicide.

#### 5.3.1.6. Venipuncture

Blood sampling carries a minimal risk of minor discomfort and the possibility of minor bruising at the site of the needle puncture, and the possibility of lightheadedness and fainting. Rarely, there is also the possibility of infection at the needle puncture site or inflammation of the vein.

#### 5.3.1.7. Allergic Reaction

As with any investigational new drug (IND) product administration and no matter what precautions are taken, there is always the risk of a serious, or even life-threatening, allergic reaction. Medical emergency equipment will be available at the study site to handle emergencies, such as anaphylaxis, angioedema, bronchospasm, and laryngospasm. A crash cart will be located in close proximity to the treatment room where subjects are residents.

#### 5.3.1.8. Unknown Risks

As with all research, there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

### 5.3.2. Alternatives to This IND Product or Study

At this time, atropine and 2-PAM are the only approved nerve agent treatments. Scopolamine HBT is being evaluated as a potential therapeutic to treat muscarinic symptoms and as an adjunct therapeutic to increase survival from lethal exposure to chemical warfare nerve agents.

An alternative is not to participate in this study.

### 5.3.3. Intended Benefit for Subjects

There is no benefit to subjects participating in this study. Payment for participation in this study is not a benefit and should not be presented as such. However, potential subjects can be told that study results may provide information required for the marketing of a new or improved product. Results of this clinical investigation will inform follow-on animal efficacy studies and a Phase 2 human clinical study of Scopolamine HBT dosing by confirming the PK upon IM administration.

PK data are key to determining the efficacious dose of Scopolamine HBT for these future studies.

### 5.3.4. Risks to the Study Personnel and the Environment

The principal risk in the clinical setting is in the handling of needles that may be contaminated and the attendant risks including hepatitis, human immunodeficiency virus (HIV), and other human pathogens. Adherence to standard operating procedures (SOPs) for working with infectious agents and universal precautions will reduce the risk of exposure.

There are no known risks to the environment other than those associated with the generation of biohazardous waste. All biohazardous waste will be disposed of as stipulated by local, state, and federal regulations and in accordance with study site SOPs.

## 5.4. Route of Administration, Dosage Regimen, Treatment Period, and Justification

Up to 240 subjects will be consented and screened for participation in the study.

This is a double-blinded, randomized, placebo-controlled, in-clinic, Phase 1, single-dose, IM, sequential dose-escalation study in healthy adults aged 18-55. Healthy volunteers will be assigned to 1 of 5 cohorts of Scopolamine HBT dosage groups: 0.005, 0.007, 0.011, 0.014, or 0.021 mg/kg, or receive the placebo, administered by IM injection to the anterior thigh. In each cohort, 6 to 9 subjects will receive active drug and 2 to 3 subjects will receive placebo. Each cohort will have at least 3 male and 3 female subjects enrolled among the first 8 subjects in the dosing group to ensure that at least 1 male subject and 1 female subject in each dosing group receive active drug. If nonextreme dose-limiting toxicities (DLTs) are observed in any of the cohorts, 4 additional subjects, 3 active and 1 placebo, may be added to each cohort.

On the first day of dosing for each cohort, 2 subjects will be dosed (1 active and 1 placebo). Upon review of the adverse event (AE) data for both subjects at 24 hours post dose (± 1 hour), the principal investigator (PI) and the medical monitor will determine if it is safe to proceed with dosing the remaining 6 of the first 8 subjects.

## 5.5. Compliance Statement

The study will be conducted according to the protocol and in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), Belmont Principles, and other applicable regulatory and DoD requirements. All identified study personnel will be trained to perform their roles and will carry out their responsibilities in accordance with ICH/GCP guidelines and clinic site SOPs.

## 5.6. Study Population

Up to 60 (30 to 45 active; 10 to 15 placebo) male and female volunteers, 18 to 55 years of age, will be enrolled in 5 dosing groups (cohorts) of 8 to 12 participants each. The actual number enrolled in the study will be determined by the safety responses noted during the study.

Each of the 5 cohorts will include at least 3 male and 3 female subjects enrolled among the first 8 subjects in the cohort to ensure that at least 1 male and 1 female subject in each dosing group receive active drug.

In addition, to assure study population diversity in an 8-subject cohort, no more than 5 subjects may be enrolled from any one of these single racial and ethnic groups: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Hispanic/Latino, or Other. If the cohort is expanded to 12 subjects, no more than 8 subjects (2/3 of the subjects) may be enrolled from any one of the above racial and ethnic groups. A specific distribution of subject gender across racial and ethnic groups is not required.

Refer to Section 12.2 for a statistical justification of the sample size.

## 5.7. Study Site

Pharmaron, a clinical pharmacology unit established in 2006, specializes in Phase 1/2a complex clinical pharmacology research. Pharmaron occupies the fifth and sixth floors of Building 1 in the University of Maryland BioPark. This location in downtown Baltimore, Maryland, is easily accessible by public transportation and/or personal vehicle, and volunteers will receive free parking in the nearby garage.

Pharmaron has the necessary experience, personnel, and technical resources to effectively conduct the study. Resources include, but are not limited to, a dedicated recruitment department; an outpatient unit for screening and follow-up visits; 96 inpatient beds with various unit configurations; an on-site, CLIA (Clinical Laboratory Improvement Amendments)-certified clinical diagnostic laboratory; and a United States Pharmacopeia (USP) 797-compliant pharmacy. Staff includes full-time physicians, physician assistants, nurse practitioners, and nursing, regulatory, quality, laboratory, pharmacy, and clinical personnel. Physicians and nursing staff are ACLS (Advanced Cardiovascular Life Support) certified.

Subjects will be recruited from the civilian population in the Baltimore, Maryland, metropolitan area and surrounding areas. Recruitment will include data mining of Pharmaron's racially diverse database, study-specific advertising, and pre-screening of potential participants.

# 6. TRIAL OBJECTIVES AND PURPOSE

## 6.1. Primary Objective

The primary objectives of this study are:

- To characterize the safety and tolerability profile of ascending doses of Scopolamine HBT administered by IM injection, and
- To characterize the PK of ascending doses of Scopolamine HBT administered by IM injection.

# 7. TRIAL DESIGN

## 7.1. Study Endpoints

The safety of Scopolamine HBT will be assessed from:

- The occurrence, intensity, and relationship of AEs from Day 1 through Day 30
- Results of clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis) at Day -1 (baseline) and Days 2, 3, and 8
- Clinically relevant changes or findings from physical examinations on Day -1 and Days 1, 3, and 8
- Vital signs and ECGs on Day -1, Days 1-3, and Day 8
- Injection site assessments:
  - Visual analog scales (VAS) for pain, pruritus, tingling, and numbness at pre dose, and 5, 10, 15, 30, and 45 minutes, at and 1, 1.5, 3, 5, 8, 12, 24, and 48 hours post dose, and at Day 8 (Appendix A)
  - Assessment of pain, tenderness, erythema, and induration at the injection site by a physician, physician assistant, or nurse to be performed immediately after the VAS (Appendix C)
- Changes in neuropsychiatric and cognitive status assessments:
  - Brief Psychiatric Rating Scale (BPRS) expended version 4.0, 24-item scale at Day -1 (baseline), at 6 (+ 2) hours post dose (timing at the discretion of the investigator or designee), 48 hours post dose (prior to discharge), and Day 8
  - Columbia-Suicide Severity Rating Scale (C-SSRS) at Day -1 (baseline) and Day 8
  - Severity of agitation or sedation using the Richmond Agitation and Sedation Scale (RASS) if AEs of general agitation or sedation are reported (Appendix D)
  - Persistent cognitive effects using the Digit Symbol Substitution Test (DSST) at Day-1 (baseline), 48 hours post dose, and Day 8 (screening DSST will serve as a practice session)

The PK of Scopolamine HBT will be determined from the following parameters calculated from plasma concentration using semi-log plots with noncompartmental analysis:

- Peak plasma concentration, $C_{max}$;
- Time of peak concentration, $T_{max}$;
- Apparent volume of distribution, $V_d\_F$;
- Elimination half-life, $t_{½}$;
- Plasma clearance, Cl_F;
- Area under the curve at last sampling point, $AUC_{last}$, and at infinity, $AUC_{\infty}$;
- Mean residence time (MRT); and

- Dose proportionality using $C_{max}$/Dose and $AUC_{\infty}$/Dose

## 7.2. Overall Study Design

The study events schedule is shown in Table 3. This is a double-blinded, randomized, placebo-controlled, in-clinic, Phase 1, single-dose, IM, sequential dose-escalation study in healthy adults aged 18-55. Healthy volunteers will be assigned to 1 of 5 cohorts of Scopolamine HBT dosage groups: 0.005, 0.007, 0.011, 0.014, or 0.021 mg/kg, or receive the placebo, administered by IM injection to the anterior thigh. In each cohort, 6 to 9 subjects will receive active drug and 2 to 3 subjects will receive placebo. Each cohort will have at least 3 male and 3 female subjects enrolled among the first 8 subjects in the dosing group to ensure that at least 1 male subject and 1 female subject in each dosing group receive active drug. If nonextreme DLTs are observed in any of the cohorts, 4 additional subjects, 3 active and 1 placebo, may be added to each cohort.

On the first day of dosing for each cohort, 2 subjects will be dosed (1 active and 1 placebo). Upon review of AE data for both subjects at 24 hours post dose (± 1 hour), the PI and the medical monitor will determine if it is safe to proceed with dosing the remaining 6 of the first 8 subjects.

New subjects will not be enrolled into the next higher dosage group until at least 8 subjects in the previous cohort have completed the Day 8 follow-up visit without the occurrence of DLTs, predefined as requiring termination of the study; the Data Safety Monitoring Board (DSMB) has reviewed data and made a dose-escalation recommendation to the sponsor; and the sponsor concurs with the DSMB recommendation. The sponsor must approve dose escalation. Dose escalation cannot occur until after sponsor approval of the DSMB recommendation and notification of the investigator(s), not at the time of the DSMB recommendation. Table 4 shows study events for pre dose through 36 hours post dose.

This Phase 1, GCP-compliant study is being performed to collect reliable PK data for Scopolamine HBT administered IM, as these are not found in the published literature, and to inform future studies. The goal of this study is to assess safety, tolerability, and PK, including the assessment of dose exposure proportionality, of Scopolamine HBT in the 5 cohorts.

**Table 3: Study Events Schedule**

| **Study Phase** | **Screening** | **Baseline**[a] | **Treatment**[a] | | | **Follow-up**[b] | | |
|---|---|---|---|---|---|---|---|---|
| **Study Day**<br><br>**Procedures** | **-30 to -2** | **-1** | **1**[c] | **2 (24 ± 1 h)** | **3 (48 ± 1 h)** | **4 (+ 2 days)** | **8 (+2 days)** | **30 (+ 7 days)** |
| Informed Consent | X | | | | | | | |
| Inclusion/Exclusion | X | X | X[d] | | | | | |
| Medical History including Demography | X | X | | | | | | |
| Physical or Brief Neurological Examination | X | X | X[e] | | X[e] | | X | |
| Serum Pregnancy Test | X | X | | | | | X | |
| Laboratory Safety Tests[f] | X | X | | X | X | | X | |
| Serology[g] | X | | | | | | | |
| Urine Drug Screen[h] | X | X | | | | | X | |
| Alcohol Breathalyzer Test | X | X | | | | | | |
| Body Weight and Height/Body Mass Index | X[i] | X[i] | | | X[i] | | X[i] | |
| Vital Signs[j] | X | X | X | X | X | | X | |
| Electrocardiogram (ECG), 12-lead (supine)[k] | X | X | X | X | X | | X | |
| **Dose Administration** | | | **X** | | | | | |
| **Pharmacokinetic Assessment** | | | **X**[l] | **X** | **X** | | | |
| Adverse Events | | | X[m] | X | X | X | X | X |
| Prior/Concomitant Medications | X | X | X | X | X | X | X | X |
| Continuous Cardiovascular Monitoring | | | X[n] | X[n] | | | | |
| Injection Site Assessment[o] | | | X | X | X | | X | |
| Injection Site: VAS[o] | | | X | X | X | | X | |
| Reminder of Study Restrictions | X | | | | X | X | X | |

**Table 3: Study Events Schedule (Continued)**

| Study Phase | Screening | Baseline[a] | Treatment[a] | | | Follow-up[b] | | |
|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-30 to -2** | **-1** | **1[c]** | **2 (24 ± 1 h)** | **3 (48 ± 1 h)** | **4 (+ 2 days)** | **8 (+2 days)** | **30 (+ 7 days)** |
| **Procedures** | | | | | | | | |
| Brief Psychiatric Rating Scale (BPRS)[p] | X | X | X | | X | | X | |
| Columbia-Suicide Severity Rating Scale (C-SSRS)[q] | X | X | | | | | X | |
| Richmond Agitation and Sedation Scale (RASS) | | | X[r] | | | | | |
| Structured Clinical Interview for DSM-5, Clinical Trial version (SCID-5-CT) | | X[s] | | | | | | |
| Digit Symbol Substitution Test[t] | X | X | | | X | | X | |

[a] Subjects will be in clinic for the baseline and treatment days. Days 2 and 3 procedures should be performed at 24 and 48 hours (± 1 hour) post dose, respectively, except for PK samples, which should be collected as close to the specified time points as possible. Refer to Table 4 for expansion of pre-dose through 36-hour post-dose activities.

[b] Day 4 and Day 30 follow-up is conducted by telephone. Day 4 follow-up may be performed on Days 4-6. Day 30 follow-up may be performed on Days 30-37. Day 8 follow-up is an in-clinic visit and may be performed on Days 8-10. Note: Subjects who withdraw/are withdrawn after receiving study drug will undergo all Day 8 follow-up procedures, including pregnancy testing for females, if possible.

[c] See Table 4 for study events occurring pre dose through 36 hours post dose.

[d] Final eligibility criteria review and completion of eligibility checklist prior to dosing.

[e] Abbreviated physical examinations with changes from Day -1 (baseline) noted; Day 1 exam is prior to dosing; brief neurological assessment at 1 hour post dosing (+30 min) to evaluate alertness/level of consciousness, orientation, ability to follow commands and coordination (refer to Section 11.1.5 and footnote [r] below).

[f] Hematology (including coagulation), serum chemistry, and urinalysis (refer to Section 11.1.9.1, Section 11.1.9.2, and Section 11.1.9.3, respectively, for specific tests). Fasting ≥ 8 hours at screening. Adequacy of venous access will be assessed and documented at screening.

[g] Hepatitis B surface antigen, hepatitis C, HIV-1/2, and syphilis testing at screening only.

[h] Urine drug screen (refer to Section 11.1.9.5 for specific tests).

[i] Body weight (kg) and height (cm; screening only) will be measured at screening and body mass index (BMI) calculated. Weight will be measured on Day -1 with BMI calculation. Day-1 weight to be used for Day 1 dose determination. Weight will be measured at Day 3 and Day 8 with no BMI calculation.

[j] Systolic and diastolic blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry will be performed after subject has been supine for at least 5 minutes. See Table 4 for vital sign time points from pre dose through 24 hours post dose.

[k] See Table 4 for time points to performing ECG (supine) from pre-dose through 24 hours post-dose.

[l] See Table 4 for PK sample collection time points from pre dose through 36 hours post dose. PK samples should be collected as close to the actual time point as possible (within the windows specified in Table 8); however, when multiple tests are scheduled at the same time, ECG and vital signs will be performed within 5 minutes prior to the time point, and injection site and AE assessments will be performed immediately after the PK blood draw. AEs identified prior to dosing will be considered part of the medical history. Urine PK samples will be collected prior to dosing (no earlier than 2 hours pre dose) and for 24 hours after dosing. All urine specimens will be pooled into 1 of 3 collection interval containers by the subject. See Table 4 for collection intervals from pre dose through 24 hours post dose. Refer to Section 9 for details.

[m] See Table 4 for AE assessment time points from pre dose through 24 hours post dose.

[n] Continuous cardiovascular monitoring of ECG (3-lead) and vital signs (blood pressure (at 5-15 min intervals), heart rate, respiration rate, and pulse oximetry) from 1 hour prior to dosing through 24 hours post dose (see Table 4 and Section 11.1.2 for details).

[o] Injection site assessments: Subject will be asked to rate the maximum intensity of pain, pruritus, tingling, and numbness using the VAS. See Table 4 for assessment time points from pre dose through 24 hours post dose. Immediately following the subjective assessment, an assessment of pain, tenderness, erythema, and induration at the injection site will be performed by a physician, physician assistant, or nurse.

[p] See Table 4 for assessment time points on Day 1. For items assessed over time (eg, items 1, 2, and 3), the period of assessment should be "over the prior week," except for the assessments performed at 6-8 and 48 hours post dose, which should be assessed "since the prior assessment."

[q] C-SSRS will be assessed at screening, Day -1 (baseline), and Day 8.

[r] RASS will be used to assess alertness/level of consciousness at 1 hour post dosing (+30 min) (see footnote [e] above), and at other times for severity if AEs of general agitation or sedation occur.

[s] SCID-5-CT will be administered at Day -1 to identify the presence of any major DSM-5 Axis I or II disorder. Note: Alternates who return for dosing on another day will not have the SCID repeated.

[t] The DSST will be administered at screening, baseline, 48 hours post dose, and Day 8 to detect any persistent cognitive impairment. The DSST will not be used to determine eligibility.

**Table 4: Study Events Schedule – Pre Dose through 36 Hours Post Dose**

| Activity/Assessment | Pre Dose | Dosing = Time 0 | Minutes Post-dose | | | | | | | Hours Post-dose | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2 | 5 | 10 | 15 | 20 | 30 | 45 | 1 | 1.5 | 2 | 3 | 4 | 5 | 8 | 12 | 24 | 36 |
| ECG | X | | | X | X | X | | X | X | X | X | | X | | X | X | X | X | |
| Vital Signs | X | | | X | X | X | | X | X | X | X | | X | | X | X | X | X | |
| Abbreviated Physical or Brief Neurological Exam[a] | X | | | | | | | | | X | | | | | | | | | |
| Injection Site: VAS[b] | X | | | X | X | X | | X | X | X | X | | X | | X | X | X | X | |
| Injection Site: Physician, Physician Assistant or Nurse | X | | | X | X | X | | X | X | X | X | | X | | X | X | X | X | |
| BPRS[c] | | | | | | | | | | | | | | | 6 | | | | |
| C-SSRS | | | | | | | | | | | | | | | | | | | |
| RASS[d] | | | At 1 hour post-dosing (+30 min) and as needed to assess severity only if adverse events of general agitation or sedation occur | | | | | | | | | | | | | | | | |
| Final Eligibility | X | | | | | | | | | | | | | | | | | | |
| Eligibility Checklist | X | | | | | | | | | | | | | | | | | | |
| Randomization | X | | | | | | | | | | | | | | | | | | |
| Urine PK Samples[e] | X | | 0-4 h | | | | | | | | | | | 4-12 h | | | 12-24 h | | |
| Blood PK Samples | X | | X | X | X | X | X | X | | X | | X | | X | | X | X | X | X |
| Safety Lab Tests | | | | | | | | | | | | | | | | | | X | |
| Adverse Events | X | | | X | X | X | | X | X | X | X | | X | | X | X | X | X | |
| Concomitant Medications | X | | | X | X | X | | X | X | X | X | | X | | X | X | X | X | |
| Continuous Cardiovascular Monitoring | Begin | | ECG (3-lead) and vital signs (blood pressure (5-15 min intervals), heart rate, respiration rate, and pulse oximetry)(see Section 11.1.2 for details) → | | | | | | | | | | | | | | | End | |

**Error! Reference source not found.** Abbreviated physical exam at pre-dose; brief neurological assessment at 1 hour post dosing (+30 min) to assess alertness, orientation, ability to follow commands and coordination (refer to Section 11.1.5 and footnote [d] below).

[b] If the PI or designee determines a subject is incapable of providing valid responses on the VAS due to the neuropsychiatric effects of Scopolamine HBT, the reason(s) why the VAS assessment(s) could not be done will be documented by time point in the source.

[c] BPRS will be performed at 6 (+ 2) hours post dose. The + 2-hour window is provided to allow the investigator some discretion should the assessment need to be delayed or cannot be performed. The timing may be dependent on the emergence and severity of neuropsychiatric symptoms. The reason(s) why the BPRS was delayed or could not be done will be documented in the source.

[d] RASS will be employed as part of the brief neurological assessment at 1 hour post dosing (+30 min) to assess alertness/level of consciousness, and at other times if adverse events of agitation or sedation occur.

[e] Record the time and estimated volume of individual voids from pre dose through 24 hours post dose. This information will assist in the assessment of urine output and hydration, and will subsequently be used to calculate the total volume of urine pooled for each PK collection interval. Refer to Section 9.1.1.3 for details.

## 7.3. Measures Taken to Minimize/Avoid Bias

### 7.3.1. Randomization

Subjects who are eligible for the study following the clinical assessments will be randomly assigned to receive Scopolamine HBT, Injection or placebo. The randomization will be balanced by using randomly permuted blocks. Randomization will be performed by coded list, provided by the study statistician, to which the pharmacist and pharmacy team will be unblinded. The pharmacist and/or pharmacy technician will prepare and document the blinded drug to be administered. The person administering the study drug will be blinded. In each cohort, 6 to 9 subjects will receive active drug and 2 to 3 subjects will receive placebo. Each cohort will have at least 3 male and 3 female subjects enrolled among the first 8 subjects in the cohort to ensure that at least 1 male subject and 1 female subject in each dosing group receive active drug.

### 7.3.2. Blinding

This study is double blinded. The study drugs (active and placebo) are filled in amber vials with a 1.2-mL fill volume, are clear and colorless liquids, and labeling is identical. The pharmacist and/or pharmacy technician at the clinical site will fill syringes for each study subject on dosing days to maintain the blind of the study staff. However, once a subject has been dosed with Scopolamine HBT, Injection, the study staff, including the investigators, will likely become unblinded as the CNS effects of Scopolamine HBT will be evident in the subjects, especially at the higher concentrations. Nevertheless, every effort should be made to maintain the blind, even at the higher concentrations. Study participants who become unblinded will be encouraged to maintain the confidentiality of the blind from other study staff if possible, as well as other study participants.

### 7.3.3. Unblinding

Unblinding of a subject should be requested only in the case of medical emergency or in the event of a serious medical condition when, in the opinion of the PI, knowledge of the investigational product is essential for the clinical management or welfare of the subject.

Whenever possible before the blind is broken, the pharmacovigilance (PVG) physician will be consulted to discuss the rationale for the request. When a request for unblinding cannot be made prior to providing emergency treatment, the PI may unblind the subject’s treatment.

The clinical site pharmacist will have access to individual randomization codes and can perform emergency unblinding in the event of a medical emergency or serious medical condition upon approval of the PI.

**Contact Information for Emergency Unblinding:**

Any emergency unblinding of individual treatment assignments and the reason for unblinding will be clearly specified by the PI in the source documentation and reported to the [redacted] immediately (within 24 hours) via the telephone number or safety e-mail address below:

[redacted]

## 7.4. Investigational Product

Table 5 shows a summary description of the investigational product, Scopolamine HBT, Injection and the comparator product, Scopolamine Hydrobromide Placebo.

**Table 5: Investigational Products**

| Product Name | Scopolamine Hydrobromide Trihydrate, Injection | Scopolamine Hydrobromide Placebo |
|---|---|---|
| **Dosage Form** | Liquid | Liquid |
| **Unit Dose** | 0.8 or 2.0 mg/mL | 0 mg/mL |
| **Route of Administration** | IM | IM |
| **Physical Description** | Amber vial with a clear, colorless liquid of 0.8 mg/mL and 2.0 mg/mL Scopolamine HBT in 1 mM citrate buffer; 150 mM sodium chloride; and adjusted to pH 3.0 ± 0.1 with hydrochloric acid and sodium hydroxide | Amber vial with a clear, colorless liquid of citrate buffer |
| **Manufacturer** | Ology Bioservices, Inc | Ology Bioservices, Inc |
| **Lot Number** | TBD | TBD |
| **Product Indication** | Scopolamine is being developed as a muscarinic receptor antagonist (SCTID 734696004) indicated for cholinergic crisis (SCTID 8563000). Scopolamine is a muscarinic antagonist indicated for temporary relief or improvement of muscarinic effects | Comparator product |

For this study, the treatments to be administered are 0.005, 0.007, 0.011, 0.014, and 0.021 mg/kg of Scopolamine HBT, depending on cohort assignment, or placebo as a one-time dose to study subjects via IM injection in the anterior thigh muscle. In each cohort, 6 to 9 subjects will receive active drug and 2 to 3 subjects will receive placebo. Each cohort will have at least 3 male and 3 female subjects enrolled among the first 8 subjects in the cohort to ensure that at least 1 male subject and 1 female subject in each cohort receive active drug.

### 7.4.1. Investigational Product Packaging and Labeling

The investigational product, Scopolamine HBT, Injection (0.8 mg/mL and 2.0 mg/mL, equivalent to 0.55 mg and 1.38 mg Scopolamine, respectively) and Scopolamine HBT placebo are packaged in amber, 2-mL Type I USP glass vials with 13-mm sterile serum stoppers and sealed with 13-mm blue, red, or white flip-off crimp seals, respectively. Each single-use vial contains 1.2 mL (± 0.2 mL).

Scopolamine HBT, Injection product components are as follows:

- Scopolamine HBT, USP
- Sterile Water for Injection
- Sodium Chloride
- Citric Acid Anhydrous
- Sodium Citrate Dihydrate
- 0.1 N Hydrochloric Acid

The Scopolamine HBT Placebo product components are as follows:

- Sterile Water for Injection
- Sodium Chloride
- Citric Acid Anhydrous
- Sodium Citrate Dihydrate
- 0.1 N Hydrochloric Acid

Examples of the investigational product vial and carton labels (0.8 mg/mL, 2.0 mg/mL, and placebo) are shown in Figure 2. Please note the label text has been enlarged for legibility purposes; the actual label dimensions and font will be smaller.

**Figure 2: Scopolamine HBT Injection 0.8 mg/mL and 2.0 mg/mL and Placebo Labels**

| 0.8 mg/mL Vial Label | 0.8 mg/mL Carton Label |
|---|---|
| **Scopolamine Hydrobromide Trihydrate, Injection, 0.8 mg/mL (0.55 mg of Scopolamine)**<br>Item Number: 10-0003825 Lot No.: XXXXX<br>Contents: 1.2 mL ± 0.12 mL Storage: 15-25°C<br>Protect from light DOM: DDMMMYYYY<br>CAUTION: New Drug-Limited by Federal (or United States) Law to Investigational Use<br>Manufactured by Ology Bioservices for the Surgeon General – Department of the Army | **Scopolamine Hydrobromide Trihydrate, Injection, 0.8 mg/mL (0.55 mg of Scopolamine)**<br>Item Number: 10-0003825 Lot No.: XXXXX<br>Storage: 15-25°C _____ vials in Carton<br>CAUTION: New Drug-Limited by Federal (or United States) Law to Investigational Use<br>Manufactured by Ology Bioservices, Alachua, FL for the Surgeon General – Department of the Army<br>State of Florida Prescription Drug Manufacturing License. 20313 |

| 2.0 mg/mL Vial Label |
|---|
| **Scopolamine Hydrobromide Trihydrate, Injection, 2.0 mg/mL (1.38 mg of Scopolamine)**<br>Item Number: 10-0003826 Lot No.: XXXXX<br>Contents: 1.2 mL ± 0.12 mL Storage: 15-25°C<br>Protect from light DOM: DDMMMYYYY<br>CAUTION: New Drug-Limited by Federal (or United States) Law to Investigational Use<br>Manufactured by Ology Bioservices for the Surgeon General – Department of the Army |

| 2.0 mg/mL Carton Label |
|---|
| **Scopolamine Hydrobromide Trihydrate, Injection, 2.0 mg/mL (1.38 mg of Scopolamine)**<br>Item Number: 10-0003826 Lot No.: XXXXX<br>Storage: 15-25°C _____ vials in Carton<br>CAUTION: New Drug-Limited by Federal (or United States) Law to Investigational Use<br>Manufactured by Ology Bioservices, Alachua, FL for the Surgeon General – Department of the Army<br>State of Florida Prescription Drug Manufacturing License. 20313 |

| Placebo Vial Label |
|---|
| **Scopolamine Hydrobromide Trihydrate Placebo**<br>Item Number: 10-0003824 Lot No.: XXXXX<br>Contents: 1.2 mL ± 0.12 mL Storage: 15-25°C<br>Protect from light DOM: DDMMMYYYY<br>CAUTION: New Drug-Limited by Federal (or United States) Law to Investigational Use<br>Manufactured by Ology Bioservices for the Surgeon General – Department of the Army |

| Placebo Carton Label |
|---|
| **Scopolamine Hydrobromide Trihydrate Placebo**<br>Item Number: 10-0003824 Lot No.: XXXXX<br>Storage: 15-25°C _____ vials in Carton<br>CAUTION: New Drug-Limited by Federal (or United States) Law to Investigational Use<br>Manufactured by Ology Bioservices, Alachua, FL for the Surgeon General – Department of the Army<br>State of Florida Prescription Drug Manufacturing License. 20313 |

### 7.4.2. Investigational Product Storage

All investigational products will be stored at 15°C-25°C and protected from light.

### 7.4.3. Investigational Product Preparation

No dilutions are required prior to administration of the investigational products. Dosing volumes are calculated by subject weight and drawn directly from the vial. For complete details of dose preparation and administration, refer to the pharmacy manual.

**Note:** For determining the clinical dosing calculations, the concentration of Scopolamine HBT (Scopolamine Hydrobromide Trihydrate, Injection 0.8 mg/mL and Scopolamine Hydrobromide Trihydrate, Injection 2.0 mg/mL) should be used.

### 7.4.4. Investigational Product Accountability

The sponsor's representative is responsible for distributing the investigational product to the study site. The sponsor's representative has delegated drug accountability responsibility for this product to the PI at the study site; however, the sponsor's representative has ultimate responsibility for product accountability. After the investigational product is distributed, the PI is responsible for and will maintain logs of investigational product receipt, storage, reconstitution, accountability by subject, and investigational product remaining before final disposition. The PI may delegate, in writing, this responsibility to another individual, but the PI is ultimately responsible for the investigational product and its proper storage upon receipt at the study site until it is transferred back to the sponsor's representative or designee or is destroyed, as directed

by the sponsor's representative. At the study site, the logs will be maintained in the product accountability files within the pharmacy.

All unused or partially used investigational product and empty vials will be destroyed or returned to the responsible party, as directed by the sponsor's representative at the end of the study, and as stipulated by local, state, and federal regulations.

## 7.5. Duration of Subject Participation

Study subject participation includes 4 days and 3 nights for the in-clinic phase. Subjects will be administered drug product on Day 1 and released on Day 3. Study staff will follow up with each subject via telephone on Day 4. Subjects will return for an in-clinic visit on Day 8, and study staff will follow up with each subject via telephone on Day 30. Total duration of subject participation in the study, including the screening period and the 30-day, post-dose telephone follow-up, may be up to 9 weeks.

## 7.6. Dose-adjustment Criteria

New subjects will not be enrolled into the next higher dosage group until at least 8 subjects in the previous cohort have completed the Day 8 follow-up visit without the occurrence of DLTs, and the DSMB has made a recommendation to the sponsor regarding dose escalation. The sponsor must approve the dose escalation and notify the investigator(s) before any new subjects can be enrolled. The occurrence of any DLT(s) would result in the immediate discontinuation of dosing and study enrollment, pending a review of study data by the PI, research monitor, PVG physician, the DSMB, and the sponsor.

### 7.6.1. Safety Criteria for Dose Adjustment or Stopping Doses

For the purposes of determining continued dosing within a cohort or dose escalation to a subsequent planned cohort, stopping rules are based on the emergence of DLTs. Nonextreme and extreme DLTs will be considered related AEs/serious adverse events (SAEs) and will be recorded/reported as such.

Dosing of study drug and study enrollment will be halted (temporarily or permanently) as follows:

- Occurrence of any extreme DLT (dosing and enrollment to be halted immediately; PI, research monitor, PVG physician, and DSMB will review and make a recommendation to the sponsor, which will determine if dosing and enrollment may continue);
- Emergence of a specified number (see Table 6) of nonextreme DLTs among subjects in a particular dosage group (DSMB will review to determine whether dosing and enrollment may continue);
- Occurrence of an SAE not already designated as an extreme or nonextreme DLT, determined to be possibly, probably, or definitely related to the investigational product; dosing and enrollment to be halted immediately until the DSMB has completed a safety review; and

- Sponsor, DSMB, or PI's clinical judgment warrants stopping based on ongoing review of the safety profile.

The maximum tolerated dose will be the highest dose at which none of the following has been observed:

- An extreme DLT in any one subject;
- A nonextreme DLT in 2 of the first 4 subjects or in 3 subjects at any time; and
- Any SAE, not already categorized as a DLT that is considered to be possibly related, probably related, or definitely related to the study drug.

#### 7.6.1.1. Extreme Dose-Limiting Toxicities

In the event that any one of the following extreme DLTs is evident, the PI is to discontinue dosing study drug and study enrollment immediately, pending review by the PI, research monitor, PVG physician, and DSMB. These extreme DLTs include:

- Respiratory
  - Prolonged apnea or respiratory distress where intubation is required
- Neuropsychiatric
  - Presence of convulsions or seizure-like activity
  - Neuropsychiatric symptoms (eg, delirium, paranoia, and/or hallucinations) requiring treatment with physostigmine or other medication(s) and, in the opinion of the investigator, did not adequately respond to treatment
- Cardiovascular
  - Cardiac arrest
  - Clinically significant hypotension that requires IV fluids or vasopressors
  - Cardiac arrhythmias
    - $1^0$ AV block (if the PR interval becomes ≥ 280 milliseconds)
    - If the QRS duration increases by more than 25% from the pre-dose measurement and is > 140 msec
    - QTc (Fridericia) is > 500 msec and increase of QTc of 60 msec from baseline
    - AV block (2nd degree, 3rd degree)
    - Bundle branch block
    - Bigeminy or trigeminy associated with hypotension
    - Atrial fibrillation or atrial flutter

#### 7.6.1.2. Nonextreme Dose-Limiting Toxicities

Nonextreme DLTs are AEs that do not meet the criteria for extreme DLTs but are serious conditions that require immediate medical attention and monitoring. The incidence and severity of these events will be used to determine whether (1) the total cohort size will be increased from 8 to 12 and (2) the need to suspend dosing until the DSMB has completed a safety review and made a recommendation to the sponsor (Table 6). Nonextreme DLTs include:

- Respiratory
  - Spontaneous respiratory rate < 8 or > 25 breaths per minute, with oxygen saturation less than 90%, which cannot be explained by agitation or other behavioral symptoms and that does not respond immediately to oxygen supplementation via nasal cannula or face mask but for which there is recovery without sequelae prior to the need for intubation
  - Dyspnea at rest
  - Symptomatic bronchospasm
- Neuropsychiatric
  - Neuropsychiatric symptoms (eg, delirium, paranoia, and/or hallucinations) requiring treatment with physostigmine or other medication(s) and, in the opinion of the investigator, responded adequately to treatment
  - Persistent neuropsychiatric symptoms, defined as a score of 4 or higher on any one item or a total score of 40 or higher on the BPRS assessment at the 48-hour, post-dose evaluation
  - Paresthesia that interferes with any activity
  - Athetoid movement
- Cardiac
  - Hypertension, which cannot be explained by agitation or other behavioral symptoms, requiring antihypertensive medication
  - Cardiac arrhythmias or changes that are deemed clinically significant but do not cause the subject to be hemodynamically unstable
  - QTc is > 450 msec for males or >470 msec for females and has increased > 60 msec from baseline
  - Supraventricular tachycardia alone without hemodynamic compromise
  - Bigeminy or trigeminy not associated with hypotension
- Renal
  - Increase of serum creatinine by ≥ 0.3 mg/dL (≥ 26.4 µmol/L) or increase to ≥ 150% from baseline or urine output < 0.5 mL/kg/hour for > 6 hours
- Injection Site Reaction

- Any reaction determined to be severe, as defined by the FDA's guidance for injection site reactions (Appendix B).

#### 7.6.1.3. Serious Adverse Events

In the event of an SAE that has not already been designated as a DLT but has been determined by the PI, research monitor, and PVG physician to be possibly, probably, or definitely related to the study drug, the PI is to discontinue dosing study drug and study enrollment immediately until the DSMB has completed a safety review and made a recommendation to the sponsor. The sponsor must concur with the recommendation and notify the investigator(s) before enrollment can be resumed (see Section 11.2.2 for SAE criteria.)

**Table 6: Progression of Dosing Related to Dose-Limiting Toxicity Events**

| Dose-Limiting Toxicity | Number of Subjects | Action | Follow-up |
|---|---|---|---|
| Extreme DLT | 1 | Dosing and enrollment halted | PI, research monitor, PVG physician, and DSMB review; sponsor determines whether trial should continue |
| Nonextreme DLT | 1 of first 4 in a cohort (or 2 in the first 8) | Dosing halted | PI, research monitor, PVG physician, and DSMB review; sponsor determines whether to increase cohort size from 8 to 12 |
| | 2 of the first 4 in a cohort (or 3 total) | Dosing and enrollment halted | PI, research monitor, PVG physician, and DSMB review; sponsor determines whether trial should continue |
| SAE Not Already Designated as a DLT (except unrelated) | 1 | Dosing and enrollment halted | DSMB to make recommendation to sponsor whether trial should continue |

In summary, if any one subject has an extreme DLT, enrollment and dosing will be halted pending review by the PI, research monitor, PVG physician, and DSMB. In making its determination, the DSMB will review all relevant data and obtain additional input as needed. As a guideline to the DSMB, it is suggested that if a nonextreme DLT is observed that the DSMB consider an increase in the cohort sample size from 8 to 12 if one nonextreme DLT is observed in the first 4 subjects or 1 or 2 nonextreme DLTs are observed in the first 8 subjects and that enrollment be halted if nonextreme DLTs are observed in 2 of the first 4 subjects in a cohort or in a total of 3 subjects at any time.

If an SAE occurs at any time that is not already designated as an extreme or nonextreme DLT, unless it is reported as **unrelated** to the study drug, enrollment and dosing will also be halted pending review by the DSMB. While the presence of any specific AE may not necessarily halt enrollment, careful reporting of these events is necessary. After thorough review by the DSMB and consultation with the investigators, a decision will be made by the sponsor whether to proceed with the dosing escalation.

If any of the above events occurs, administration of investigational product will be discontinued until a thorough review of the events is undertaken by the investigators, local Institutional Review Board (IRB) and/or [redacted], research monitor, and/or sponsor's safety office [redacted]. The study may be resumed with the concurrence of the research monitor, PVG physician, sponsor's representative, PI, and the FDA.

### 7.6.2. Pharmacokinetic Criteria for Dose Adjustment or Stopping Doses

A goal of this clinical study is to determine the PK parameters of Scopolamine HBT after IM administration. The predicted efficacious $C_{max}$, based on limited nonclinical studies, is

16-18 ng/mL. At the end of each cohort, the PI, DSMB, and sponsor will evaluate the safety outcomes and PK data associated with the Scopolamine HBT dosing for that group.

#### 7.6.3. Study Termination Criteria

The PI, research monitor, sponsor's representative, the local IRB, and/or the [redacted], DSMB, or the FDA may stop or suspend the use of this product at any time.

## 7.7. Trial Treatment Randomization Assignments

Randomization tables, containing the dosing assignments (active or placebo) for up to 12 subjects in each cohort, will be provided by the statistician to the unblinded pharmacist at the clinical site. The tables will be maintained in the secure, limited-access pharmacy and accessed by unblinded pharmacy staff only. Refer to Section 7.3.3 for unblinding procedures.

## 7.8. Identification of Data to Be Recorded on the Case Report Forms

The electronic case report form (eCRF) data will be transcribed from source documentation. No source data will be recorded directly in the eCRF (ie, without prior written or electronic record of data). The transcribed data will be consistent with the source documents or the discrepancies will be explained.

For more information on data handling, refer to Section 16.

# 8. SELECTION AND WITHDRAWAL OF SUBJECTS

## Recruitment of Subjects

Refer to Section 5.6 for a detailed description of the subject population.

Subjects will be recruited from the civilian population in the Baltimore, Maryland, metropolitan area and surrounding areas via advertisement, word-of-mouth, the Internet to include social media, and other media methods. Interested subjects who meet the prescreening criteria will be scheduled for an in-clinic visit. Any questions asked of subjects during the recruitment process (prior to informed consent) will respect the privacy of their protected health information and will have been reviewed and approved by the IRB.

After reviewing the informed consent form, subjects will have the opportunity to ask any questions related to the study. All subjects who wish to enroll in the study must provide written informed consent. After providing written consent, subjects will be given an IRB-approved ICF assessment test to verify each subject has a clear understanding of the study and study procedures. Subjects will have three attempts to pass the test. Incorrect responses will be discussed with the subject between attempts.

## Eligibility Screening

Each subject must meet all inclusion and no exclusion criteria. The PI or designee will make the final decision on eligibility. Only eligible subjects will be given the investigational product. Before any study-related procedures are conducted, a written, signed informed consent form (ICF) must be obtained and the subject assigned a subject number. Study material, including

ICFs, will be available only in English. AEs will be recorded from the time of investigational product administration on Day 1. AEs reported or observed after the screening visit but prior to administration should be added to the subject's medical history. After informed consent is obtained, screening procedures can begin. Subjects who are prescreened on the telephone but who do not sign an ICF will not be assigned a subject number. The investigator or designee will maintain a subject master list of every subject who has signed an ICF. A copy of the list should be retained in the investigator's study files.

Informed consent must be obtained and an IRB-approved ICF signed and dated by the subject before any study-related procedures can be performed. After obtaining informed consent, the following will be completed:

- A complete medical history with demography including date of birth, gender, race and/or ethnicity, any surgeries/hospitalizations (including childbirth), past or current treatments, past and current illnesses (including psychiatric history), and other information, as specified on the eCRF. Females of childbearing potential will be asked to list their current contraceptive method(s) for comparison with the requirements of this study (refer to Section 5.3.1.5).
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry, will be measured after the subject has been supine for at least 5 minutes.
- Weight (kg) and height (cm; screening only) will be recorded and body mass index (BMI) calculated.
- A complete physical examination including the review of all major systems including general appearance; eyes, ears, nose, and throat (EENT); chest/respiratory; heart/cardiovascular; abdomen/gastrointestinal; lymph nodes/spleen; genitourinary (prostate exam is not required); musculoskeletal (including assessment of upper leg muscle tissue (ie, adequacy for IM injection); skin; neurological; and hepatic
- Prior/concomitant medications review
- ECG (12-lead) will be performed after the subject has been supine for at least 5 minutes.
- BPRS will be administered by a psychologist or trained clinician
- C-SSRS (Baseline/Screening version) and DSST will be administered by study staff
- Blood samples (fasting ≥ 8 hours) for hematology, coagulation, and serum chemistry (refer to Section 11.1.9.1 and Section 11.1.9.2 for specific tests)
- Venous access assessment (performed during blood collection)
- Serum pregnancy test (all females regardless of childbearing potential)
- Blood sample for serology testing (hepatitis B surface antigen, hepatitis C, HIV-1/2, and syphilis)
- Urine samples for urinalysis (refer to Section 11.1.9.3 for specific tests)
- Urine drug screen (refer to Section 11.1.9.5 for specific tests)

- Alcohol breathalyzer test
- Assessment of inclusion/exclusion criteria
- Reminder of study restrictions

Subjects will be notified at the time of the screening visit if any completed tests will exclude them from the study. However, because not all test results will be known by the end of the screening visit, subjects will be contacted by telephone a few days after their screening visit and told whether they qualify for the study and any reason for exclusion. Any subjects who have been found to be positive (reactive) for hepatitis B surface antigen, hepatitis C, HIV-1/2, or syphilis will be asked to come to the study site to discuss the results of the screening test, and results will be reported to the local health department. These subjects will be provided counseling and referrals to the appropriate healthcare providers.

## 8.1. Subject Inclusion Criteria

A subject must meet all of the following criteria to be included in the study:

1. Male or female, 18 to 55 years of age, inclusive, at the time of drug administration
2. Without clinically significant abnormities on physical examination at screening or prior to drug administration
3. Generally healthy, as determined by medical history review, physical examination, and laboratory testing at screening and prior to drug administration
4. Must have a BMI of ≥ 19.0 and ≤ 30.0, and weight range of 55.0 to 85.0 kg at screening or prior to drug administration
5. Must have adequate venous access and sufficient upper leg muscle tissue for drug administration
6. If female, the subject must be nonpregnant and nonbreastfeeding, and have a negative serum pregnancy test at screening and prior to drug administration
7. If female of childbearing potential, the subject must have been using adequate contraception (as defined in Section 5.3.1.5), for at least 3 months prior to drug administration and must agree to use an adequate method of contraception for at least 30 days following drug administration
8. Females of nonchildbearing potential are also eligible, defined as a subject who is postmenopausal (continuous amenorrhea for 24 months) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or total hysterectomy)
9. A male with a female partner of childbearing potential must agree to use a barrier method of contraception (defined as condoms with spermicide) for at least 30 days following drug administration
10. If male, must not have past diagnoses of benign prostatic hypertrophy or urinary tract obstruction and must not have on screening history/review of systems symptoms suggestive of urinary tract obstruction (eg, urinary hesitancy, urgency, frequency, or nocturia)

11. Nonsmoker/tobacco/nicotine product (including e-cigarettes) user within 3 months of first dosing and must have a total lifetime exposure to cigarettes of < 15 pack-years
12. No evidence of significant neuropsychiatric disorders based on the BPRS at screening and prior to drug administration, which is defined as having a global score of ≤ 25 with no score higher than 2 on any one item, with the exception of a score of 1 (ie, Not Present) to disorientation, hallucinatory behavior, and suspiciousness (ie, paranoia)
13. No evidence of suicidal ideation or behavior at screening and prior to drug administration, which is defined as having a global score of 0 on the C-SSRS
14. Ability to read, speak, and comprehend English and a willingness to sign informed consent

## 8.2. Subject Exclusion Criteria

A subject meeting any of the following criteria will be excluded from the study:

1. Received any other investigational drug within 30 days prior to drug administration
2. Known allergies to any component of the study drug, other belladonna alkaloids, or the recovery medications (physostigmine, atropine, or benzodiazepines [diazepam or lorazepam])
3. History of migraine headaches or seizures
4. History of psychosis or psychotic episodes
5. Clinically relevant abnormal physical findings (including vital signs) as determined by the investigator at screening or prior to drug administration that could interfere with the objectives of the study or the safety of the subject
6. Has ongoing drug abuse/dependence (including alcohol), recent history (over the past 5 years) of treatment for alcohol or drug abuse, or a current positive alcohol breathalyzer test or current positive urine test for drugs of abuse (as defined in Section 11.1.9.5) at screening or prior to drug administration
7. Has consumed Seville orange (bitter orange), grapefruit, grapefruit juice, other grapefruit-containing products, or starfruit within 7 days prior to dosing
8. Has consumed caffeine or other xanthine-containing products within 7 days prior to dosing
9. Has any specified laboratory values (eg, hematology, serum chemistry, and urinalysis) outside of the normal range for age and sex and deemed clinically significant by the investigator within 30 days before drug administration
10. Has positive (reactive) test results for hepatitis B surface antigen, hepatitis C, syphilis, HIV-1, or HIV-2
11. Has narrow-angle glaucoma or high intraocular pressures in either or both eyes
12. Has pyloric obstruction or urinary bladder neck obstruction
13. Has impaired liver or kidney functions

14. Clinically relevant ECG abnormalities on any 12-lead ECG obtained at screening or prior to dosing
15. ECG with a PR interval ≥ 200 msec at screening or prior to dosing
16. ECG with QRS duration > 120 msec at screening or prior to dosing
17. ECG RR interval > 1500 msec at screening or prior to dosing
18. ECG with a QTc interval > 450 msec for males or 470 msec for females (QT interval corrected with Fridericia correction (QTcF)) at screening or prior to dosing
19. Systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg at screening or prior to dosing
20. Systolic blood pressure < 90 mm Hg and/or diastolic blood pressure < 50 mm Hg at screening or prior to dosing
21. Currently taking or has taken other antimuscarinic drugs such as phenothiazines, tricyclic antidepressants, antihistamines (including meclizine), meperidine, or other anticholinergics that have weak antimuscarinic activity or that cause drowsiness, including antidepressants, benzodiazepines, alcohol, sedatives (used to treat insomnia), pain relievers, anxiety medicines, and muscle relaxants within 72 hours prior to dosing
22. Has taken, within 14 days of planned dosing, any prescription or nonprescription medication (including home remedies, herbal supplements, or nutritional supplements) unless the PI/subinvestigator, in consultation with the medical monitor, provides a statement justifying that the medication taken will not impact the results of this study (with rare exceptions taking prescriptions drugs will be grounds for exclusion)
23. History of major DSM-5 Axis I or II disorder, or evidence of such disorder at Day -1 as determined via the Structured Clinical Interview for DSM-5, customized Clinical Trials version (SCID-5-CT)
24. Has any skin condition, scars, or tattoos that would interfere with injection of study drug
25. Donated > 480 mL of blood within 8 weeks of drug administration
26. Any other reason, in the opinion of the investigator, the subject should not participate in the study

## 8.3. Subject Withdrawal Criteria

Each subject may withdraw consent at any time during the study without penalty. If a subject wishes to withdraw after dosing, he or she will be encouraged to continue with the follow-up procedures (to the extent possible) for safety reasons. If the subject agrees to continue, he or she will not be considered withdrawn from the study. If the subject refuses all post-dosing follow-up, he or she will be considered withdrawn.

Counseling about the subject's health will be provided if he or she decides to discontinue participation in the study. Medical advice regarding the best interests of the subject will be provided.

The PI may discontinue a subject's activity without the subject's consent if any of these criteria is met:

- A subject fails to comply with study procedures
- A subject's safety or health may be compromised by further participation

### 8.3.1. When and How to Withdraw Subjects

If a subject withdraws, the investigator or designee will make a reasonable effort to determine the reason for the withdrawal from the study and to complete termination procedures as described in Section 8.3.4. Telephone calls, registered letters, and e-mail correspondence are considered reasonable effort (ie, at least 3 attempts to contact the subject by phone and/or e-mail followed by a registered letter if there is no response to the phone/e-mail attempts). A subject may be withdrawn for an AE or SAE resulting in a safety concern or for noncompliance with protocol requirements. When a subject withdraws due to an AE or is withdrawn by the PI due to an AE, the sponsor's safety office [redacted] must be notified within 24 hours of identification [redacted]. Investigators must follow specific policy regarding the timely reporting of AEs and SAEs to the local IRB (Section 11.5.1.2). In all cases, the PI or designee will make a reasonable effort to complete study termination procedures.

If a subject meets withdrawal conditions for a concomitant medication violation or noncompliance, this should clearly be stated in the source document and the study termination eCRF.

### 8.3.2. Data Collected for Withdrawn Subjects

All data collected up to the time of withdrawal will be reported. The end-of-study eCRF will be completed with the reason for withdrawal specified.

### 8.3.3. Replacement of Subjects

Subjects who withdraw from the study prior to receiving study drug will be replaced. Replacements can be of a different sex than the replaced subject as long as 3 females and 3 males are included in the cohort. Subject numbers should not be reused.

### 8.3.4. Follow-up for Withdrawn Subjects

Subjects who withdraw/are withdrawn after receiving study drug will undergo all Day 8 follow-up procedures, if possible.

# 9. TREATMENT OF SUBJECTS

## 9.1. Dose Administration and Follow-up Periods/Study Visits

### 9.1.1. Treatment

Subjects will be assigned to 1 of 5 cohorts/dosage groups (Scopolamine HBT: 0.005, 0.007, 0.011, 0.014, or 0.021 mg/kg or placebo). The investigational product will be administered by

IM injection to the anterior thigh. In each cohort, 6 to 9 subjects will receive active drug and 2 to 3 subjects will receive placebo. Each cohort will have at least 3 male and 3 female subjects enrolled among the first 8 subjects in the dosing group to ensure that at least 1 male subject and 1 female subject in each dosing group receive active drug. If nonextreme DLTs are observed in any of the cohorts, 4 additional subjects, 3 active and 1 placebo, may be added to each cohort.

On the first day of dosing for each cohort, 2 subjects will be dosed (1 active and 1 placebo). Upon review of the AE data for both subjects at 24 hours post dose (± 1 hour), the PI and the medical monitor will determine if it is safe to proceed with dosing the remaining 6 of the first 8 subjects.

New subjects will not be enrolled into the next higher dosage group until at least 8 subjects in the previous cohort have completed the study Day 8 follow-up visit without the occurrence of DLTs, predefined as requiring termination of the study; the DSMB has made a recommendation to the sponsor; and the sponsor concurs with the DSMB recommendation regarding dose escalation following a review of study data. The sponsor must approve dose escalation. Dose escalation cannot occur until after sponsor approval of DSMB recommendations and notification of the investigator(s), not at the time of the DSMB recommendation.

All subjects participating in the study will be monitored closely throughout the in-clinic phase of the study. Staff will be available with the appropriate expertise to assess and manage neuropsychiatric problems that may arise. The PI and/or physician designee will be in the treatment room during dosing and for 4 hours post dose. A psychiatrist will be available by phone to consult with the investigator throughout the study. At the investigator's request, the psychiatrist will come to the clinic to evaluate a subject. A crash cart, which will include specific drugs to treat Scopolamine HBT effects (eg, physostigmine and diazepam), will be in the immediate area where subjects are residents.

During the in-clinic phase, continuous cardiovascular monitoring of ECG (3-lead) and vital signs (blood pressure (at 5-15 minute intervals), heart rate, respiration rate, and pulse oximetry) will be performed starting at 1 hour prior to and for 24 hours following Scopolamine HBT or placebo administration (refer to Section 11.1.2 for details). In addition, 12-lead ECG and vital signs (including body temperature), clinical laboratory tests, neuropsychiatric status, and injection site assessments will be performed at specified times through 48 hours post dose. Subjects will be monitored for AEs continuously during the inpatient phase, and AEs will be documented as they are reported. A cardiologist will be available to consult with the investigator, as needed, throughout the study.

#### 9.1.1.1. Informed Consent for Screening Procedures

All applicants will be given copies of the following before participating in any screening procedures:

- The study ICF
- Site-required informed consents and agreements for Health Insurance Portability and Accountability Act (HIPAA) Authorization, HIV testing, hepatitis testing, medical release authorization, database authorization, and subject conduct

- [redacted]Form 60-R (Volunteer Registry Data Sheet) to be completed for each volunteer to document participation in a US Army research trial

Regulatory agencies have issued regulations to provide protection for human subjects in clinical investigations and to describe the general requirements for informed consent. The ICF shall contain all of the elements of informed consent specified in the Code of Federal Regulations (21 CFR 50.25). Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. Regulations require that investigators permit the sponsor, sponsor's representative, and appropriate regulatory agencies to conduct inspections and review records pertaining to clinical investigations. The delegation of investigator responsibilities including obtaining informed consent must be documented in the study records.

Prior to giving a copy of the [redacted] Form 60-R (Volunteer Registry Data Sheet) to any volunteer, the clinical site will complete Part A, Investigator Information. The volunteer will be asked to complete Part B, Volunteer Information, during the screening visit. The form will then be filed in the subject binder, pending determination of eligibility. When a subject is enrolled into the study (dosed), the investigator/designee will complete Part C, Additional Information. At the end of the study, a copy of the completed form for each enrolled subject will be sent to the [redacted].

#### 9.1.1.2. Study Day -1 (One Day Prior to Dosing)

If subjects qualify, they will be asked to return to the clinic on the day prior to dosing to check in for the in-clinic stay. Subjects will be given standardized meals during their in-clinic stay. Subjects with dietary restrictions will receive the appropriate food substitutes to ensure proper nutrition and to prevent potential biological material from interfering with the PK evaluation of the blood samples.

All eligible subjects are considered alternates until they are dosed. Eligible subjects not dosed on Day 1 will be considered for the next dosing day. Subjects who are administered the study drug will remain at the study site for 48 hours after dosing (until the morning of Day 3).

On the day prior to dosing (ie, Day -1), the following will be performed:

- Physical examination of all major systems including general appearance, EENT, chest/respiratory, heart/cardiovascular, abdomen/gastrointestinal, lymph nodes/spleen, genitourinary, musculoskeletal, skin, neurological, and hepatic
- Medical history update: AEs identified/reported prior to dosing will be added to the medical history
- 12-lead ECG after the subject has been supine for at least 5 minutes
- Vital signs (including systolic and diastolic blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry) collected after the subject has been resting in a supine position for at least 5 minutes
- Weight measurement and BMI confirmation; Day -1 weight will be used for dose determination on Day 1

- Clinical laboratory tests to include hematology and coagulation (Section 11.1.9.1) and serum chemistry (Section 11.1.9.2)
- Urinalysis (Section 11.1.9.3)
- Serum pregnancy test (Section 11.1.9.4) for all females regardless of childbearing potential
- Urine drug screen (Section 11.1.9.5)
- Alcohol breathalyzer test
- SCID-5-CT (customized) will be administered by a psychologist to determine whether there is evidence of major DSM-5 Axis I or II disorder

  Note: Subjects who are designated alternates and readmitted on another day will not have the SCID repeated (see Section 11.1.6).
- BPRS will be administered by a psychologist or trained clinician
- C-SSRS (Since Last Visit version) and DSST will be administered by study staff
- Prior/concomitant medications/treatments
- Review of inclusion/exclusion criteria

Starting the evening of Day -1, all subjects will be required to fast (water and clear liquids only) overnight (for at least 8 hours) prior to injection of the study drug; all liquids will be stopped 1 hour prior to dosing. Subjects will be permitted to begin consuming liquids at 1 hour after dosing and to eat solid foods as long as they are clinically well.

Adequate hydration should be ensured by having subjects drink at least 1000 mL of water within 24 hours prior to administration of study drug and 1000 mL within 24 hours following the administration of study drug. The consumption of this (total) 2000 mL of water should be recorded in the source documentation.

Note: Except for the SCID-5-CT (as noted above), the Day-1 assessments will be repeated on alternates who are readmitted on another day. Repeat testing includes the BPRS, C-SSRS, DSST, weight measurement and BMI calculation, and all other Day-1 assessments with the following possible exception. If an alternate does not leave the clinic, the serum pregnancy, urine drug screen, and alcohol breathalyzer tests do not have to be repeated.

#### 9.1.1.3. Drug Administration (Study Day 1 at 0 Hour)

One hour prior to dosing, subjects will be placed on continuous cardiovascular monitoring that includes ECG (3-5 lead) and vital signs (blood pressure, heart rate, respiration rate, and pulse oximetry). Within 2 hours prior to IM injection, the following will be performed:

- Physical examination (abbreviated)
- 12-lead ECG will be obtained after the subject has been supine for at least 5 minutes
- Vital signs ( blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry) will be measured after the subject has been supine for at least 5 minutes
- Blood sample for pre-dose PK

- Urine sample for urine PK assessment. The pre-dose urine PK specimen will be collected no earlier than 2 hours before dosing. If a second pre-dose specimen is collected, then it will become the pre-dose specimen, and the first pre-dose specimen will be disposed of.
- Baseline injection site assessment for pain, pruritus, tingling, and numbness (subject rating using VAS)
- Baseline injection site assessment for pain, tenderness, erythema, and induration by physician, physician assistant, or nurse
- Concomitant medications and AEs: AEs identified/reported prior to dosing will be added to the medical history
- Inclusion/exclusion criteria will be confirmed and eligibility checklist signed by a physician investigator
- Randomization form will be signed by a physician investigator and sent to the pharmacy. Weight measurement from Day -1 will be used for dose determination.
- The unblinded study pharmacist or pharmacy technician will remove a predetermined dosing volume from a single-use vial (refer to the Pharmacy Manual).
- Subjects will be administered the drug product formulation at the assigned dosage of Scopolamine HBT, Injection or placebo IM to the anterior thigh using an appropriate size syringe.
- Administration of individual injections will be performed by a blinded study staff member (licensed medical personnel). Injections should be completed within 20 seconds.
- The PI and/or physician designee must be in the treatment room during drug administration.
- Regardless of the injection duration, blood sampling for PK analyses will begin with Time 0 at the completion of administration of the injection. Time 0 for the purpose of timing pre-injection procedures and post-dosing data collection is defined as the time the needle is removed at the completion of study drug injection. Both the injection start and end times should be recorded in the source documentation by hours, minutes, and seconds.

Table 7 summarizes treatment groups and dose levels.

**Table 7: Treatment Groups and Dose Levels**

| Cohort | Scopolamine HBT Target Dose (mg/kg) |
|---|---|
| 1 | 0.005 |
| 2 | 0.007 |
| 3 | 0.011 |
| 4 | 0.014 |
| 5 | 0.021 |

In addition to continuous cardiovascular monitoring during the 24 hours following administration of study drug, subjects will undergo the following procedures:

- Subjective injection site assessments: a physician, physician assistant, or nurse will ask the subject to rate the intensity of pain, pruritus, tingling, and numbness using the VAS at 5, 10, 15, 30, and 45 minutes and 1, 1.5, 3, 5, 8, and 12 hours after dosing.
- A physician, physician assistant, or nurse will assess the injection site for presence and severity of pain, tenderness, erythema, and induration at 5, 10, 15, 30, and 45 minutes and 1, 1.5, 3, 5, 8, and 12 hours after dosing. This assessment will follow the subjective assessment at each time point.
- 12-lead ECG (supine for at least 5 minutes) will be obtained at 5, 10, 15, 30, and 45 minutes and 1, 1.5, 3, 5, 8, and 12 hours after dosing.
- Vital signs (blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry) will be recorded at 5, 10, 15, 30, and 45 minutes and 1, 1.5, 3, 5, 8, and 12 hours after dosing after the subject has been supine for at least 5 minutes.
- Brief neurological assessment will be performed at 1 hour post dosing (+30 min), after all of the other 1 hour post dosing activities have been completed. Alertness/level of consciousness, orientation, ability to follow commands and coordination will be documented (refer to Section 11.1.5).
- Neuropsychiatric assessments: BPRS will be administered by a psychologist or trained clinician at 6 (+ 2) hours post dose. The + 2 hour window is provided to allow the investigator some discretion should he or she determine the assessment needs to be delayed. The timing may be dependent on the emergence and severity of neuropsychiatric symptoms.
- The RASS will be performed as part of the brief neurological assessment (refer to Section 11.1.5) and at other times if needed to assess agitation and sedation (refer to Section 11.1.6).
- AE assessment: The subject will be observed for any clinical adverse signs and asked “how are you feeling?” at 5, 10, 15, 30, and 45 minutes and 1, 1.5, 3, 5, 8, and 12 hours after dosing. All AEs will be documented.

- Concomitant medication assessments will be performed at 5, 10, 15, 30, and 45 minutes and 1, 1.5, 3, 5, 8, and 12 hours after dosing. All medications taken will be documented.
- Urine for separation and identification of urinary Scopolamine HBT and its metabolites will be collected ("clean catch") from each subject at intervals of 0-4, 4-12, and 12-24 hours post dose. The pre-dose specimen will be collected no earlier than 2 hours before dosing. If a second pre-dose specimen is collected, then it will become the pre-dose specimen and the first pre-dose specimen will be disposed of. The post-dosing urine specimens for each subject will be collected as often as voiding occurs for 24 hours, and these specimens will be pooled into 1 of 3 collection interval containers by subject (ie, 0-4–hour interval, 4-12–hour interval, or 12-24–hour interval).

  Note: Prior to pooling the urine, the time and estimated volume of each individual void will be recorded to assist in the assessment of urine output and hydration. The time and volume information will also be used to calculate the total volume of the three collection intervals (see additional instructions following Table 8).
- Blood samples will be obtained for PK assessments prior to dosing and at 2, 5, 10, 15, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 36, and 48 hours post dose. For purposes of scheduling the post-dose blood collection target time point, the time of dosing will be the time immediately after administration of the injection for that subject. Approximately 10 mL of blood will be collected for each PK sample.

The acceptable deviations before and after the target sample collection time are shown in Table 8. Time points from 2 minutes to, and including, 2 hours will be collected within ± 5% of the target time point. Time points greater than 2 hours through, and including, 48 hours will be collected within ± 15 minutes of the target time point.

**Table 8: Pharmacokinetic Blood Sample Deviation Windows**

| Target Time Point | Acceptable Sample Collection Time Point Range | |
|---|---|---|
| | **Low-End Range** | **High-End Range** |
| 2 min | 1 min 50 s | 2 min 10 s |
| 5 min | 4 min 40 s | 5 min 20 s |
| 10 min | 9 min 30 s | 10 min 30 s |
| 15 min | 14 min 15 s | 15 min 45 s |
| 20 min | 19 min | 21 min |
| 30 min | 28 min 30 s | 31 min 30 s |
| 1 h (60 min) | 57 min | 63 min |
| 2 h (120 min) | 114 min | 126 min |
| 4 h (240 min) | 228 min | 252 min |
| 8 h (480 min) | 465 min | 495 min |

| Target Time Point | Acceptable Sample Collection Time Point Range | |
|---|---|---|
| | **Low-End Range** | **High-End Range** |
| 12 h (720 min) | 705 min | 735 min |
| 24 h (1440 min) | 1425 min | 1455 min |
| 36 h (2160 min) | 2145 min | 2175 min |
| 48 h (2880 min) | 2865 min | 2895 min |

The value recorded as the actual time after dosing that a given blood sample is collected will be based on when blood first appears in the tube (as opposed to the time after the mid or entire blood sample is collected). By using the "first appearance" of blood as the guideline for determining the actual collection time, the documented sample collection time points will be more consistent among technicians. In addition, good agreement between target and actual collection time points will be achieved since the time needed to collect the full sample will not need to be taken into consideration prior to the collection.

Approximately 10 mL of whole blood per collection time point per subject will be collected into individual lithium heparin, vacutainer-type tubes that are appropriately and uniquely labeled. Immediately upon collection, the tubes will be mixed well (eg, hand rocked or rocker table) to ensure the whole blood and anticoagulant are sufficiently mixed to prevent clotting. After mixing, the blood samples will be placed in wet ice until centrifuged for separation and collection of plasma, which will occur within 1 hour after the blood sample collection time. Each plasma sample will be split into 2 aliquots, a primary aliquot "A" of approximately 3 mL of plasma and a backup aliquot "B" containing all remaining plasma. The plasma will be stored in wet ice until transferred to a freezer ($\leq$ -20°C) where it will remain until removed for shipment. The samples must remain frozen during storage and shipment.

For urine samples for separation and measurement of metabolites, "clean catch" urine specimens will be collected. For each subject, the date and time of collection, as well as the estimated volume of each void, will be recorded from pre-dose through 24 hours post dose. Note: The time and volume of each void will be used for the assessment of urine output and hydration and do not need to be entered into the CRF. However, the time and volume of each individual void will also be used to calculate the total volume for each of the urine PK collection intervals, and the pre-dose and collection interval volumes will be entered into the CRF for use in the analysis of metabolites.

The urine specimens will be stored in a polyethylene, screw-cap container by interval and subject and, immediately upon collection, will be stored refrigerated. The urine will be mixed well before transferring two 10-mL aliquots into 2 separate 15-mL screw-cap, polypropylene conical-shaped vials, a primary aliquot "A" and a backup aliquot "B." The urine specimen container caps will be taped in place to prevent leakage and stored upright in a freezer at approximately $\leq$ -20°C until shipped for analysis. The specimens must remain frozen during storage and shipment.

Samples will be shipped by traceable carrier for analysis to:

Battelle Memorial Institute
[redacted]

651 W. Fifth Avenue
Columbus, Ohio 43201-2693
[redacted]

### 9.1.2. Follow-up

After receiving the study drug or placebo on Day 1, subjects will be monitored in clinic for 48 hours (until the morning of Day 3). Follow-up for AEs will be made via telephone on Days 4 and 30, and via an in-clinic visit on Day 8. Additional monitoring and assessments may be performed if, in the judgment of the investigator, they are warranted for the safety of the subject. AEs will be followed until resolution/stabilization.

The following is the schedule of post-dose events.

#### 9.1.2.1. Study Day 2 (24 Hours ± 1 Hour)

Continuous cardiovascular monitoring of ECGs (3-5 lead) and vital signs will continue until 24 hours post dose on Day 2. At 24 hours post dose (± 1 hour for all assessments except PK sample collection), the following will be performed:

- 12-lead ECG will be obtained after the subject has been supine for at least 5 minutes.
- Vital signs (blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry) will be measured after the subject has been supine for at least 5 minutes.
- Blood samples will be obtained for PK assessments at 24 and 36 hours post dose (± 15 minutes) using a 10-mL, lithium heparin vacutainer-type tube; mixed well; and immediately placed on wet ice.
- Blood samples will be obtained for serum chemistry, hematology, and coagulation (approximately 16 mL).
- Urine sample will be obtained for urinalysis.
- End of urine PK sample collection for the 12-24–hour interval.
- RASS (if needed)
- Medications taken since dosing will be recorded.
- AEs experienced by the subject will be recorded.
- Pain, pruritus, tingling, and numbness at injection site will be rated by the subject using the VAS.
- Pain, tenderness, erythema, and induration at injection site will be assessed by a physician, physician assistant, or nurse.

#### 9.1.2.2. Study Day 3 (48 Hours ± 1 Hour; Discharge)

Subjects will be asked to remain at the study site until the 48-hour assessment on Day 3. At 48 hours post dose (± 1 hour for all assessments except PK sample collection), the following will be performed before subjects are released from the in-clinic portion of the study:

- Physical examination (abbreviated)
- Body weight will be measured.
- 12-lead ECG will be obtained after the subject has been supine for at least 5 minutes.
- Vital signs (blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry) will be measured after the subject has been supine for at least 5 minutes.
- Blood sample will be obtained for PK assessment at 48 hours post dose (± 15 minutes) using a 10-mL, lithium-heparin vacutainer-type tube; mixed well; and immediately placed on wet ice.
- Blood samples will be obtained for serum chemistry, hematology, and coagulation (approximately 16 mL).
- Urine sample will be obtained for urinalysis.
- Medications taken since the 24-hour assessment will be recorded.
- AEs experienced by the subject since the 24-hour assessment or present at the physical examination will be recorded.
- Pain, pruritus, tingling, and numbness at injection site will be rated by the subject using the VAS.
- Pain, tenderness, erythema, and induration at injection site will be assessed by a physician, physician assistant, or nurse.
- BPRS will be performed by a psychologist or trained clinician
- DSST will be administered by study staff.
- Male subjects with a female partner of childbearing potential will be reminded that they must use a barrier form of birth control (defined as condoms with spermicide) for 30 days after receipt of study drug.
- Female subjects of childbearing potential will be reminded to continue their current form of birth control for 30 days after receipt of study drug.
- Subjects will be reminded of all study restrictions, including to refrain from donating blood or other blood components for 8 weeks after completion of the study.
- Days 4, 8, and 30 follow-up appointments will be scheduled.

#### 9.1.2.3. Study Day 4 (+ 2 Days; Telephone Follow-up)

Subjects will be contacted via telephone on Day 4. During this call, the following will be performed:

- Medications taken since the Day 3 assessment will be recorded.

- AEs experienced by subject since Day 3 will be recorded, and subjects will be queried regarding AEs that were persisting at discharge (Day 3).
- Male subjects with a female partner of childbearing potential will be reminded that they must use a barrier form of birth control (defined as condoms with spermicide) for 30 days after receipt of study drug.
- Female subjects of childbearing potential will be reminded to continue their current form of birth control for 30 days after receipt of study drug.
- Subjects will be reminded of all study restrictions, including to refrain from donating blood or other blood components for 8 weeks after completion of the study.
- Subjects will be reminded of the Day 8 follow-up visit.

#### 9.1.2.4. Study Day 8 (+ 2 Days; Follow-up Visit)

Subjects will be required to return to the study site on Day 8. At this visit the following will be performed:

- Complete physical examination including general appearance, EENT, chest/respiratory, heart/cardiovascular, abdomen/gastrointestinal, lymph nodes/spleen, genitourinary, musculoskeletal, skin, neurological and hepatic.
- Body weight will be measured.
- 12-lead ECG will be obtained after the subject has been supine for at least 5 minutes.
- Vital signs (blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry) will be measured after the subject has been supine for at least 5 minutes.
- BPRS will be administered by a psychologist or trained clinician.
- C-SSRS (Since Last Visit) and DSST will be administered by study staff.
- Blood samples will be obtained for serum chemistry, hematology, and coagulation (approximately 16 mL).
- Serum pregnancy test for all females regardless of childbearing potential.
- Urine samples will be obtained for drug screening and urinalysis.
- Medications taken since the Day 4 assessment will be recorded.
- AEs experienced by the subject since Day 4 or present at the physical examination will be recorded; subjects will be queried regarding any AEs that were persisting at Day 4.
- Pain, pruritus, tingling, and numbness at injection site will be rated by the subject using the VAS.
- Pain, tenderness, erythema, and induration at injection site will be assessed by a physician, physician assistant, or nurse.

- Male subjects with a female partner of childbearing potential will be reminded again that they must use a barrier form of birth control (defined as condoms with spermicide) for 30 days after receipt of study drug.
- Female subjects of childbearing potential will be reminded to continue their current form of birth control for 30 days after receipt of study drug.
- Subjects will be reminded of all study restrictions, including to refrain from donating blood or other blood components for 8 weeks after completion of the study.
- Subjects will be reminded of the study Day 30 telephone follow-up.

If a subject does not return for his or her Day 8 assessment, a reasonable effort will be made to contact this subject and schedule another visit (ie, at least 3 attempts to contact the subject by telephone and/or e-mail, followed by a registered letter if there is no response to the telephone/e-mail attempts).

#### 9.1.2.5. Study Day 30 (+ 7 Days; Telephone Follow-up)

Subjects will be contacted via telephone on Day 30 (+ 7 days). During this call, the following will be performed:

- Medications taken since the Day 8 assessment will be recorded.
- AEs experienced by the subject since the Day 8 visit will be recorded; subjects will be queried regarding any AEs that were persisting at the Day 8 visit.
- Subjects will asked whether they have donated blood or other blood components since the Day 8 visit and will be reminded to refrain from donating blood or other blood components for 8 weeks after completion of the study.
- Male subjects with a female partner of childbearing potential and female subjects of childbearing potential will be asked whether they continued to use birth control through 30 days after receipt of study drug.
- Females will be asked if they have become pregnant since the Day 8 visit and to notify the PI if they later discover that they have become pregnant within the previous 30-day period.

### 9.1.3. Biological Samples

Samples collected under this protocol will be used to conduct protocol-related safety and PK evaluations. No genetic testing will be performed on these samples.

Plasma for PK evaluations will be stored at Battelle Memorial Institute in a quality-controlled environment. Transport and storage of these biological samples will be handled according to institute SOPs. Any study for the future use of these biological samples will have IRB/Human Use Committee approval. In addition, a subject may decide at any point to withdraw consent for the future use of his or her samples. Should a subject withdraw consent for the use of his or her samples, the samples will be destroyed according to institute SOPs.

## 9.2. Rescue Medications and Concomitant Medications

This protocol places restrictions on all medication use during the study including the use of rescue medications. The PI will recommend medication for symptomatic relief, if necessary.

### 9.2.1. Rescue Medications

Physostigmine should be used as needed to reverse the effects of scopolamine in any instance where there is a concern that the symptoms may result in harm (self-induced or otherwise) to the subject or a concern that the subject may pose a risk to others. The following circumstances would indicate a need for physostigmine treatment:

- A rating of severe (ie, score of 5 or greater) on any of the following 5 items on the BPRS:
  - #4 Suicidality
  - #5 Hostility
  - #10 Hallucinations
  - #11 Unusual Thought Content Item
  - #12 Bizarre Behavior
- Severe agitation (score of 3 or greater) on the RASS

A physician investigator must make the determination to administer physostigmine. Administration may be performed by a physician, physician assistant, or nurse; however, a physician must be present to evaluate the response and determine the need for additional treatment.

If used, a physician, physician assistant, or nurse will administer 0.5 mg physostigmine IV over 1 minute, which may be repeated every 5 minutes until a total dose of 2 mg has been given (ie, a total of 4 doses). Atropine and a benzodiazepine (eg, diazepam or lorazepam) should be at the bedside in case of bradycardia or seizures. If the subject is not already on continuous cardiovascular monitoring when physostigmine is administered, the subject will be placed on continuous monitoring of ECG (3-lead) and vital signs (refer to Section 11.1.2 for details). The effects of physostigmine last only 1-2 hours; therefore, a repeat dose may be necessary.

If there is an adequate response to treatment with physostigmine, the event should be considered a nonextreme DLT; however, if there is not an adequate response to treatment, the event should be considered an extreme DLT (refer to Section 7.6.1 for further detail regarding procedures related to DLTs).

When a physician investigator determines that physostigmine administration is necessary, the following will be recorded in the subject's record to ensure adequate information is available for evaluation of the associated DLTs by the PI, research monitor, DSMB members, and the sponsor's PVG physician:

- Study day and date (to be recorded by study staff)
- Circumstance(s) indicating the need for treatment (see above) and physician investigator's authorization to administer physostigmine

- For each dose given, the following will be recorded:
  - Dose number (eg, 1-4), dose administered (mg; see above), and start and stop times of administration (to be recorded by staff member administering the dose)
  - Response to treatment, and reason(s) for administering an additional physostigmine dose, if needed
- Total number of physostigmine doses (1-4) and total dose (mg) administered
- Whether the overall response to physostigmine was adequate or inadequate (refer to Section 7.6.1 for further detail regarding procedures related to DLTs)
- Any other information deemed relevant by the physician investigator authorizing the treatment and by the physician(s) providing follow up care
- If any other treatment (eg, atropine and/or benzodiazepine) is provided, the drug name, reason(s) for administration, dose and time given, and route of administration will be recorded for each.

### 9.2.2. Concomitant Medications and Prohibitions

Concomitant medications should be collected from the screening visit through 30 days after the investigational product is administered.

All prescription drugs and nonprescription medication (excluding hormonal contraceptives) are prohibited within 14 days of planned dosing unless the PI/subinvestigator, in consultation with the medical monitor, provides a statement justifying that the medication taken will not impact the results of this study (with rare exceptions taking prescriptions drugs will be grounds for exclusion).

Smoking and tobacco and nicotine-containing (including e-cigarettes) products are prohibited within 3 months of dosing and throughout the study period; subjects must also have a total lifetime exposure to cigarettes of < 15 pack-years.

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Alcohol: 72 hours before dosing and throughout the period of sample collection
- Seville orange (bitter orange), grapefruit, grapefruit juice, grapefruit-containing products, or starfruit: 7 days before dosing and through 48 hours post dose
- Any prescription or nonprescription medication (including home remedies, herbal supplements, or nutritional supplements) 14 days before dosing (see above for rare exceptions)
- Any food 8 hours prior to dosing (water and clear liquids only up to 1 hour pre dose) and 1 hour post injection
- Liquids 1 hour before and 1 hour after dosing
- Caffeine or other xanthine-containing products: 7 days before dosing and throughout the period of PK sample collection

- Strenuous physical activity of any kind is prohibited starting 48 hours prior to admission on Day -1 and until after the Day 8 visit is completed.

## 9.3. Procedures for Monitoring Subject Compliance

Subject compliance for investigational product administration is not an issue because the study materials will be administered by study staff. Subjects will be reminded to return to the clinic for the Day 8 follow-up. In addition, attempts to reschedule missed appointments, within allowable day ranges, will be made.

# 10. PHARMACOKINETIC SAMPLE COLLECTION

Blood samples (approximately 10 mL each draw) will be obtained for PK assessments within 2 hours prior to dosing and at 2, 5, 10, 15, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 36, and 48 hours post dose. These sampling points should allow for adequate and full characterization of the Scopolamine HBT PK profile.

Scopolamine HBT PK assessments will include determination of the following parameters: observed $C_{max}$ and $T_{max}$, $V_d\_F$, $t_{½}$, $Cl\_F$, $AUC_{last}$, $AUC_{\infty}$, $C_{max}$/Dose, MRT, and $AUC_{\infty}$/Dose. Samples will be analyzed for Scopolamine HBT at Battelle in Columbus, Ohio, using a high-performance liquid chromatography-tandem mass spectrometry method validated with respect to accuracy, precision, linearity, sensitivity, and specificity. Samples will be shipped as agreed upon by the site and Battelle. It is expected that plasma samples will be analyzed and concentration time profiles constructed for each cohort to assist the DSMB in making dose-escalation recommendations. After analysis, samples will be stored until study report approval and permission from the sponsor has been received to dispose or ship the samples to a sponsor-designated location.

The backup ("B") PK samples will be stored at the investigator site at -20°C or lower until directed to ship by Battelle. These samples will be shipped to Battelle's Chemistry Technical Center in Columbus, Ohio, for confirmatory testing, if applicable. Approximately 2 mL of plasma for each PK assessment will be transferred to a long-term storage facility where samples will be stored at -20°C or lower for at least 2 years after FDA approval of the last indication for this product. These backup samples may be used for additional or repeat PK testing, as required.

## 10.1. Clinical Blood Sample Collection

Blood samples (approximately 24 mL at screening and 16 mL on subsequent days) will be obtained for clinical laboratory testing. Serum chemistry and hematology (including coagulation) tests will be performed at screening, baseline (Day-1), at 24 and 48 hours post dose, and at Day 8 (refer to Section 11.1.9.1 and Section 11.1.9.2 for specific tests). Serum pregnancy testing will be performed at screening, Day-1, and at Day 8 (refer to Section 11.1.9.4). Serology will be performed at screening only (refer to Section 11.1.9.5 for specific tests).

The total blood volume to be collected in this study is approximately 250 mL. This includes blood collection for PK assessments and clinical laboratory testing but does not include additional clinical testing deemed necessary by the investigator or designee for subject safety.

## 10.2. Urine Sample Collection

Urine samples will be obtained for urinalysis at screening, baseline (Day-1), at 24 and 48 hours post dose, and at Day 8 (refer to Section 11.1.9.3 for specific tests). Urine drug screening will be performed on an aliquot of the urine sample at screening, baseline (Day-1), and at Day 8 (refer to Section 11.1.8 for specific tests).

Urine will also be obtained for separation and identification of urinary Scopolamine HBT and its metabolites. For urine samples for separation and measurement of metabolites, a "clean catch" urine specimen will be collected. For each subject, the date and time of collection, as well as the estimated volume of each void, will be recorded from pre-dose through 24 hours post dose. The urine specimens will be stored in a polyethylene, screw-cap container by interval and subject and, immediately upon collection, will be stored refrigerated. The urine will be mixed well before transferring two 10-mL aliquots into 2 separate 15-mL screw-cap, polypropylene, conical-shaped vials. Refer to Section 9.1.1.3 and the PK Sample Instruction Manual for collection and processing details.

## 10.3. Sample Analysis

The plasma concentration time profiles for Scopolamine HBT will be subject to a model-independent PK analysis (noncompartmental analysis) using WinNonlin software by a Battelle Memorial Institute pharmacokineticist to estimate the PK parameters shown in Table 9. PK and safety ± will undergo PD analysis and evaluation.

**Table 9: Pharmacokinetic Parameters**

| Parameter | Description |
|---|---|
| $C_{max}$ | Maximum measured plasma time concentration over the time span specified |
| $T_{max}$ | Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, $T_{max}$ is defined as the first time point with this value. |
| Apparent Volume of Distribution (Vz/F) | Volume of distribution during terminal phase calculated as $Dose/AUC_{\infty}/\lambda z$ |
| $t_{½}$ | Apparent first-order terminal elimination half-life will be calculated as $0.693/k_e$. |
| Apparent Clearance (Cl_F) | Volume of blood or plasma cleared of drug per unit time |
| MRT | Mean residence time calculated as AUMC/AUC |
| $AUC_{last}$ | The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method |
| $AUC_{\infty}$ | The area under the plasma concentration versus time curve from time 0 to infinity. $AUC_{\infty}$ is calculated as the sum of $AUC_{last}$ plus the ratio of the last measurable plasma concentration to the elimination rate constant ($k_e$). The elimination rate constant will be determined from the terminal linear phase of the plasma concentration time profile. |

| Parameter | Description |
|---|---|
| $C_{max}$/Dose and $AUC_{\infty}$/Dose | Dose normalization of $C_{max}$ and $AUC_{\infty}$ for evaluation of dose proportionality. |

No value for $V_d$_F, Cl_F, $AUC_{\infty}$, $t_{½}$, or MRT will be reported for profiles that do not exhibit a terminal log-linear phase in the concentration versus time profile.

# 11. SAFETY ASSESSMENT

Safety monitoring will be conducted throughout the study; therefore, safety concerns will be identified by continuous review of data by the PI, clinic staff, clinical trial monitor, research monitor, and [redacted].

**Study Safety Management:** The PI, research monitor, [redacted] PVG physician, and IRB will review any safety concern.

An independent DSMB is required for this study. The DSMB will be convened to review safety data and provide recommendations to the sponsor's representative. Prior to any data being provided to the DSMB, it must be reviewed and approved for release by a study biostatistician in collaboration with the [redacted] biostatistician. The DSMB will review cumulative study data during scheduled in-process and ad hoc reviews to evaluate safety, study conduct, and the scientific validity and integrity of the trial. After each review of study data, the DSMB will make a recommendation to the sponsor's representative. DSMB recommendations will be documented and provided in writing (via the DSMB Chair Recommendation Form) to the [redacted]. The sponsor's representative will then decide whether to continue, modify, or suspend the study. The [redacted] will communicate the final decision to the investigator, who in turn will notify the IRB as appropriate. The [redacted] regulatory affairs scientist will communicate the final decision to the FDA, as appropriate. A description of the DSMB's roles and responsibilities, functions, reporting requirements, meeting frequency, and the study stopping/continuation criteria is included in the DSMB charter.

**Research Monitor:** The DoD research monitor is responsible for overseeing the safety of the research and reporting observations/findings to the IRB or a designated institutional official. The research monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The research monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the research monitor's report; and shall have the responsibility to promptly report his or her observations and findings to the IRB or other designated official and the [redacted].

In addition to the responsibilities above, the research monitor is required to review and provide an unbiased written report for all SAEs and subject deaths to the [redacted] within 24 hours of his or her awareness of the event. The report provided must include, at a minimum, a brief summary of the research monitor's review of the event and event outcome, relationship of the event to the investigational product, and whether the research monitor concurs with the details of the study investigator's SAE report.

The PI (or designee) will report SAEs to the DoD research monitor. Upon receipt of an SAE report (initial or follow-up), the DoD research monitor will provide the unbiased written report using the [redacted] Research Monitor Report Form for each assessment. The DoD Research Monitor's report may be submitted to the [redacted] by the Research Monitor or the PI. Multiple follow-up reports may be necessary for a single event, depending on when additional information becomes available. The PI (or designee) will also report all events that meet extreme and non-extreme DLT criteria, unanticipated problems, and other events with the potential to impact a subject's clinical care to the research monitor. The occurrence of any DLT(s) would result in the immediate discontinuation of dosing and study enrollment, pending a review of study data by the PI, research monitor, PVG physician, the DSMB, and the sponsor.

**Medical Monitor:** The medical monitor's role is separate and distinct from that of the research monitor. The medical monitor is available to serve as a resource to the clinical site and may provide consultations relating to issues such as general conduct of the study, subject eligibility, or potential protocol exceptions. The medical monitor may discuss with on-site medical staff any clinical situations that arise and provide recommendations. After the first day of dosing for each cohort, the medical monitor will review safety data with the PI to determine if it is safe to proceed with dosing the remaining subjects. The medical monitor may also perform additional tasks such as reviewing safety data listings for identification of data trends.

[redacted]**:** The [redacted] is responsible for the review of safety data regarding The Surgeon General, Department of the Army (TSG-DA)-sponsored products. The [redacted] reviews all safety events and follows them until resolution.

[redacted] **PVG Physician:** The [redacted] PVG physician, as delegated by the sponsor, evaluates all safety cases and provides the final determination on relatedness and expectedness to the product, and whether expedited reporting is warranted per current FDA regulation and guidance.

## 11.1. Specification of Safety Assessments

PK samples should be collected as close to the actual time point as possible (within the windows specified in Table 8); however, when multiple tests are scheduled at the same time, ECG and vital signs will be performed within 5 minutes prior to the nominal time point, and injection site and AE assessments will be performed immediately after the PK blood draw.

### 11.1.1. Demographic/Medical History

A complete medical history including demography will be collected at the screening visit after informed consent is obtained but before any other procedures are performed. A review of systems will be conducted by the PI or designee to ensure that subjects meet eligibility criteria. Females of childbearing potential will be asked to list their current method(s) of birth control for comparison with the requirements of this study.

### 11.1.2. Continuous Cardiovascular Monitoring

A DRE Waveline EZ Portable Patient Monitor (Avante Medical Surgical, Louisville KY) will be employed for continuous measurement of 3-lead ECG and vital signs (SpO2, blood pressure, heart rate, and respiratory rate). Each subject will have the Patient Monitor placed at the bedside, and monitoring will be performed from pre-dose until 24 hours post dose. Subjects may be

monitored for a longer period of time at the discretion of the investigator, based on clinical indication.

- SpO2 is the saturation of arterial blood with oxygen as measured by pulse oximetry, and reported as a percentage. The SpO2 sensor will be placed on the index finger of the non-dominant arm using a clip device.
- Blood pressure will be monitored via a standard size-appropriate cuff placed on the non-dominant arm, and measurements will be obtained every 5 minutes until 1 hour post dose, and every 15 minutes thereafter. The frequency of blood pressure sampling may be increased up to every 5 minutes at any time after 1 hour post dose at the discretion of the investigator, based on clinical indication.
- Heart rate and ECG will be obtained using 3 standard chest leads.
- Respiratory rate will be measured by thoracic impedance, via an electrode placed at approximately the right lateral 8th intercostal space.

Note: the measurements obtained during continuous monitoring will not be recorded unless an AE occurs. Safety assessments will be recorded according to the time points below (also refer to Table 3 and Table 4, Study Events Schedules).

### 11.1.3. Vital Signs

Vital signs will include systolic and diastolic blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry, and will be measured after the subject has been resting in a supine position for at least 5 minutes. Vital signs will be performed at screening, Day -1, Day 1 (prior to dosing, at 5, 10, 15, 30, and 45 minutes, and at 1, 1.5, 3, 5, 8, and 12 hours after dosing), Day 2 (24 hours post-dose ± 1 hour), Day 3 (48 hours post dose ± 1 hour), and Day 8. Vital signs may be taken at other times if deemed necessary by the investigator or site SOPs.

In addition, starting at 1 hour prior to dosing on Day 1, vital signs (excluding body temperature) will be continuously monitored for 24 hours post dose (refer to Section 11.1.2 for details).

Where the time of vital signs monitoring coincides with a blood draw, vital signs will be performed within 5 minutes prior to the nominal time point (refer to Section 11.1 for details).

### 11.1.4. Weight and Height

Subjects will have a height (cm; screening only) and weight (kg) measurement during screening with BMI calculation, a weight measurement on Day -1 with BMI calculation, and a weight measurement only on Days 3 and 8. The Day -1 weight will be used for dose determination.

### 11.1.5. Physical Examination

Each subject will have a complete physical examination at screening, Day -1, and Day 8. Abbreviated (targeted) physical examinations will be performed as needed prior to dosing on Day 1 and prior to discharge on Day 3. A complete physical examination includes all major systems, including general appearance, EENT, chest/respiratory, heart/cardiovascular, abdomen/gastrointestinal, lymph nodes/spleen, genitourinary, musculoskeletal, skin, neurological, and hepatic. The screening physical exam includes an assessment of upper leg

muscle tissue (ie, adequacy of tissue for IM injection). Targeted physical examinations may be performed at other times as deemed necessary by the investigator.

In addition, at the request of the DSMB for Cohorts 3-5, a brief neurological assessment will be performed at 1 hour post dosing (+30 min) on Day 1 to assess alertness/level of consciousness, orientation, ability to follow commands and coordination. The assessment will be documented in the subject's medical record. At the end of each cohort, the PI will provide narratives (per cohort and subject) for inclusion in the DSMB data reviews.
The brief neurological assessment will be performed as follows in this sequence:

1) To assess alertness and level of consciousness, the RASS (Appendix D) will be employed and the completed scale will be added to the subject's medical record.
   The RASS score will be entered into the eCRF; however, the scores for orientation and ability to follow commands (see below) will not be entered into the eCRF.
2) Orientation will be assessed using questions 1 and 2 of the Folstein Mini-Mental Status Examination (Rovner and Folstein, 1987), as shown below. The answers to each question will be noted in the subject's medical record, along with the combined score for the two questions. Scoring will be performed according to Rovner and Folstein (1987).
   - "What is the year? Season? Date? Day of the week? Month?"
   - "Where are we now: State? County? Town/city? Hospital? Floor?"
3) Ability to follow commands and coordination (to the extent possible) will be assessed using a modified question 8 of the Folstein Mini-Mental Status Examination as shown below. The total score will be noted in the subject's medical record. Scoring will be performed according to Rovner and Folstein (1987).
   - "Take the paper in your right hand, fold it in half, and hand it back to me." (The examiner gives the patient a piece of blank paper).

### 11.1.6. Neuropsychiatric/Behavioral/Cognitive Assessments

The SCID-5-CT (customized) (First et al-2015) will be administered by a psychologist at Day-1 as a screening tool to exclude any subjects with major DSM-5 Axis I or II disorders. Due to the nature of the assessment, the SCID should not be repeated during this study. Therefore, for any subject who receives the SCID on Day -1, but is subsequently designated an alternate and readmitted on another day, the initial SCID will serve as their assessment of record.

Other assessments of neuropsychiatric/behavioral symptoms will be performed by appropriately experienced and trained study staff using the C-SSRS (Posner et al-2011), BPRS (expanded version 4.0, 24 items) (Ventura et al-1993), and RASS (Sessler et al-2002, Ely et al-2003). A psychiatrist will be available by phone to consult with the investigator throughout the study. At the investigator's request, the psychiatrist will come to the clinic to evaluate a subject.

The C-SSRS Baseline/Screening version will be administered by study staff at screening, and the C-SSRS Since Last Visit version will be administered at Day -1 and at follow-up on Day 8. Scoring and analysis will be performed according to the Columbia-Suicide Severity Rating Scale Scoring and Data Analysis Guide. Study staff administering the C-SSRS will complete C-SSRS training.

The BPRS will be performed by a psychologist or trained clinician at screening, Day -1 (baseline), at 6 (+ 2) hours post dose (timing at the discretion of the investigator), 48 hours post dose (prior to discharge), and on Day 8. For BPRS items assessed over time (eg, items 1, 2, and 3), the period of assessment should be over the prior week, except for assessments performed at 6 and 48 hours post dose, which will be assessed since the prior assessment. The + 2-hour window for the 6-hour post-dose BPRS is intended to allow the investigator some discretion should the assessment need to be delayed. The timing may be dependent on the emergence and severity of neuropsychiatric symptoms. If the investigator determines a subject is incapable of providing valid responses during the + 2-hour window, the reason(s) why the BPRS was delayed or could not be done will be documented in the source documentation.

Mental health/behavioral symptoms, judged to be clinically significant, should be reported as AEs at whatever time point they may be observed. As part of the reporting process, if the AE corresponds to an item on the BPRS, the relevant item on the BPRS scale should be used for assessing the severity of the event. In addition, if AEs of general agitation or sedation are reported, since these do not correspond to a specific item on the BPRS, the RASS should be used by a physician, physician assistant, or nurse to assess severity (see Appendix D).

The DSST (Strauss et al-2006) will be administered by appropriately trained study staff at screening, baseline (Day -1), 48 hours post dose (Day 3), and Day 8 to detect any persistent cognitive effects. The screening time point is included to reduce practice effects between baseline and re-administrations thereafter. The DSST will not be used to determine eligibility.

Note: Alternates who are readmitted on another day will have the BPRS, C-SSRS, and DSST repeated.

### 11.1.7. Injection Site Assessments

At approximately 5 minutes after injection, the subject will be asked by the study staff to rate the maximum intensity of pain, pruritus, tingling, and numbness at the injection site using the VAS (Appendix A). The VAS will also be completed at pre dose and at 10, 15, 30, and 45 minutes and 1, 1.5, 3, 5, 8, 12, 24, and 48 hours post dose, and at Day 8. In addition, an injection site assessment for presence and severity of pain, tenderness, erythema, and induration/swelling will be performed by a physician, physician assistant, or nurse approximately 5 minutes after injection and for all subsequent time points (as stated above; Appendix C). Refer to Appendix B for the Toxicity Grading Scale for Injection Site Reactions.

The anticipated neuropsychiatric effects of Scopolamine HBT may hinder obtaining reasonable subjective data on the VAS, especially at the earlier post-dose time points. If the PI or designee determines a subject is incapable of providing valid responses at one or more time point(s), the reason(s) why the VAS assessment(s) could not be done will be documented by time point in the source documentation.

Note: All mild (grade 1) events, including all nonzero VAS scores, will be recorded as an AE, (refer to Section 11.3.1 and Appendix B).

### 11.1.8. Electrocardiogram

A 12-lead ECG will be performed supine at screening, Day-1, Days 1-3, and Day 8 (prior to the blood draws, if applicable). On Day 1, 12-lead ECG will be performed prior to dosing and at 5,

10, 15, 30, and 45 minutes and 1, 1.5, 3, 5, 8, and 12 hours after dosing. The 12-lead ECG tracings will be reviewed and signed and dated by the investigator or designee on the same study day. ECGs may be performed at other times if deemed necessary by the investigator.

When the time of an ECG coincides with a blood draw, the ECG will be performed within 5 minutes prior to the nominal time point (refer to Section 11.1for details).

A cardiologist will be available to consult with the investigator, as needed, throughout the study.

P-R intervals will be determined for each of these ECGs from single reading (invalid measurements will be repeated). QTc will be calculated using both Bazett's and Fridericia's corrections as follows:

- Fridericia correction: $QTc = QT/RR^{0.33}$
- Bazett's correction: $QTc = QT/RR^{0.5}$

The 3-lead ECG will be utilized for continuous monitoring starting at 1 hour prior to dosing and ending at 24 hours post dose.

Due to the continuous monitoring and large number of 12-lead ECGs during the first 24 hours, the ECG electrodes may be left in place from pre dose through 24 hours post dose (and replaced as necessary).

Note: Subjects will not be allowed to shower from pre dose until after all 24-hour, post dose procedures have been completed and the electrodes removed.

### 11.1.9. Laboratory Assessments

Clinical laboratory tests will primarily be performed by Pharmaron with the remaining tests to be performed by Quest Diagnostics (refer to the Clinical Laboratory Manual for details).

#### 11.1.9.1. Hematology and Coagulation

The following hematological tests will be performed:

- Red Blood Count
- White Blood Count Total
- Hematocrit
- Hemoglobin
- Platelet Count
- Absolute Eosinophil Count
- Absolute Basophil Count
- Absolute Monocyte Count
- Absolute Neutrophil Count
- Mean Corpuscular Volume
- Mean Corpuscular Hemoglobin Concentration

- Mean Corpuscular Hemoglobin
- Absolute Lymphocyte Count
- Red (cell) Distribution Width

The following coagulation tests will be performed:

- Prothrombin Time
- Partial Thromboplastin Time
- Fibrinogen

#### 11.1.9.2. Serum Chemistry

The following serum chemistry tests will be performed:

- Glucose
- Uric Acid
- Blood Urea Nitrogen
- Creatinine
- Creatine kinase
- Sodium
- Potassium
- Chloride
- Calcium
- Phosphorous
- Protein, Total
- Albumin
- Globulin
- Albumin/Globulin Ratio
- Bilirubin, Total
- Bilirubin, Direct
- Alkaline Phosphatase
- Lactic Dehydrogenase
- Aspartate Aminotransferase
- Alanine Aminotransferase
- Gamma Glutamyl Transferase
- Iron

- Total Cholesterol
- Triglycerides
- Magnesium
- Carbon Dioxide

#### 11.1.9.3. Urinalysis

The following urinalysis tests will be performed:

- Color
- Appearance
- Specific Gravity
- pH
- Protein
- Glucose
- Ketones
- Occult Blood
- Leukocyte Esterase
- Nitrite
- Bilirubin
- Urobilinogen
- Magnesium (with calculation of fractional excretion)
- Creatinine
- Potassium (with calculation of fractional excretion)

#### 11.1.9.4. Pregnancy Screen

All female subjects, regardless of childbearing potential, will undergo 2 pregnancy tests prior to receiving the study drug. A serum pregnancy test to measure human β-chorionic gonadotropin will be administered during screening and also within 24 hours prior to dosing in a controlled environment. A pregnancy test will also be conducted on Day 8, or at study termination, if it occurs before Day 8.

#### 11.1.9.5. Additional Tests

The following tests will be performed:

- Serology (screening only)
  - HIV Test (1 and 2)
  - FTA-ABS Test for Syphilis

  - Hepatitis B Virus Surface Antigen
  - Hepatitis C Virus
- Alcohol Breathalyzer
- Urine Drug Screen (screening, Day -1, Day 8)
  - Barbiturates
  - Benzodiazepines
  - Cannabinoids
  - Cocaine
  - Opiates
  - Methadone
  - Phencyclidine
  - Propoxyphene
  - Oxycodone
  - Tricyclic Antidepressants
  - Amphetamines
  - Methylenedioxymethamphetamine

## 11.2. IND Safety Reporting

All AEs regardless of group (treatment or placebo) or suspected causal relationship to the investigational product will be reported as described in the following sections.

The following terms, as defined by 21 CFR 312.32, apply to IND safety reporting.

### 11.2.1. Adverse Event or Suspected Adverse Reaction

Adverse event means any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related. This includes any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### 11.2.2. Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE – An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 11.2.3. Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed or, if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator's brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator's brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

### 11.2.4. Unanticipated Problems Involving Risks to Subjects or Others

Federal regulations (45 CFR Part 46/32 CFR 219) require that unanticipated problems involving risks to subjects or others be promptly reported to the IRB. These events encompass a broader category of events than SAEs and may include issues such as problems with loss of control of subject data or the investigational product, adverse psychological reactions, or breach of confidentiality. Risks to others (eg, program personnel) must also be reported.

Unanticipated problems involving risks to subjects or others are any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the procedures that are described in the protocol, investigator's brochure, or ICF and (b) the characteristics of the subject population;
- Related or possibly related to a subject's participation in the study; and
- Suggests that the study places subjects or others at a greater risk of harm than was previously known or recognized.

The IRB and/or the ORP will evaluate the PI's and research monitor's reports to determine whether a given incident, experience, or outcome constitutes an unanticipated problem involving risks to subjects or others and, in coordination with the sponsor, ensure upward reporting of the unanticipated problems involving risks to subjects or others to the appropriate investigative sites and regulatory offices, as applicable.

## 11.3. Relationship to Investigational Product

The investigator must assign a relationship of each AE to the receipt of the investigational product. The investigator will use clinical judgment in conjunction with the assessment of a plausible biologic mechanism, a temporal relationship between the onset of the event in relation to receipt of the investigational product, and identification of possible alternate etiologies including underlying disease, concurrent illness, or concomitant medications. The following guidelines should be used by investigators to assess the relationship of an AE to study product administration. **ONLY A PHYSICIAN CAN MAKE THIS DETERMINATION**.

**Not related:** No relationship to investigational product. Applies to those events for which evidence exists that there is an alternate etiology.

**Unlikely:** Likely unrelated to the investigational product. Likely to be related to factors other than investigational product but cannot be ruled out with certainty.

**Possible:** An association between the event and the administration of investigational product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology such as the subject's clinical status or underlying factors including other therapy.

**Probable:** There is a high degree of certainty that a relationship to the investigational product exists. There is a reasonable temporal association, and the event cannot be explained by known characteristics of the subject's clinical state or factors including other therapy.

**Definite:** An association exists between the receipt of investigational product and the event. An association to other factors has been ruled out.

### 11.3.1. Severity Assessment

All AEs will be assessed for severity by an investigator. Inherent in this assessment is the medical and clinical consideration of all information surrounding the event including any medical intervention required. The *Common Terminology Criteria for Adverse Events (CTCAE)*, version 5.0 (November 27, 2017) is a descriptive terminology that will be utilized for grading all AEs, with the exception of injection site reactions, which will be graded using the Local Reaction to Injectable Product table from the FDA's *Guidance for Industry: Toxicity Grading*

*Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (see Appendix B).

Both guidance documents provide a grading (severity) scale for each AE term. Each event will be assigned one of the following categories: mild (grade 1), moderate (grade 2), severe (grade 3), or potentially life threatening (grade 4).

All events (Grade 1 or higher) must be recorded, regardless of group assignment (treatment or placebo), suspected causal relationship or clinical significance (e.g., including those determined by the Investigator as non-clinically significant).

Refer to Appendix A for assessing the severity of pain, pruritus, tingling, and numbness at the injection site (subject rating using the VAS); Appendix C for severity of pain, tenderness, erythema, and induration at the injection site (assessed by a physician, physician assistant, or nurse); and Appendix D for assessing the severity of agitation and sedation (using the RASS). The following criteria may be used for any symptom not included in the grading scale.

**Any Grade 4 (potentially life-threatening) or Grade 5 (fatal) AE must be reported as an SAE**.

The eCRF for AEs will reflect only the highest severity for continuous days an event occurred.

| | |
|---|---|
| **Mild** | Grade 1 Does not interfere with routine activities<br>Minimal level of discomfort |
| **Moderate** | Grade 2 Interferes with routine activities<br>Moderate level of discomfort |
| **Severe** | Grade 3 Unable to perform routine activities<br>Significant level of discomfort |
| **Potentially Life Threatening** | Grade 4 Hospitalization or ER visit for potentially life-threatening event |
| **Fatal** | Grade 5 Death |

If a subject is evaluated in an emergency room for non-life-threatening illness or symptoms (ie, visits the emergency department over the weekend for mild problems because the physician's office is closed), the information from that visit will be reviewed and the severity of the AE will be assessed by the PI according to the subject's clinical signs and symptoms.

As defined by the ICH guideline for GCP, the term "severe" is often used to describe intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is **not** the same as "serious," which is based on subject/event **outcome** or **action** criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

## 11.4. Recording Adverse Events

Section 7.3.3 presents procedures to request unblinding of a subject's randomization code due to a medical emergency or serious medical condition.

### 11.4.1. Methods/Timing for Assessing, Recording, and Analyzing Safety Endpoints

AEs and SAEs will be documented in the source records, and recorded on the eCRFs and the sponsor-approved Serious Adverse Event Reporting Form, using accepted medical terms and/or the diagnoses that accurately characterize the event. It should be noted that the form for collection of SAE information is not the same as the AE case report form. If the same data are collected on both forms, the forms must be completed in a consistent manner (ie, the same event term should be used on both forms. When a diagnosis is known, the AE term recorded on the eCRF will be the diagnosis rather than a constellation of symptoms. The investigator will assess all AEs for seriousness, relationship to investigational product, severity, and other possible etiologies. When an event has not resolved by study closure, it will be documented on the AE eCRF as "not recovered/not resolved."

The time frame for the collection of AEs and SAEs begins at the administration of investigational product through 30 days after the investigational product is administered.

Any condition recorded on the medical history should not be reported as an AE unless it worsens in frequency, intensity, or severity, or there are clinically significant changes in laboratory values after administration of study drug.

### 11.4.2. Duration of Follow-Up of Subjects after Serious Adverse Events

Investigators are required to follow SAEs to resolution, even if this extends beyond the prescribed reporting period. Resolution is the return to baseline status or stabilization of the condition; determined to have become chronic. The SAE outcomes will be reported to the [redacted] using the Serious Adverse Event Report Form. The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the updated information.

Investigators are not obligated to actively seek SAEs in former subjects; however, if an SAE, considered to be related to the investigational product is brought to the attention of the investigator *at any time* following completion of the study, the event will be reported to the sponsor's safety office as defined in Section 11.5.1.1.

## 11.5. Reporting Adverse Events

The PI or designee will report all AEs to the local IRB and/or the [redacted] in the appropriate safety, annual, and/or final reports. The sponsor's safety office [redacted] only receives SAEs, not all AEs. After appropriate data cleaning and query resolution between the clinical site, sponsor's clinical monitor, and clinical data manager, SAEs from the clinical database will be reconciled with the sponsor's SAE database. SAEs and AEs for inclusion in annual and final reports to the FDA will be provided from the clinical database by the clinical data manager in [redacted].

### 11.5.1. Reporting Serious and Unexpected Adverse Events

Contact information for reporting SAEs is provided in Table 10.

#### 11.5.1.1. Reporting to the Sponsor

**All SAEs** must be reported promptly (within 24 hours) to the sponsor's safety office [redacted] per 21 CFR 312.64 whether or not the event is considered related to study product. Further, the investigator should comply with relevant study site SOPs on reporting SAEs.

The minimum information that the investigator will provide to the [redacted] is specified in Table 11. The sponsor's representative may request additional information for purposes of the study.

**Table 10: Study Contacts for Reporting Serious Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others**

| | |
|---|---|
| **Sponsor's Safety Office** | [redacted] |
| **Institutional Review Board** | **IntegReview IRB**<br>**3815 S. Capital of Texas Highway**<br>**Suite 320**<br>**Austin, TX 78704**<br>**Fax: 512-697-0085**<br>**Telephone: 512-326-3001**<br>**E-mail: integreview@integreview.com**<br>**AND**<br>[redacted] |
| **Research Monitor** | [redacted] |

**Table 11: SAE Information to Be Reported to the Sponsor's Safety Office**

| Notification Method | Information to Be Provided |
|---|---|
| **E-mail or Telephone (within 24 hours)** | **IND number, sponsor study number, name of the investigational product, and investigator name and contact number** |
| | Subject identification number |
| | SAE event term and description, onset date, date(s) of investigational product administration, severity, relationship to investigational product, and subject's current status |
| **AND** | |
| **E-mail or Fax** | **Cover sheet or letter** |
| | Sponsor-approved serious adverse event report form |
| | Admission/discharge summary or medical record progress notes including pertinent laboratory/diagnostic test results |
| NOTE: When submitting SAE reports via e-mail, the subject line of each email notification will read as follows:<br>**SAFETY REPORT – IND # 130620, Sponsor Study # S-16-14, Subject # ____, Event Term: ____** | |

To comply with regulations mandating sponsor notification of specified SAEs to the FDA within 7 calendar days, investigators must submit additional information as soon as it is available on the SAE report form. The sponsor's representative will report unexpected SAEs associated with the use of the drug to the FDA as specified in 21 CFR 312.32 (c).

Investigators must follow all relevant regulatory requirements as well as specific policy regarding the timely reporting of SAEs to the research monitor and the local IRB and/or the [redacted].

Reporting to the sponsor's safety office does not fulfill the investigator's duty to report all unanticipated problems involving risks to subjects or others to the IRB. The PI will notify the local IRB and/or the [redacted] and the research monitor.

### 11.5.1.2. Reporting to the IRB

Unanticipated problems involving risks to subjects or others, SAEs related to participation in the study, and all subject deaths related to participation in the study should be promptly reported by telephone, e-mail, or fax to the local IRB and/or the [redacted]. A complete written report should follow the initial notification.

Investigators are required to forward safety information provided by the sponsor's representative to the IRB.

### 11.5.2. Reporting Additional Immediately Reportable Events to the Sponsor's Safety Office and Local IRB and/or the [redacted]

#### 11.5.2.1. Pregnancy

Each pregnancy must be reported *immediately* **(within 24 hours of identification)** by completing and submitting the initial sponsor-approved Pregnancy Report Form by e-mail or fax to the sponsor's safety office [redacted]. In addition, each pregnancy must be reported to the local IRB and/or the [redacted] in accordance with IRB policy.

Subjects who become pregnant after dose administration on Day 1 will not receive any additional investigational product. The subject will be followed for safety to term, and the following information will be documented on the Pregnancy Report form: type and date of delivery, Apgar scores, and health status of the mother and child including the child's sex, head circumference, gestational age at delivery, length, and weight. Complications and or abnormalities should be reported including any premature terminations. A pregnancy is reported as an AE or SAE only when there is suspicion that the investigational product may have interfered with the effectiveness of contraception or there was a serious complication in the pregnancy including a spontaneous abortion or an elective termination for medical rationale. Otherwise, pregnancy will not be categorized as an AE. It may be necessary to obtain authorization to access a subject's medical records for details pertaining to the pregnancy and/or pregnancy outcome.

#### 11.5.2.2. AE-related Withdrawal of Consent

Any AE-related withdrawal of consent during the study must be reported *immediately* **(within 24 hours of identification)** to the sponsor's safety office [redacted]. The PI should report the withdrawal to the local IRB and the [redacted] in accordance with local policies.

#### 11.5.2.3. Pending Inspections/Issuance of Reports

The knowledge of any pending compliance inspection/visit by the FDA, [redacted], Department of Health and Human Services, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any regulatory agency including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to the local IRB and/or the [redacted] and the sponsor's representative.

### 11.5.3. IND Annual Report to the FDA

The PI will be responsible for the preparation of a detailed annual synopsis of clinical activity, including AEs, for submission to the sponsor's representative [redacted]. Each annual report will summarize IND activity for 1 year beginning approximately 3 months before the IND FDA anniversary date. The sponsor's representative will notify the PI of the due date with sufficient time for the PI to assemble the required information.

### 11.5.4. Final Report

A final study report will be prepared in accordance with FDA's *Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications* and ICH E3 Guideline *Structure and Content of Clinical Study Reports* and provided to the sponsor's representative for review and approval. The sponsor's representative will use this report to prepare the final clinical study report for submission to the FDA.

# 12. STATISTICS

## 12.1. Description of Statistical Methods

Detailed statistical procedures, listings, table shells, and figures will be provided in a separate statistical analysis plan (SAP).

This Phase 1 trial has two objectives:

- To characterize the safety and tolerability profile of ascending doses of Scopolamine HBT administered by IM injection (0.005mg/kg to 0.021mg/kg) and set upper limits on the probability of extreme and non-extreme DLTs across dosage levels
- To characterize the PK of ascending doses of Scopolamine HBT administered by IM injection and assess dose proportionality for $C_{max}$ and $AUC_{\infty}$ over the dosing range

Table 12 shows the study objectives and endpoints.

**Table 12: Study Objectives and Endpoints**

| Study Objective | Study Endpoints |
|---|---|
| Safety | Extreme and nonextreme DLTs<br>SAEs related to drug<br>All AEs that are not SAEs<br>Vitals signs, ECG, and clinical laboratory values and their changes from baseline<br>Injection site assessments<br>Clinically relevant physical exam findings<br>Neuropsychiatric measures (BPRS, C-SSRS, and RASS)<br>Cognitive measures (DSST) |
| Pharmacokinetics | $C_{max}$, $T_{max}$, $t_{1/2}$, $V_d\_F$, Cl_F, MRT, $C_{max}$/Dose, $AUC_{\infty}$/Dose |

Detailed descriptions of the endpoints and their measurements can be found in Section 10 and Section 11. Additional discussion of the statistical methodology and assumptions can be found in the SAP.

### 12.1.1. Pharmacokinetic Analysis

The PK analysis will be performed on the pharmacokinetics analysis set. Blood samples will be obtained for PK assessments prior to dosing and at 2, 5, 10, 15, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 36, and 48 hours post dose. Scopolamine HBT PK assessments will include

determination of the following parameters: observed $C_{max}$, $T_{max}$, $V_d\_F$, $t_{½}$, $Cl\_F$, $AUC_{last}$, $AUC_{\infty}$, $C_{max}$/Dose, MRT, and $AUC_{\infty}$/Dose. Plasma concentration time profiles for each subject tested will be evaluated using semi-log plots and characterized using noncompartmental analysis (WinNonlin). PK data will also be summarized graphically by dose group. PK and safety endpoints will undergo PD analysis and evaluation.

Data for PK parameters will be summarized by group using descriptive statistics including mean, standard deviation, minimum, maximum, and may include median and quartiles. All PK data for individual participants will be provided in listings.

Dose proportionality will be tested for $C_{max}$/Dose and $AUC_{\infty}$/Dose using ANOVA models. Likelihood ratio tests will be used to test the joint hypothesis of equivalence across dose levels. Equivalence will be tested for each dose level against the next higher dose level. Equivalence of parameters across doses (dose equivalence) will be tested for $T_{max}$, $t_{1/2}$, $V_d\_F$, and MRT. All ANOVA models of PK parameters will adjust for sex.

### 12.1.2. Safety Analyses

Safety analysis will include data collected from the safety analysis set. DLT and AE data will be coded using the current MedDRA version at the time of study setup, listed individually (including intervention and outcome), and summarized by system organ class and preferred terms within a body system for each treatment group. Data will be summarized by both event (counting each event regardless of subject) and by subject (counting only one event within each system organ class or preferred term). Serious and/or unexpected AEs will also be discussed on a case-by-case basis.

Changes in pulse rate, systolic and diastolic blood pressure, weight, and respiratory rate will be summarized (mean, median, minimum, maximum, standard deviation) by dose level and time point. Clinical laboratory assessment results will be presented.

Upper bounds of 80% confidence intervals of the true probability of events (extreme DLTs, non-extreme DLTs, and severe AEs) will be estimated from the number of events in each cohort using the Pearson-Clopper method.

Descriptive statistics of BPRS, C-SSRS, DSST, RASS (if conducted), and injection site VAS scores (mean, median, standard deviation, minimum, and maximum) will be presented for each dose level and time point.

Changes in the BPRS score (6 hours, 48 hours, and 8 days) from baseline will be compared between placebo and active dose levels using ANOVA models for each time point. The null hypothesis of no difference between placebo and the active dose will be tested for each dose level using a one-sided alternative hypothesis of higher increases among the participants receiving the active drug than among the placebo group.

Participants have C-SSRS scores of zero at baseline. The proportion of individuals having any increase in their C-SSRS score from zero will be compared for each drug dosage level to the placebo group using Fisher's exact test.

The DSST will be conducted at screening, Day -1, Day 3, and Day 8. Changes from baseline (Day -1) will be compared between placebo and active dose levels using ANOVA models for each time point. Placebo control will help to exclude any remaining practice effects or changes

unrelated to the study drug. The null hypothesis of no difference in DSST scores between active Scopolamine and placebo will be tested for each dose level using a one-sided alternative hypothesis of more negative changes in DSST scores among participants receiving the active drug than among the placebo group. A pooled analysis will compare all Scopolamine dosage levels to placebo. Individual participants' DSST scores will be presented by study day, and persistent declines in scores at Day 3 or Day 8 will be noted.

Frequencies of severity (None, Mild, Moderate, Severe, Potentially Life Threatening) from injection site assessments performed by clinicians will be summarized by type (pain, tenderness, erythema/redness, induration/swelling) and time point by dosage group. Semi-log graphs of mean VAS scores will be plotted (VAS score vs. log-time since injection). Differences between placebo and active drug injection site VAS scores will be compared statistically by dosage level using 3 different ANOVA models corresponding to the first hour, next 4 hours, and 8-48 hours after injection. A Wald test with a one-sided alternative will be used.

### 12.1.3. Clinical Laboratory Data Analyses

For hematology and serum chemistry tests, the median, mean, standard deviation, minimum, and maximum of all values for each test within each treatment group at baseline and for all raw values and change for baseline for subsequent time points will be provided in a summary table. A second table (a "shift table") will be made, showing for each laboratory variable the percentage of subjects in each treatment group whose values decreased, stayed the same, or increased between the baseline or pretreatment period and the subsequent visits. A third table will be prepared displaying the numbers of subjects in each treatment group who had values below, within, and above the normal range at baseline and at subsequent time points.

These tables will be reviewed by the PI or research monitor to evaluate whether any significant trends in laboratory values occurred. The PI or research monitor will also review urinalysis data by inspecting the laboratory data tabulations, but no summary tables of these will be prepared.

### 12.1.4. Subgroup Analysis

The small sample size of this study limits meaningful subgroup analyses; however, descriptive statistics by sex will be provided as appropriate. Sex will be included as a covariate in the analysis of PK parameters. Any subgroup analyses specified after data unblinding will be labeled as post hoc.

## 12.2. Planned Enrollment and Reason for Sample Size

The sample size calculation of 40-60 healthy subjects has been chosen to provide adequate numbers of subjects for characterization of the safety and tolerability of Scopolamine HBT administered in 1 to 5 dose-escalating cohorts in normal, healthy volunteers as well as a placebo group. No formal statistical sample size computation was performed; however, the 6 to 9 active subject and 2 to 3 control subject design is commonly employed in Phase 1 clinical trials because it provides adequate power to detect non-rare events (true probability, $P > 0.20$-$0.25$) events within each cohort. Enrollment may be stopped at any dosing level if stopping criteria are met; therefore, the total sample size may be substantially smaller than 40-60.

## 12.3. Interim Analysis and Stopping Rules

Criteria for halting enrollment and recruitment have been outlined in Section 7 of the protocol. These criteria are pre-specified and not related to the statistical analysis. No interim statistical analysis is planned, and there are no statistical criteria for study termination in this Phase 1 clinical trial. Summary tables and listings for safety and PK parameters will be provided to the DSMB for review prior to dose adjustment. Prior to any data being provided to the DSMB, it must be reviewed and approved for release by a study biostatistician in collaboration with the [redacted] biostatistician. The DSMB will not use statistical tests in making determinations about whether to halt or terminate the study.

## 12.4. Procedures for Reporting Deviations from the Original Statistical Plan

Any deviation(s) from the original SAP as indicated in the protocol will be described in an amendment to the protocol and the SAP. If the amendment is approved prior to unblinding, the outcome will be presented in the main statistical report. Any additional analyses proposed after data lock and unblinding will be noted as "post hoc" in the final statistical report. Deviations from the SAP will be documented in accordance with study site SOPs.

## 12.5. Key Assumptions

Some of the hypothesis testing planned for this study relies on ANOVA, which requires normality and equal variance across dosing levels (homoskedasticity). If the normality assumption for ANOVA does not hold, link functions will be assessed for use in generalized linear models. In the event that no appropriate link function can be identified to attain normality, non-parametric bootstrap replication will be used to generate standard errors for coefficients. The Koenker-Bassett/generalized Breusch-Pagan Test will be used to test the assumption of homoskedasticity. If homoskedasticity is rejected, unequal variance ANOVA will be used with robust (Huber-White) standard errors.

## 12.6. Selection of Subjects to Be Included in Analyses

### 12.6.1. Safety Analysis Set

The safety analysis set is defined as those subjects who meet eligibility requirements and received at least one dose of study drug or placebo. Subjects will be analyzed according to the dose they received.

### 12.6.2. Pharmacokinetics Analysis Set

The pharmacokinetics analysis set is defined as those subjects who meet eligibility requirements, received at least one dose of study drug, and have at least one PK data point. Subjects will be analyzed according to the dose they received.

# 13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by the unique subject identification number and subject initials. The unique

identification number will be assigned to each subject at screening, and this number will be used to identify the subject throughout the study.

No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject. Representatives of [redacted], the sponsor's representative, the local IRB and/or the [redacted], and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research. Personal identifiers will be removed from photocopied medical and research records.

## 13.1. Accounting for Missing, Unused, and Spurious Data

Instances of missing data will be reported along with a reason that data is missing. If multiple measurements are collected, a reason for repeat measurement will be recorded, and the data point corresponding to erroneous or incomplete data collection will be censored. Otherwise, all data will be included in the analysis as specified in the SAP. Data collected following administration of rescue medication will be censored in the analysis of endpoints that are likely to be affected by the rescue medications (BPRS, RASS, DSST, C-SSRS). However, injection site VAS scores will not be censored following administration of rescue medications.

## 13.2. Study Monitoring

Study monitoring will be the responsibility of the [redacted], as designated by the sponsor. Upon successful approval of the protocol and establishment of the regulatory file, the clinical trial monitor will draft a clinical monitoring plan. To ensure that the investigator and the study staff understand and accept their defined responsibilities, the clinical monitor will maintain regular correspondence with the site and may be present during the course of the study to verify the acceptability of the facilities, compliance with the investigational plan and relevant regulations, and the maintenance of complete records. As needed, the clinical monitor may witness the informed consent process or other applicable study procedures to ensure the safety of subjects and the investigators' compliance with the protocol and GCPs.

Monitoring visits by the [redacted] clinical trial monitor will be scheduled to take place at pre-study (for site qualification), the initiation of the study, during the study at appropriate intervals, and after the last subject has completed the study. A report of monitoring observations will be provided to the PI (for corrective actions), [redacted], and the product manager. The clinical trial monitor will perform complete investigational product accountability at the end of the study. If it is deemed necessary by the Sponsor, an unblinded clinical trial monitor (or product compliance scientist) will visit the site pharmacy during the study to monitor accountability and/or follow up on concerns.

## 13.3. Audits and Inspections

Authorized representatives of the sponsor, the FDA, the independent ethics committee, or IRB may visit the site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guideline of the ICH, and any applicable regulatory requirements.

The investigator should contact the sponsor's representative and [redacted] immediately if contacted by a regulatory agency about an inspection.

## 13.4. Institutional Review Board

As the IRB of record, the local IRB will serve as the responsible IRB and will review the protocol, informed consent, and progress reports on a continuing basis in accordance with all applicable regulations, including 21 CFR Parts 50 and 56. The [redacted] will provide a second review.

The PI must obtain IRB approval for the study. Initial IRB approval and all materials approved by the IRB for this protocol, including the patient consent form and recruitment materials, must be maintained by the protocol physician and made available for inspection.

The PI will be responsible for preparing and submitting continuing review reports per institution and IRB requirements. The PI or a designee will submit the approved continuing review reports and the local IRB approval notifications to [redacted] as soon as the documents are available.

# 14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor's representative may conduct quality assurance audits. Refer to Section 13.3 for more details regarding the audit process.

Auditing of the clinical trial may be conducted at any time during the study to ensure continued compliance with regulations, policies, and procedures. Auditing will be undertaken, as needed, by independent personnel designated by the [redacted]. Audit findings will be documented in a formal audit report that will detail the conduct of the audit and summarize the observations noted.

# 15. ETHICS

## 15.1. Ethics Review

The study is based on adequately performed laboratory and animal experimentation and will be conducted under a protocol reviewed by the local IRB and/or [redacted]. The study is to be conducted by scientifically and medically qualified persons. The IRB will determine whether the benefits of the study are in proportion to the risks. The rights and welfare of the subjects will be respected, the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits, the results to be reported will be accurate, subjects will give their informed consent and will be competent to do so and not under duress, and all study staff will comply with the ethical principles in 21 CFR Part 50 and the Belmont Principles.

### 15.1.1. Review/Approval of Study Protocol

Before a clinical study can be initiated, the study protocol and other required documents will be submitted to the following departments in the order listed for review and/or approval, with the final review by the FDA:

- Integrated Product Team
- Scientific Review Committee
- Sponsor's Representative Team (Senior Regulatory Affairs Advisor; [redacted])
- Protocol Review Board, [redacted]
- Local IRB and the [redacted]
- Sponsor's Representative (acting for TSG-DA)
- [redacted] Commanding General, if applicable

Enrollment in this protocol may not begin until all approvals have been obtained and the formal authorization letter is received by the PI from the sponsor's representative.

### 15.1.2. Protocol Modifications

All modifications to the protocol and supporting documents (informed consent, study-specific procedures, SOPs, recruitment materials, etc.) must be reviewed and approved prior to implementation. Any protocol amendment will be agreed upon and approved by the sponsor's representative prior to submission to the local IRB and/or the [redacted] and prior to implementation of any change or modification. Any modification that could potentially increase risk to patients must be submitted to the FDA prior to implementation. The ICF must be revised to concur with any amendment as appropriate and must be reviewed and approved with the amendment. Any patient already enrolled in the program will be informed about the revision and asked to sign the revised ICF if the modification directly affects the individual's participation in the program. A copy of the revised, signed, and dated ICF will be given to the patient. All original versions of the ICF will be retained in the protocol regulatory file, and a copy will be retained in the protocol regulatory file.

### 15.1.3. Protocol Deviation Procedures

All subject-specific deviations from the protocol (eg, failure to return for follow-up visits or blood collection within the time indicated in the protocol) are to be documented. The PI or designee will be responsible for identifying and reporting all deviations, which are defined as isolated occurrences involving a procedure that did not follow the study protocol or study-specific procedure. Deviations will be reported annually in the continuing review report to the local IRB and/or the [redacted] and, if appropriate, in the final study report. Action taken in response to the deviation and the impact of the deviation will be assessed by the PI or subinvestigator and recorded as significant or nonsignificant.

Any protocol deviation that adversely affects the safety or rights of a subject or the scientific integrity of the study will be reported immediately to the sponsor's representative, local IRB, and/or the [redacted].

## 15.2. Ethical Conduct of the Study

This study will be conducted in accordance with all applicable federal and DoD human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice.

The procedures set out in this study are designed to ensure that the sponsor's representative and all study personnel abide by the principles of the ICH GCP Guidelines and the CFR. The PI confirms this by signing this study protocol and FDA Form 1572.

### 15.2.1. Confidentiality

HIPAA requires that researchers obtain the subject's permission (HIPAA Authorization) to use and disclose health information about the subject that is either created by or used in connection with this research. The information includes the entire research record and supporting information from the subject's medical records, results of laboratory tests, and both clinical and research observations made during the individual's participation in the research.

In this research, the subject's health information will be collected and used to conduct the study; to monitor the subject's health status; to measure effects of the investigational product; to determine research results, and possibly to develop new tests, procedures, and commercial products. Health information is used to report results of research to the sponsor's representative and federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. After the study ends, each subject has the right to see and receive a copy of his or her information.

Representatives of the TSG-DA as the IND sponsor, the sponsor's representative, the local IRB and/or the [redacted], the DoD, and the FDA are eligible to photocopy and review records related to this protocol as a part of their responsibility to protect the participants of this protocol. In addition, these representatives are eligible to witness the applicable study procedures to ensure the safety of subjects.

No personal identifier will be used in any publication or communication used to support this research study. The subject's identification number will be used in the event it becomes necessary to identify data specific to a single subject.

### 15.2.2. Medical Care for Research-Related Injury

All nonexempt research involving human subjects shall, at a minimum, meet the requirement of 32 CFR 219.116(a)(6).

If a subject is injured because of participation in this research, s/he may choose to seek care under their personal health insurance, and their workers' compensation/disability coverage may also apply. No reimbursement is available for medical expenses to treat research-related injuries. No compensation is available for research-related injuries. This does not constitute a waiver or release of legal rights.

## 15.3. Written Informed Consent

The informed consent process and document will be reviewed and approved by the local IRB and/or the [redacted] and sponsor's representative prior to initiation of the study. The consent form

contains a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with 21 CFR 50. The consent form indicates that by signature, the subject, or where appropriate, legal guardian, permits witnessing of applicable study procedures by the sponsor's representative, as well as access to relevant medical records by the sponsor's representative and by representatives of the FDA. The sponsor's representative will submit a copy of the initial IRB- and sponsor's representative-approved consent form to the FDA and will maintain copies of revised consent forms that have been reviewed and approved by the local IRB and/or the [redacted].

A written ICF, in compliance with 21 CFR Part 50, 32 CFR Part 219, the Belmont Principles, and HIPAA Authorization will be signed by the subject before any study-related procedures are initiated for that subject. This consent form must be retained by the investigator as part of the study records. Each subject will receive a copy of the signed ICF. The investigators or their designees will present the protocol in lay terms to individual subjects. Questions on the purpose of the protocol, protocol procedures, and risks to the subjects will then be solicited. Any question that cannot be answered will be referred to the PI. No subject should grant consent until questions have been answered to his or her satisfaction. The subject should understand that the study product is an investigational drug and is not licensed by the FDA for commercial use but is permitted to be used in this clinical research. Informed consent includes the principle that it is critical the subject be informed about the principal potential risks and benefits. This information will allow the subject to make a personal risk versus benefit decision and understand the following:

- Participation is entirely voluntary,
- Subjects may withdraw from participation at any time,
- Refusal to participate involves no penalty, and
- The individual is free to ask any questions that will allow him or her to understand the nature of the protocol.

Should the protocol be modified, the subject consent form must be revised to reflect the changes to the protocol. If a previously enrolled subject is directly affected by the change, the subject will receive a copy of the revised ICF. The approved revision will be read, signed, and dated by the subject.

The subject will be informed that a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US law.

# 16. DATA HANDLING AND RECORDKEEPING

The primary source document for this study will be the subject's medical record. Source documents will be retained at the site.

Paper source documents will be used for this study and source data will be entered into an electronic database system. The eCRF layouts and specifications will define and identify the applicable source data that will be collected and entered into the system. Applicable source data will be electronically transcribed by the site designee onto the eCRF (data entry screens). The investigator is ultimately responsible for the accuracy of data transcribed onto the eCRF. Data

monitoring and management will be performed in the database system by the [redacted] clinical trial monitor and the designated clinical data management contract research organization.

All individuals who will be expected to transcribe data into the eCRF will be given the training necessary to perform their assigned tasks as described in 21 CFR 11.10(i)). Training will be conducted by qualified individuals from the designated clinical data management contract research organization, both initially and on a continuing, as-needed basis. The training documentation will be maintained at the trial site. The sponsor will also keep a record of the training files.

A detailed data management plan will be written prior to study start, with approval by the sponsor's data manager in the [redacted] Clinical Data Management Branch. All updates to the data management plan must be approved before study closeout and database lock.

## 16.1. Inspection of Records

The sponsor's representative or designee will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, investigational product stocks, drug accountability records, subject charts, study source documents, and other records relative to study conduct.

Subjects' health information is used to report results of research to the sponsor's representative and federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. The consent form indicates that by signature, the subject permits access to relevant medical records by the sponsor's representative and by representatives of the FDA.

Upon a subject's termination from the trial, completed eCRFs will be ready and available for on-site review by the sponsor's representative or the designated representative within 14 days after receipt of the subject's data.

## 16.2. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved for 2 years following the discontinuance of the investigational product for investigation. If it becomes necessary for the sponsor's representative or designee or the FDA to review any documentation relating to the study, the investigator must permit access to such records.

Completed, monitored eCRFs will be stored in a secure location by the sponsor's representative or designee. A copy of each completed eCRF will be retained by the investigator.

The PI will be responsible for retaining sufficient information about each subject (ie, name, address, telephone number, Social Security number, and subject identifier in the study) so that the sponsor's representative, the local IRB, the FDA, employees of [redacted], or other regulatory authorities may have access to this information should the need arise.

It is the policy of the [redacted] that data sheets are to be completed for all subjects participating in research (Form 60-R, Volunteer Registry Data Sheet). The data sheets will be entered into this Command's Volunteer Registry Database. The information to be entered into

this confidential data base includes the subject's name, address, and Social Security Number; study title; and dates of participation. The intent of this database is twofold: first, to readily answer questions concerning an individual's participation in research sponsored by [redacted] and second, to ensure that [redacted] can exercise its obligation to ensure research subjects are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at [redacted] for a minimum of 75 years. The Volunteer Registry Database is a separate entity and is not linked to the study database.

## 17. PUBLICATION POLICY

All data collected during this study will be used to support this IND. All data may be published in the open medical or military literature with the identity of the subjects protected. Anyone desiring to publish or present data obtained during the conduct of the study will conform to local site policies and then forward the publication for review to the Director, [redacted].

# 18. LIST OF REFERENCES

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## 18.2. Study Reports

[redacted]

# 19. APPENDICES

# APPENDIX A. VISUAL ANALOG SCALES

Note: This example is for illustration purposes and may not be to scale. The horizontal line should be exactly 10 cm in length after the form is printed, with a vertical line in the exact center of the horizontal line. After completion, the distance (cm) from the "zero" point to the subject's mark is measured and recorded in the source.

| VISUAL ANALOG SCALES (VAS): INJECTION SITE ASSESSMENT | |
|---|---|
| PAIN | Place a vertical mark on the line below to indicate how **PAINFUL** the injection site feels currently.<br>0 NO PAIN — 10 SEVERE PAIN |
| ITCHING | Place a vertical mark on the line below to indicate how **ITCHY** the injection site feels currently.<br>0 NO ITCHING — 10 SEVERE ITCHING |
| TINGLING | Place a vertical mark on the line below to indicate level of **TINGLING** at the injection site currently.<br>0 NO TINGLING — 10 SEVERE TINGLING |
| NUMBNESS | Place a vertical mark on the line below to indicate how **NUMB** the injection site feels currently.<br>0 NO NUMBNESS — 10 SEVERE NUMBNESS |
| Subject Signature: | Staff Signature: |

# APPENDIX B. TOXICITY GRADING SCALE FOR INJECTION SITE REACTIONS

| Local Reaction to Injectable Product | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| Pain | Does not interfere with activity | Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity | Any use of narcotic pain reliever or prevents daily activity | Emergency room (ER) visit or hospitalization |
| Tenderness | Mild discomfort to touch | Discomfort with movement | Significant discomfort at rest | ER visit or hospitalization |
| Erythema/ Redness[a] | 2.5-5 cm | 5.1-10 cm | > 10 cm | Necrosis or exfoliative dermatitis |
| Induration/ Swelling[b] | 2.5-5 cm and does not interfere with activity | 5.1-10 cm or interferes with activity | > 10 cm or prevents daily activity | Necrosis |

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

# APPENDIX C. INJECTION SITE ASSESSMENT FORM

| **Injection Site Assessment** | | | |
|---|---|---|---|
| **Nominal Time Point: _____** | | **Time of Assessment: __ __: __ __** | |
| **Injection Site Location (circle one): Right Thigh Left Thigh** | | | |
| **Local Reaction** | **Severity (circle one)** | **Comments** | **Staff Initials** |
| **Injection Site Pain** | **None Mild Moderate Severe Potentially Life Threatening** | _____ _____ _____ _____ _____ | |
| **Tenderness** | **None Mild Moderate Severe Potentially Life Threatening** | _____ _____ _____ _____ _____ | |
| **Erythema/ Redness** | **None Mild Moderate Severe Potentially Life Threatening** | _____ _____ _____ _____ _____ | |
| **Induration/ Swelling** | **None Mild Moderate Severe Potentially Life Threatening** | _____ _____ _____ _____ _____ | |
| ***SEE APPENDIX B: Toxicity Grading Scale for Injection Site Reactions*** | | | |
| ***Mild = Grade 1, Moderate = Grade 2, Severe = Grade 3, Potentially Life Threatening = Grade 4*** | | | |

# APPENDIX D. RICHMOND AGITATION AND SEDATION SCALE (RASS)

| Score | Term | Description | |
|---|---|---|---|
| +4 | Combative | Overtly combative, violent, immediate danger to staff | |
| +3 | Very agitated | Has aggressive behavior toward staff | |
| +2 | Agitated | Frequent non-purposeful movement | |
| +1 | Restless | Anxious but movements not aggressive vigorous | |
| 0 | **Alert and calm** | | |
| -1 | Drowsy | Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice **(>10 seconds)** | Verbal Stimulation |
| -2 | Light sedation | Briefly awakens with eye contact to *voice* **(<10 seconds)** | |
| -3 | Moderate sedation | Movement or eye opening to *voice* **(but no eye contact)** | |
| -4 | Deep sedation | No response to voice, but movement or eye opening to *physical* stimulation | Physical Stimulation |
| -5 | Unarousable | No response to *voice or physical* stimulation | |

**Procedure for RASS Assessment**

1. Observe patient
    a. Patient is alert, restless, or agitated — Score 0 to +4
2. If not alert, state patient's name and say to open eyes and look at speaker.
    b. Patient awakens with sustained eye opening and eye contact. — Score -1
    c. Patient awakens with eye opening and eye contact, but not sustained. — Score -2
    d. Patient has any movement in response to voice but no eye contact — Score -3
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum
    e. Patient has any movement in response to voice but no eye contact. — Score -4
    f. Patient has no response to any stimulation — Score -5