IND 130620; Protocol S-16-14

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

Statistical Analysis Plan

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List of Abbreviations and Definitions

Abbreviation	Explanation
AEs	Adverse Events
ANOVA	Analysis of Variance (also known as multivariate regression)
ATC	Anatomical Therapeutic Chemical
AUC_{∞}	Area under the Curve at Infinity
AUC_{last}	Area under the curve at last measurement
AV	Atrioventricular
BLQ	Below Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure
BPRS	Brief Psychiatric Rating Scale
C_{max}	Maximum concentration
CNS	Central Nervous System
CRF	Case Report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of Variation
DLTs	Dose-limiting toxicity
DSMB	Data and Safety Monitoring Board
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
FDA	Food and Drug Administration
FDR	False Discovery Rate
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM	Intramuscular
IND	Investigational New Drug
IV	Intravenous
Kg	Kilogram
L	Liter
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minute
mL	milliliter
MRT	Mean Residence Time
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PR interval	Time between P and R waves
[redacted]	[redacted]
QRS interval	Time between Q, R, and S waves
QTc	QT interval adjusted for heart rate
QTcF	QTC (Fridericia)

RASS	Richmond Agitation Sedation Scale
SAE	Sever Adverse Event
SAP	Statistical Analysis Plan
Scop HBT	Scopolamine Hydrobromide Trihydrate
SD	Study Day
Sec	Second
SEM	Standard Error of the Mean
Ng	Nanogram
$t_{1/2}$	Half life
TEAEs	Treatment-emergent Adverse Events
T_{max}	Time to maximum concentration
VAS	Visual Analog Scale
V_d/F	Apparent Volume of Distribution
WHO	World Health Organization

Summary of Changes

Version	Change	Sections	Made By	Approved by
2.0	Updated personnel	Page 1-2	[redacted]	[redacted]
	Corrected typographical error	3.1		
	Clarified references to protocol appendices	5.1.3.1 5.1.10		
	Corrected references to other parts of the SAP	6.3		
	Updated to clarify PK analysis will be presented in separate PK report	6.6.2		
	Revised statistical modeling for PK parameters to better reflect the Protocol specified analyses.	6.3, 6.15		
	Updated to add imputation rules for missing or partial dates for AEs and concomitant medications	6.6.3		
	Updated to remove figures based on discussion and agreement from client Biostatistician. No figure shells will be provided.	5.1.9, 6.2 6.14.2, 6.14.3, 6.14.4, 6.14.6, 6.14.8, 6.18		
	Add Table and Listing shells.	Table and Listing Shells		

1. INTRODUCTION/BACKGROUND

This statistical analysis plan (SAP) describes the data analysis specifications for IND 130620; Protocol S-16-14 entitled "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." The preparation of this SAP adheres to the IRB-approved protocol S-16-14 version 2.0 dated March 12, 2020.

This SAP follows the International Conference on Harmonisation (ICH) Guidelines E3 and E9. In cases in which the analyses in this SAP differ from those in the study protocol, the analyses in the SAP supersede those in the protocol. Should differences exist, these will be described in Section 6.2 of this document.

This initial Phase 1 trial is a single, ascending dose study in healthy volunteers with single doses of Scopolamine Hydrobromide Trihydrate (Scop HBT) ranging from 0.005 to 0.021 mg/kg administered in a single intramuscular (IM) injection. The dosing regimen to be evaluated in future trials will be determined in part on the basis of the pharmacokinetic (PK) and safety data obtained in this Phase 1 study. All statistical analyses will be performed using SAS®, Version 9.4 or higher.

2. STUDY OBJECTIVES

The objectives of this study are:

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

3. STUDY DESIGN

3.1 OVERVIEW AND LENGTH OF STUDY

This is a double blinded, placebo-controlled, Phase 1 sequential dose escalation study to evaluate the safety, tolerability, and PK of Scop HBT in healthy participants. Healthy volunteers will be assigned to one of five target dosage groups to receive Scop HBT or placebo, administered by IM injection. In each dosing cohort, the ratio of participants receiving placebo vs. active drug will be 1 placebo subject for every 3 active participants. Up to 60 participants *will* be enrolled.

Participants will be assigned, sequentially, to one of five escalating target dosage groups or to the placebo group beginning with the lowest dose first. New participants will not be enrolled into the next higher dose until at least eight participants in the previous dosing cohort have completed 8-day follow-up visits without the occurrence of DLTs, pre-defined as requiring termination of the study, and until approval by the data safety monitoring board (DSMB) following its review of the study data. Four additional participants, three active and one placebo, may be added to each cohort, depending upon AEs exhibited in the first eight participants.

The study drug or placebo will be administered IM into the anterior thigh using a consistent procedure. The dose will be based on the subject's weight. Treatment will begin at the lowest of

five Scop HBT target doses (0.005, 0.007, 0.011, 0.014, and 0.021 mg/kg) and progress to the next higher dosage escalating by multiples that range between 1.25 and 1.6 for each cohort. Escalation to the next dose level will only occur after safety has been determined by the DSMB in at least eight and up to twelve participants (of whom 6-9 will receive study drug), based on the clinical responses of the participants to each dosage level. Escalation will occur no sooner than six weeks after the first subject in each cohort has been dosed.

Participants will report to the study site on the day prior to scheduled dosing. On the day of dosing, ECG (3-5 lead) and vital signs (excluding body temperature) will be monitored continuously for 24 hours. Blood pressure (BP) will be evaluated and documented at specified times through the 48-hours post administration. Echocardiograms will be conducted at screening, baseline (Day -1), and at Study Days (SD) 1,2,3 & 8. Blood and urine samples for safety monitoring will be collected prior to dosing and according to a specified schedule through 48 hours post-dosing, as well as during the subject's return visit on SD 8. Blood and urine samples for PK analyses will be collected prior to dosing and according to a specified schedule through 24 hours post-dosing.

All participants will be observed as in-patients at the research center for the first 48 hours (post-dose) for AEs. Participants will also return for a study visit on SD 8 and receive a follow-up telephone call on SD 4 and SD 30. The study schedule of visits (time and events table) is presented in Section 3.2.

3.2 STUDY SCHEDULE (TIME AND EVENTS TABLE)

Table 1: Timeline of Key Events

Study Phase	**Screening**	**Baseline**[a]	**Treatment**[a]			**Follow-up**[b]		
Study Day **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	X	X						
Physical 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	

Study Phase	Screening	Baseline[a]	Treatment[a]			Follow-up[b]		
Study Day **Procedures**	**-30 to -2**	**-1**	**1[c]**	**2 (24 ± 1 h)**	**3 (48 ± 1 h)**	**4 (+ 2 days)**	**8 (+2 days)**	**30 (+ 7 days)**
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	
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] (DSST)	X	X		X			X	

[a] Participants 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 2 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.

[c] See Table 2 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.

[f] Hematology (including coagulation), serum chemistry, and urinalysis (refer to Section 5.1.6 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 protocol Section 5.1.6 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 2 for vital sign time points from pre dose through 24 hours post dose.

[k] See Table 2 for time points to performing ECG (supine) from pre-dose through 24 hours post-dose.

[l] See Table 2 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); 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 2 for collection intervals from pre-dose through 24 hours post dose.

[m] See Table 2 for AE assessment time points from pre dose through 24 hours post dose.

[n] Continuous cardiovascular monitoring of ECG (3-5 lead) and vital signs (blood pressure, heart rate, respiration rate, and pulse oximetry) from 1 hour prior to dosing through 24 hours post dose (see Table 2)

[o] Injection site assessments: Subject will be asked to rate the maximum intensity of pain, pruritus, tingling, and numbness using the VAS. See Table 2 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 2 for assessment time points on Day 1. For items assessed over time (e.g., 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 severity only 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.

[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 2: 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	
Abbrev Physical Exam	X																		
Injection Site: VAS[a]	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[b]															6				
C-SSRS																			
RASS			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	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 (3-5 lead) & vital signs (blood pressure, heart rate, respiration rate, & pulse oximetry) ⟷															End	

[a] If the PI or designee determines a subject is incapable of providing valid responses on the VAS or DSST due to the neuropsychiatric effects of Scop HBT, the reason(s) why the VAS assessment(s) could not be done will be documented by time point, and VAS or DSST assessments will be conducted once deemed subject is capable of providing responses.

[b] BPRS will be performed 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.

3.3 STUDY DRUG ADMINISTRATION AND EXTENT OF EXPOSURE

3.3.1 Dose Limiting Toxicity and Progression of Groups

New participants will not be enrolled into the next higher dosage group until at least 8 participants in the previous cohort have completed the SD 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 participants can be enrolled. The occurrence of any extreme DLT(s) or serious adverse events (SAEs), except unrelated, would result in the immediate discontinuation of dosing and study enrollment, pending a review of study data by the PI, the DSMB, and the sponsor. Nonextreme DLTs can result in halting of dosage pending review. Enrollment will also be halted if two nonextreme DLTs occur in the first four participants in a cohort or 3 participants in total.

Table 3: Progression of Dosing Related to Dose-Limiting Toxicity Events

Dose-Limiting Toxicity	Number of Participants	Action	Follow-up
Extreme DLT	1	Dosing and enrollment halted	PI and DSMB to make recommendation to sponsor whether trial should continue
Nonextreme DLT	1 of first 4 in a cohort (or 2 in the first 8)	Dosing halted	PI and DSMB to make recommendation to sponsor 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 and DSMB to make recommendation to sponsor 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

3.4 STUDY POPULATION

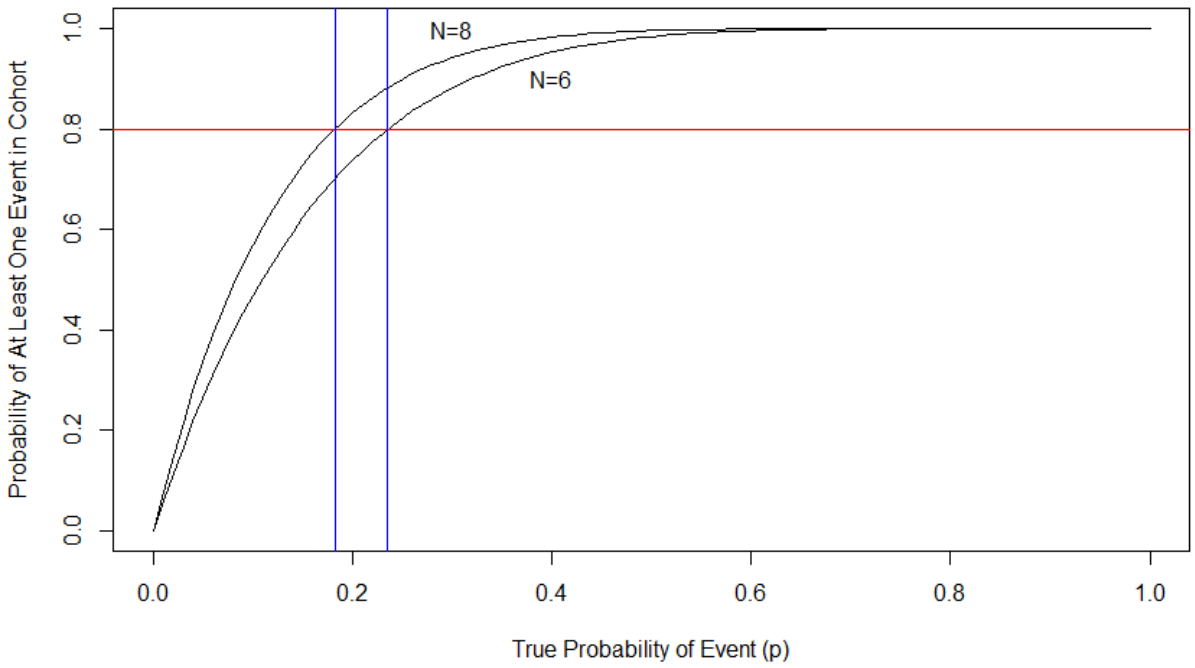
The study will include up to 60 male and female volunteers, 18 to 55 years of age, who will be enrolled in 5 dosing groups (cohorts) of 8 to 12 participants each. The actual number enrolled in the study will be determined by the safety responses noted during the study. Each of the 5 cohorts will include at least 3 male and 3 female participants enrolled among the first 8 participants in the cohort to ensure that at least 1 male and 1 female subject in each dosing group receive active drug. Each cohort will include 6 to 9 individuals receiving active and 2-3 receiving placebo doses (total of 30-45 active and 10-15 placebo).

3.5 SAMPLE SIZE CALCULATION/JUSTIFICATION

The planned sample of 40-60 healthy participants was chosen to provide a cohort size of 8–12 per dose (6-9 active, 2-3 placebo). This cohort size is customary in Phase 1 clinical trials with safety and tolerability as primary endpoints as it allows detection of common dose-limiting

toxicities or SAEs. In a cohort of *N* individuals dosed with the active drugs, the probability that one non-extreme DLT or SAEs with a true probability of occurrence, p, will be observed is $1-(1-p)^N$. There is 80% chance that at least one event with true probability of occurrence of 23.5% will occur within a cohort of 6 active participants. In a cohort of 8 participants, there is 80% probability of an event occurring if its true probability of occurrence is 18.2%. The addition of placebo controls is intended to help distinguish drug-related and unrelated events and for comparison of injection site reactions, cognitive, and neuropsychiatric responses.

Figure 1: Power to Detect an Adverse Event with Probability of Occurrence, *P*, in an Active Drug Cohort of Size *N*



3.6 RANDOMIZATION SCHEME

Participants will be randomized to receive either active Scop HBT or placebo injections using a blocked randomization design. In each cohort, 6 to 9 participants will receive active drug and 2 to 3 participants will receive placebo. Each cohort will have at least at least 3 male and 3 female participants enrolled among the first 8 participants in the cohort to ensure that at least 1 male subject and 1 female subject in each dosing group receive active drug. The study PI will create cohorts of 8 to 12 participants. If a participant withdraws or is excluded, the participant will be replaced by a participant of the same or opposite sex so long as the sex of all participants in the block conforms to the requirements.

Randomization will assign cohort members to active Scop HBT or Placebo at a ratio of 3 active to 1 placebo. Randomization will be conducted using blocking with three different block sizes per cohort. A block of 2 (1 active and 1 placebo) will be used for the first two participants in each cohort (Table 4A). A block of 6 (5 active and 1 placebo) will be used to assign the next 6 participants in each cohort (Table 4B). A block of 4 (3 active and 1 placebo) will be used to randomized participants in a possible expansion cohort. The blocks will be randomly permuted using a randomization program for each dosage level to yield a randomization plan.

Table 4: Blocks with Sample Randomization Assignment

A. Block of Two for the First Two Participants in a Cohort

Participant Order	Randomization Assignment (Only visible to unblinded individuals)
1	Placebo
2	Active Scop HBT

B. Block of Six for Third to Eighth Participants in a Cohort

Participant Order	Randomization Assignment (Only visible to unblinded individuals)
3	Active Scop HBT
4	Active Scop HBT
5	Active Scop HBT
6	Active Scop HBT
7	Placebo
8	Active Scop HBT

C. Block of Four for Cohort Expansion Participants

Participant Order	Randomization Assignment (Only visible to unblinded individuals)
9	Active Scop HBT
10	Placebo
11	Active Scop HBT
12	Active Scop HBT

For cohorts of 8 participants, only the first two blocks will be used. The third block will be used only if the cohort is expanded from 8 to 12. A sample randomization assignment for a dosing cohort is included in Table 5.

Table 5: Sample Randomization Scheme for a Dosing Cohort

Cohort	Block	Participant	Sex	Randomization Assignment *(Only visible to unblinded individuals)*
Primary (N=8)	1	1	F	Placebo
		2	M	Active Scop HBT
	2	3	M	Active Scop HBT
		4	F	Active Scop HBT
		5	F	Active Scop HBT
		6	M	Active Scop HBT
		7	M	Placebo
		8	M	Active Scop HBT

Expansion (N=4)	3	9	F	Active Scop HBT
		10	F	Placebo
		11	F	Active Scop HBT
		12	M	Active Scop HBT

4. ANALYSIS SETS

4.1 INTENT-TO-TREAT POPULATION

The Intent-To-Treat Population is defined as all participants who are enrolled and randomized into the trial.

4.2 SAFETY POPULATION

The Safety Population consists of all participants who received any amount of study medication, regardless of disposition. All safety analyses will be performed on this population.

4.3 PHARMACOKINETICS POPULATION

The PK Population will include any subject who receives a dose of active Scop HBT and has at least one blood draw to determine the concentration of scopolamine in plasma or one urine sample to determine concentration in urine. All PK analyses will be performed on this population. Please note, the calculation of PK parameters will not be described or performed within this SAP. A separate PK manual and the report will detail the procedures, results, and limitations for the PK parameters.

4.4 OTHER ANALYSIS POPULATIONS (INCLUDING SUBGROUPS)

No subgroup analyses are proposed. PK analyses will include adjustment for sex of the participant. Although no additional analyses of sub-populations are planned at this time, additional populations and analyses may be conducted at the discretion of the Sponsor to supplement the results or for research purposes. Analysis of subgroups conducted after the final SAP is approved will be labeled as “post hoc” in the final statistical report/and or CSR.

4.5 TREATMENT MISALLOCATIONS

Should any treatment misallocations occur, all participants will be analyzed in the Safety and PK populations “As Treated” instead of “As Randomized”. Due to the nature of this study whereby the biological effect of the study medication is being examined without respect to efficacy assessment, analyzing the participants “As Treated” is sufficient. A listing will be provided to display any participants with treatment misallocations, should they occur.

5. ENDPOINTS AND COVARIATES

5.1 SAFETY ENDPOINTS

The first objective of this study is to characterize the safety of Scop HBT at varying dosages. The study specifically defines three types of safety endpoints in the protocol: extreme dose-limiting toxicities (DLTs), nonextreme DLTs, and serious adverse events (SAEs) related to the drug. Any events or issues not defined as extreme/nonextreme DLTs or SAEs will be considered as Adverse Events (AEs). In addition to AEs, data will be collected and analyzed on injection site

assessments and changes in cognitive function, neuropsychiatric status, vital signs, clinical laboratory results, heart rhythm, and physical health status.

5.1.1 Extreme Dose-Limiting Toxicities

Extreme DLTs include specific respiratory, neuropsychiatric, cardiac, renal, and severe injection site reaction events as outlined below and in the protocol section 7.6.1.1. These events are defined in the protocol and will be determined by the study PI, Pharmacovigilance 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 (e.g., 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

5.1.2 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. 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 (e.g., 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[1] for injection site reactions (See protocol Appendix B).

5.1.3 Adverse Events (AEs)

The term "AE," as used by the Sponsor, is synonymous with the term "adverse experience," which is used by the FDA. 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. 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. "Unexpected," as used

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical

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.

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

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.

5.1.3.1 Severity

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 protocol* 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).

Note that use of rescue medications may be appropriate in response to the SAEs.

5.1.3.2 Relationship

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.

5.1.4 Serious Adverse Events

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.

Hospitalization is to be considered only as an overnight admission. Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. In the absence of an AE, the participating Investigator should not report hospitalization or prolongation of hospitalization on a form. This is the case for Hospitalization for survey visits or annual physicals.

In addition, a hospitalization planned before the start of the study for a preexisting condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the study).

If there is any doubt whether the information constitutes an AE or SAE, the information is treated as an AE or SAE.

5.1.5 Vital Signs

Vital signs, (minus body temperature), will be continuously monitored for 24 hours post-dosing. For reporting purposes, observations at specific time points as defined in Section 3.2 will be used. Where the time of vital signs monitoring coincides with a blood draw, vital signs will be taken prior to the scheduled blood draw. Vital signs may be taken at other times, if deemed necessary.

5.1.6 Clinical Laboratory Tests

5.1.6.1 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

5.1.6.2 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

5.1.6.3 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)

5.1.6.4 Pregnancy Screen

All female participants, 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 SD 8, or at study termination, if it occurs before SD 8.

5.1.6.5 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

5.1.7 Electrocardiograms

The 3-5-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 with 3-lead 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: Participants will not be allowed to shower from pre dose until after all 24-hour, post-dose procedures have been completed and the electrodes removed.

5.1.8 Neuropsychiatric/Behavioral Assessments

Assessments of neuropsychiatric/behavioral symptoms will be performed by study staff using the C-SSRS, BPRS (expanded version 4.0, 24 items), and RASS (if general agitation or sedation are reported). A psychiatrist will be available on-site 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 a physician, physician assistant, or nurse at screening, and the C-SSRS Since Last Visit version will be administered at SD -1 and at follow-up on SD 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 C-SSRS has excellent inter-rater reliability[2].

The BPRS will be performed by a psychologist or trained clinician. The BPRS will be assessed at screening, SD -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 on SD 8. In order to improve reliability between administrations, a structured interview guide will be used and the same clinician will administer the BPRS to each participant. For BPRS items assessed over time (e.g., items #1, 2, and 3), the reference 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 BPRS has low inter-rated reliability, and measures will be taken to ensure that it is captured consistently over time.

5.1.9 Cognitive Assessment

The digit symbol substitution test (DSST) will be used to measure cognitive impairment associated with Scop HBT. Study staff are experienced at performing the test, which typically takes 8 minutes to complete. The DSST will be administered at screening, at SD -1 (baseline), 48 hours after injection (SD 3), and at the SD 8 follow-up visit. The DSST conducted at screening is intended to reduce practice effects. If the PI or designee determines a subject is incapable of engaging in the DSST at one or more time point(s), the reason(s) why the DSST assessment(s) could not be done will be documented by time point in the source documentation.

The DSST will be used test for persistent cognitive impairment associated with Scop HBT at the individual and population levels. Differences in raw scores (number of correct pairings in 120 seconds) between baseline and SD 3 and SD 8 will be presented individually in listings. The

[2] Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ (2011). *The Columbia-Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults.* American Journal of Psychiatry 168(12): 1266-77.

persistent effects of Scop HBT on cognition will also be assessed through comparison of within-person changes in scores from baseline between active and placebo groups

5.1.10 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 (*see protocol* 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; *see protocol* Appendix C). Refer to *protocol* Appendix B for the Toxicity Grading Scale for Injection Site Reactions.

The anticipated neuropsychiatric effects of Scop 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.

5.1.11 Physical Examinations

Each subject will have a complete physical examination at screening, Day -1, pre-injection (abbreviated) and at 48 hours (abbreviated) and SD 8 post-injection. A complete physical examination will include the assessment of the following body systems: general appearance, eyes, ears, nose and throat, chest/abdominal, heart/cardiovascular, abdomen/gastrointestinal, lymph nodes/spleen, genitourinary, musculoskeletal, skin, neurological, hepatic and other. The results of the physical examination will be recorded in the subject's medical record and clinically significant findings will be recorded in the case report form (CRF). The abbreviated physical examination will include documentation of any changes from the screening assessment.

5.2 PHARMACOKINETICS ENDPOINTS

Determination of PK parameters at varying dose levels is an objective of this study, as is investigation of dose proportionality for C_{max} and AUC_{∞}. The PK measures, their definitions, methods of calculation, and methods for their statistical interpretation are described further.

5.2.1 Plasma Pharmacokinetics

The PK parameters will not be calculated as part of this SAP, but they will undergo statistical analysis according to this SAP. The PK parameters will be calculated by the Battelle Chemistry Technical Center according to their Standard Operating Procedures and conventions, using WinNonlin Phoenix v8.1). Plasma concentration time profiles for each subject tested will be evaluated using semi-log plots and characterized using noncompartmental analysis.

Descriptive statistics for the concentration of Scopolamine in plasma and for the PK parameters will be calculated at each scheduled time point. The summary of descriptive statistics at each time point will be displayed by cohort and dose level. The statistics will include sample size, mean, median, standard deviation (SD), standard error of the mean (SEM), percent coefficient of variance (CV), minimum, and maximum for continuous variables, and 95% confidence intervals. Additionally, geometric means will be calculated for AUC_{∞} and C_{max}.

Analysis of plasma concentrations will be performed for each subject on samples collected prior to dosing and at the following post-dose target time points: 2, 5, 10, 15, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 36, and 48 hours post dose. Table 6 describes the time windows for blood draw. PK parameters will be calculated using the time points of the actual blood draw, rather than the target time. The serum PK parameters that will be analyzed are listed below and are outlined and defined as in the protocol:

- **C_{max}**: Maximum measured plasma concentration over the time span specified.
- **T_{max}**: Time of 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.
- **$t_{1/2}$**: Apparent first-order terminal elimination half-life will be calculated as $0.693/k_e$.
- **V_d/F**: Apparent Volume of distribution.
- **Cl/F**: Apparent Volume of blood or plasma cleared of drug per unit time.
- **MRT (Mean Residence Time)**: Mean time the drug spends in the body before being eliminated.
- **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_∞**: The area under the plasma concentration versus time curve from time 0 to infinity. AUC_∞ 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.
- **C_{max}/Dose**: Dose normalization of C_{max} for evaluation of dose proportionality.
- **AUC_∞/Dose**: Dose normalization of AUC_∞ for evaluation of dose proportionality.

The terminal elimination phase is used to estimate a number of PK parameters. No value for V_d/F, Cl/F, AUC_∞, or $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile. The PK analyses will not include the placebo group.

Outlier screens will first be carried out. For each PK parameter a one-way, heterogeneous variance analysis will be carried out across dose groups. Studentized residuals (i.e. residuals divided by their standard errors) will be calculated within each group and combined across groups. Studentized residuals in excess of three in absolute value will be considered "tentative outliers". The tentative outliers will be examined by Battelle to determine if they are due to testing errors or data entry errors. If so, they will be reported and omitted from subsequent analyses. If the tentative outliers are correctly determined they will be treated as outliers and subsequent analyses will be carried out both including and excluding the outlying values.

Table 6: Pharmacokinetic Blood Sample Deviation Windows

Target Time Point	Acceptable Sample Collection Time Point Range		
	Low-End Range	High-End Range	Window
2 min	1 min 50 s	2 min 10 s	20 seconds
5 min	4 min 40 s	5 min 20 s	40 seconds
10 min	9 min 30 s	10 min 30 s	60 seconds
15 min	14 min 15 s	15 min 45 s	60 seconds
20 min	19 min	21 min	2 minutes
30 min	28.5 min	31.5 min	3 minutes
1 h (60 min)	57 min	63 min	6 minutes
2 h (120 min)	114 min	126 min	12 minutes
4 h (240 min)	228 min	252 min	24 minutes
8 h (480 min)	465 min	495 min	30 minutes
12 h (720 min)	705 min	735 min	30 minutes
24 h (1440 min)	1425 min	1455 min	30 minutes
36 h (2160 min)	2145 min	2175 min	30 minutes
48 h (2880 min)	2865 min	2895 min	30 minutes

5.2.2 Urine Pharmacokinetics

Urine will be collected continuously for 24 hours post dosing. A sample of urine will also be collected within 2 hours prior to dosing. Urine samples for PK will be pooled into four periods: pre-dose, 0-4 hours post dose, 4-12 hours, and 12-24 hours. Urine samples will be analyzed for concentrations of Scopolamine. Urine samples may also be analyzed for metabolites of Scopolamine.

5.3 COVARIATES

In general, covariates are not applicable for this study, with the exception of PK analysis. The influence of the dose of Scopolamine will be evaluated in various analyses including the PK dose-response relationship, with sex included as a covariate. Sex is valid as a covariate in models of PK parameters based on plasma concentrations, as males typically have higher plasma volumes per unit body mass than females.

6. STATISTICAL METHODOLOGY AND ANALYSES

6.1 GENERAL CONSIDERATIONS

The first and second objective of this study will primarily be addressed through descriptive statistics of safety and PK data. Hypothesis testing and interval estimation will be limited. Specific hypotheses are detailed in 6.3 and interval estimation in 6.4. All data analyses and statistical testing will be conducted using SAS Version 9.4 or Stata version 15 or higher.

6.2 CHANGES FROM PROTOCOL SPECIFIED ANALYSES

Changes to the protocol specified analyses that are made prior to unblinding the data will be noted in a revised protocol and be approved by study sponsor, statistician, and ethical review committee. Upon approval, such analyses will be incorporated into the final SAP. The results of analyses not specified in the protocol but specified in the SAP prior to unblinding will be included in the final statistical report/and or CSR as "additional analyses".

Changes to the protocol-specified analyses made after unblinding of the data will be considered as "post-hoc". Post hoc analyses will not be included in the protocol amendments or the final SAP. In the final statistical report/and or CSR, post hoc analyses will be presented separately and subsequent to all analyses specified in the final protocol.

No interim analyses are planned. DSMB and [redacted] safety reviews are planned and do not constitute an interim analysis or changes from protocol-specified analyses.

No graphs/figures will be produced for final analysis based on discussion and agreement from client Biostatistician.

6.3 HYPOTHESES AND DECISION RULES

As the objective of this study is to characterize the safety and tolerability of escalating doses of Scop HBT, three sets of safety endpoints will be compared statistically between placebo and active dosing groups. Some PK parameters will also be compared statistically across dose levels. Table *7* describes the hypothesis testing pre-specified in the statistical analysis.

The null hypothesis of no worse scores for Injection Site VAS (pain, itching, tingling, numbness); change in BPRS Score (6 hours, 48 hours, 8 days); change in DSST (48 hours, 8 days); and C-SSRS (SD 8) between dose levels of active Scop HBT and placebo will be tested statistically using a one-sided alternative of worse (higher for C-SSRS, VAS, and BPRS, lower for DSST scores for Scop HBT vs. placebo. Each dose level will be tested against the same placebo group (all participants receiving placebo). Methods for analysis of neuropsychiatric scales and injection site reactions are described in Sections ~~6.13.4~~ *6.14.6* and *6.14.8*, respectively.

For PK parameters, variation across doses will be tested for T_{max}, $t_{1/2}$, V_d/F, Cl_F, and MRT against the null hypothesis of no difference across doses. A joint significance test (1 test per parameter) will be used.

Dose-proportionality will be tested using the dose-normalized parameters C_{max}/Dose and AUC_∞/Dose. A likelihood ratio test will be used for testing the joint null hypothesis of equivalence across all doses using a two-sided alternative. Each dose level will also be tested against the next dose level using a two-sided test. The methods for analysis and hypothesis testing are described in Section - *6.15*. A total of 110 hypothesis tests will be performed. Procedures for multiple comparisons are detailed in Section 6.8.

Table 7: Pre-Specified Hypothesis Tests

Drug Characteristic	Null Hypothesis	Relevant Endpoints [Count]	Number of Comparisons Per Parameter	Total Number of Hypothesis Tests
Safety	Equivalence with Placebo	Injection site VAS (pain, itching, tingling, numbness) x (10-45 minutes, 1-5 hours, 8-48 hours) [12] Change in BPRS score from baseline (6 hours, 48 hours, SD 8) [3] Change in DSST scores from baseline (48 hours, SD 8) [2]	5 (Each dose level vs. Placebo)	90
Safety	Equivalence with Placebo	C-SSRS (SD 8) [1] Change in DSST scores from baseline (48 hours, SD 8) [2] Proportion with lower raw DSST scores compared to baseline (48 hours, SD 8) [2]	1 (All dose levels vs. Placebo)	5
PK Dose-Equivalence	Equivalence across doses	T_{max}, $t_{1/2}$, V_d/F, MRT, Cl_F	1 Joint Test	5
PK Dose-Proportionality	Equivalence across doses	C_{max}/Dose AUC_{∞}/Dose	1 (joint test) 4 (each dose vs. next higher dose)	10
Total				110

6.4 UPPER-BOUND ESTIMATION FOR DLTS & SAES

As part of the first objective, to characterize the safety and tolerability of Scop HBT IM injection at varying dosages, upper limits for the probability of an event at each dosage will be estimated using data on the occurrence of extreme DLTs, non-extreme DLTs, and SAE.

Dose progression follows rules that require dosing be halted if an extreme DLT or a SAE related to the drug occurs within any cohort. Therefore, the maximum number of extreme DLTs that can occur in a cohort prior to stopping is one. Should one nonextreme DLT occur in the first four participants or two in the first 8 participants, dosing will be halted. If dosing is resumed (upon determination of the PI, DSMB, and sponsor) and a second nonextreme DLT occurs among the first 4 in cohort or 3 total DLTs occur, dosing and enrollment will be halted.

Confidence intervals will be determined using 80% confidence interval, such that there is a 10% probability that the true value exceeds the upper-bound. The Pearson-Clopper interval is the most conservative among the binomial intervals, resulting in the highest upper confidence bounds.

Should no events of any type occur within a cohort, with 6 participants dosed, the 80% confidence interval upper bound for the probability of any event is 0.32. Should one extreme

DLT or SAE occur in any cohort, the upper bound for the SAE/extreme DLT will depend on the number dosed prior to the event occurring. Table 8 shows the upper bounds of confidence intervals based on the number of participants receiving active Scop HBT.

Table 8: Upper-bound estimates of Risk Inferred from Events in Cohort

		Number Receiving Active Scop HBT			
		2	**4**	**6**	**9[1]**
Event Type	**Number of Participants with Event**	**80% C.I. Upper Bound (Pearson-Clopper Method)**			
No Events	0	N/A	N/A	0.32	N/A
Extreme DLT	1	0.95	0.68	0.51	0.37
Nonextreme DLT	1 of first 4 in a cohort, none thereafter	0.95	0.68	0.51	0.37
	2 in the first 8 in a cohort	1.0	0.86	0.67	N/A
	2 of the first 4 in a cohort	1.0	0.86	N/A	N/A
	3 in any cohort	N/A	0.97	0.80	0.60
SAE not already designated as a DLT (except unrelated)	1	1.0	0.68	0.51	0.37

[1]If nonextreme DLT occurs in a given cohort, the cohort may be expanded to 12 participants, a maximum of 9 of whom will receive active Scop HBT.

6.5 BLINDING AND UNBLINDING

This study is double-blinded. Study drugs 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 Scop HBT, Injection, the study staff will likely become unblinded as the CNS effects of Scop HBT will be evident in the participants, especially at the higher concentrations. Nevertheless, every effort should be made to maintain the blind, even at the higher concentrations.

In addition to the study pharmacist, another Pharmaron team member is unblinded in order to verify the dosing calculations at the time of subject treatment. One (1) Battelle statistician, one (1) pharmacokineticist, and PK sample analysts will be unblinded. The unblinded statistician will prepare the study data for the DSMB closed session meetings, including the PK data received from the pharmacokineticist.

Battelle will have a blinded statistician. The blinded statistician and all other Battelle staff responsible for cleaning the data and creating and validation of the tables, listings, and figures (TLFs), specifically the data management, statistics and programming staff, will be blinded throughout the study. Unblinding of the treatment levels will occur after all analysis populations are finalized and the final database is locked.

6.6 HANDLING OF MISSING VALUES, PARTICIPANT WITHDRAWAL, AND STUDY TERMINATION

Missing data can occur due to protocol deviations and withdrawal of participants from the study. All data documented in the CRFs will be presented in data listings. This means that missing values are listed as missing values. Repeated and additional measurements are listed as well.

6.6.1 Assessment of Missing

All missing datapoints will be identified from review of data listings. A table and listing of all missing data points will be generated for each endpoint with any missing. For each missing observation, the cause of missing will be identified from protocol deviations and participant disposition. Endpoints censored due to administration of rescue medication (as detailed in 6.11) will be presented separately. All protocol deviations will be listed by participant. The number of protocol deviations and the number of participants with protocol deviations will also be summarized by deviation category and by deviation classification (major/minor). If missing data is identified without a protocol-related reason or a protocol deviation, the missing measure will be added as protocol deviation.

6.6.2 Handling of Missing PK Data

For PK, a subject will be included in the calculation of the PK endpoints even if the subject has missing data at certain time points, as long as the subject has post-baseline data to define the PK plasma profile, i.e. a well-defined Cmax, Tmax, and at least three concentration time points to characterize the terminal linear phase.

Plasma concentration below the level of quantification (BLQ) will be censored. For the intended assay for Scopolamine, the limit of quantification is 0.010ng/mL. The upper limit of quantification is 10.0ng/mL. For samples that exceed the upper limit of quantification, dilution will be used to obtain quantifiable samples.

6.6.3 Handling of Other Missing Data

Other than AE data, for which missing will be imputed as the most severe, missing values will not be imputed for statistical summaries or analysis. All planned analyses of non-AE data will be conducted using all available data, including for participants who withdraw, with the exception of data to be censored following administration of rescue medications (as detailed in 6.11). In the event of study termination, all available data will be used for analysis of cohorts with at least one participant receiving the study drug.

Unless indicated otherwise, summary statistics will be reported for observed data only, with the exception of the cases described below.

Partial or incomplete start/end dates of the AEs or concomitant medications will be imputed to help determine treatment-emergent adverse events and prior or concomitant medications.

For incomplete start dates, following imputation rules will be implemented:

- *Missing day - Impute as the 1st of the month unless month is same as month of first dose of study drug then impute using the day of first dose date.*
- *Missing day and month – impute as 1st January unless year is the same as first dose date then impute using the day and month of first dose date.*

- *Completely missing – impute using the first dose date unless the end date suggests it could have started prior to this in which case impute as 1st January of the same year as the end date.*

When imputing a start date, ensure that the new imputed date is sensible i.e. is prior or equal to the end date of the AE or medication.

For incomplete end dates following imputation rules will be implemented:

- *Missing day - Impute as the last day of the month unless month and year are the same as the month and year of the end of study, then impute as the end of study date.*
- *Missing day and month – Impute as 31st December unless year is the same as the year of the end of study date then impute as the end of study date.*

Completely Missing – need to look at whether the AE/medication is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is not missing then assume that AE is still present / medication is still being taken (i.e. do not impute a date). If the AE/medication has stopped and start date is prior to first dose date then impute as the 1st dose date, if it started on or after first dose date then impute as the end of study date.

For partial or completely missing datetime (s), impute 00:00 if both minutes and seconds are missing. If minutes or seconds are missing, impute 00 accordingly. Make sure the new imputed datetime are sensible and does not affect the assignment of the AEs or Concomitant medication as treatment-emergent or ongoing respectively.

6.7 INTERIM ANALYSES

No interim analyses are planned. DSMB review will review data from each cohort. Dosing or enrollment may be halted if escalation criteria are not met. The DSMB may also recommend halting the trial at any point.

6.7.1 Dose Progression Criteria

Dosing may be halted prior to study completion. The criteria that require halting enrollment are specified in Table 3. Once halted the PI and DSMB will make recommendations to the sponsor on whether to resume enrollment.

6.7.2 Independent Data Safety Monitoring Board (DSMB) Analyses

An independent data safety monitoring board (DSMB) is required for this study. The DSMB will review safety and PK data for each cohort prior to cohort escalation. The DSMB will not conduct any statistical analyses or use a statistical test to determine whether to halt or terminate the trial.

6.8 ADJUSTMENT FOR MULTIPLE COMPARISONS

Section 6.3 specifies the hypotheses to be tested in this Phase 1 trial of the safety and pharmacokinetics of IM injection of Scop HBT. Given the large number of hypothesis tests, the Benjamini-Hochberg method will be used to determine statistical significance. As this trial is exploratory, a relatively high false discovery rate (FDR), the proportion of significant findings that are spurious, will be used. For this study, the FDR will be set at 0.20. The choice of a high FDR prevents rejecting marginally significant findings, which may provide important information about the drug's safety and pharmacokinetic properties. With 110 tests and an FDR of 0.20, the threshold for statistical significance for the five lowest p-values will be 0.0018,

0.0036, 0.0055, 0.0073, and 0.0091. Statistical significance of tests will be noted using at the alpha = 0.05 level as well as through the Benjamini-Hochberg method. Study sponsors should note that one-in-five significant findings obtained through this process are expected to be spurious.

6.9 POOLING OF SITES

Not applicable for the study since only 1 investigative site is being utilized.

6.10 DISTRIBUTIONAL ASSUMPTIONS

The residuals of ANOVA models will be assessed for normality using a Shapiro-Wilk test in conjunction with visual inspection of quantile-quantile plots. Lognormality is commonly assumed for PK parameters. If the normality assumption is not met, logarithmic (natural or base-10) transformation will be assessed. If lognormality is rejected, non-parametric bootstrap replication with a minimum of 10,000 replications will be used to calculate confidence intervals and perform hypothesis testing.

With small samples, the normality of parameters, such as the sample mean, cannot be assured. Therefore, quantile-based confidence intervals will be obtained, and hypothesis testing will be conducted using comparisons of observed test statistics to test statistics obtained under the null hypothesis. For hypotheses of equivalence between two populations (e.g. placebo and dosage groups, $\beta_1 = 0, \mu_1 = \mu_2$), an unequal sample unequal variance T-statistic will be used:

$$T = \frac{\widehat{\mu_1} - \widehat{\mu_2}}{s_p \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}} \quad (1)$$

where, $\widehat{\mu_1}$ and $\widehat{\mu_2}$ are the observed sample means, and

$$s_p = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}} \quad (2)$$

Where s_1^2 and s_2^2 are the sample variances. The null distribution will be generated by resampling from the values at their two groups shifted to their pooled sample mean.

For joint significance tests (e.g. H_0: $\beta_1 = \beta_2 = \beta_3 = \beta_4 = 0$), the F-statistic will be used with the formula,

$$F_b = \frac{\left(\frac{RSS_1 - RSS_2}{p_2 - p_1}\right)}{\left(\frac{RSS_2}{n - p_2}\right)} \quad (3)$$

where RSS_1 is the residual sum of squares for an ANOVA model fit under the null with p_1 parameters and RSS_2 a model fit with all parameters p_2 included. The null distribution will be generated through resampling from the distributions of each dosage cohort shifted to their common mean. With bootstrap resampling, p-values will be calculated by comparing observed values of the test statistic to the null distribution:

$$p = \frac{1}{B} \sum_{b=1}^{B} I(F_b \geq F_{obs} \; or \; |T_b| \geq |T_{obs}|) \quad (4)$$

where B is the number of bootstrap samples taken.

ANOVA also assumes homogeneity of variance (i.e. homoskedasticity). Homogeneity of variance will be assessed. If variances are equal, homogenous variance ANOVA will be

performed, otherwise heterogeneous variance ANOVA will be performed, unless bootstrapping is used.

6.11 Extent of Exposure and Treatment Compliance

This is a single dose study where the treatment is given in a single IM injection. The study medication (active or placebo) will be prepared by the pharmacist in accordance with the Drug Preparation Manual. Therefore, exposure will be closely monitored, and treatment compliance is not a major risk.

In the event that rescue medications (physostigmine, atropine, diazepam or lorazepam) are administered, data for the participant will be analyzed according to the dosage of Scop HBT received for measures taken up to the administration of the rescue medication. Thereafter, participant data will be treated differently by endpoint. Data collected after administration of the rescue medication for the BPRS, DSST, and/or RASS will be censored in analyses, though presented descriptively. Adverse events, injection site VAS, and PK data will not be censored.

6.12 Subject Disposition

Subject disposition will be summarized in terms of the number of participants who were screened, failed screening (by criteria), consented, randomized, treated, completed all follow-up assessments, or discontinued early from the study. Frequency counts and percentages of participants by disposition status will be presented for each cohort and dose level with all data from Placebo participants pooled and summarized as a single group. Disposition will be summarized for the Safety population.

6.12.1 Discontinuations/Early Terminations

All participants who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be summarized. Participants who withdraw or are excluded from participation in the study prior to receiving study drug will be replaced; however, withdrawing or terminating participants who have received study drug or placebo will not be replaced.

6.13 Demographic and Baseline Characteristics

Demographic characteristics, including age, gender, weight, BMI, race, and ethnicity will be summarized. The subject's age is calculated as the number of years from the subject's date of birth to the date the Informed Consent signed, rounded down to the nearest integer:

Age = Integer ([Date Informed Consent Signed - Date of Birth] / 365.25)

Demographics will be summarized for the Safety and PK populations, should these populations be different. Demographic and baseline data will be listed for all participants to supplement summary results. Results will be presented for each cohort and dose level with all data from Placebo participants pooled and summarized as a single group.

6.14 Safety Analyses

6.14.1 Physical Examination

For the complete physical examination performed at Screening, the proportion of participants reporting results of "Normal", "Abnormal, Not Clinically Significant", and "Abnormal,

Clinically Significant" will be calculated and presented for each body system and cohort/dose level. Any changes between the Screening and SD -1 physical examinations will be captured as part of medical history and any changes between the serial post-dose examinations and the SD -1 physical examination will be captured as an AE and will be presented in those tabulations and/or listings. The proportion of participants that report changes in physical examination between SD -1 and SD 8 will be calculated and presented for each body system and cohort and dose level with all data from Placebo participants pooled and summarized as a single group. The physical examination data will be summarized for the Safety population. A listing of all physical examination results will be provided to supplement the tabulated results.

6.14.2 ECG Data

Descriptive statistics of ECG results (ventricular HR, PR interval, QRS interval, QT interval, QTcF interval) will be calculated at each scheduled time point and will include the change from baseline. The summary of descriptive statistics at each time point will be displayed by cohort and dose level, with all data from Placebo participants pooled and summarized as a single group.

In addition, the frequency and percentage of participants classified as "Normal", "Abnormal, Not Clinically Significant" or "Abnormal, Clinically Significant" will be summarized at each time point. The frequency and percentage of participants with ECGs that are classified as "Normal" at baseline but change to "Abnormal, Clinically Significant" or "Abnormal, Not Clinically Significant" after dosing, or that are classified as "Abnormal, Not Clinically Significant" at Baseline but change to "Abnormal, Clinically Significant" after dosing will also be summarized.

ECG results and changes from baseline in ECG results will be categorized with the number and proportion of participants reporting changes presented as categorical variables.

The ECG data will be summarized for the Safety population and a listing of all ECG data will be provided to supplement the tabulated results.

6.14.3 Vital Signs

Descriptive statistics of vital signs (pulse rate, BP, temperature, respiratory rate, pulse oximetry) will be calculated at each scheduled time point and will include the change from baseline. The summary of descriptive statistics at each time point will be displayed by cohort and dose level, with all data from Placebo participants pooled and summarized as a single group. The vital signs data will be summarized for the Safety population and a listing of all vital signs data will be provided to supplement the tabulated results.

6.14.4 Clinical Laboratory Tests

Descriptive statistics of clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be calculated at each scheduled time point and will include the change from baseline for each analyte. The summary of descriptive statistics at each time point will be displayed by cohort and dose level, with all data from Placebo participants pooled and summarized as a single group for each analyte.

In addition, shift tables summarizing changes from normal to out-of-normal range will be provided. -

The laboratory data will be summarized for the Safety population and a listing of all laboratory data will be provided to supplement the tabulated results.

6.14.5 Adverse Events

Treatment-emergent AEs (TEAEs) are defined as those AEs with onset date and time equal to or after start of study medication or those events in which the onset date and time are before the start of study medication but worsened after the start of study medication. To be conservative, in the case of a missing onset time for an AE, an AE with a start date equal to or after the dosing date will be considered treatment-emergent. All AEs will be coded using the MedDRA dictionary, version as noted in the Data Management Plan, using System Organ Class and Preferred Terms.

All TEAEs will be summarized by cohort and dose level, with all data from Placebo participants pooled and summarized as a single group. The number of TEAEs as well as the number and percentage of participants who experienced at least one TEAE will be summarized for each system organ class and each preferred term. The percentage will be based on the number of safety participants in a particular treatment group. Each subject will contribute at most one count per summarization category. All TEAEs will be sorted in descending order of the incidence rate of system organ classes in the highest dosing group and then within each system organ class by descending order of incidence rate of preferred terms in the same group. TEAEs potentially related to study medication, serious TEAEs, and TEAEs leading to withdrawal will be summarized in a similar manner. A separate table will present all TEAEs that are coded as unexpected and possibly,probably, or definitely related to treatment.

If a subject has more than one AE that codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a system organ class category, the subject will be counted only once in that system organ class category.

TEAEs will also be summarized by maximum severity and by strongest relationship to treatment within each cohort and dose level. SAEs will be tabulated and listed in a manner similar to TEAEs. The AE data will be summarized for the Safety population and a listing of all AE data will be provided to supplement the tabulated results.

6.14.6 Neuropsychiatric Scales

Descriptive statistics (mean, standard deviation, minimum, maximum, median) of scores on the neuropsychiatric status assessments (BPRS and C-SSRS) will be presented for each timepoint by dosing group (placebo, 0.005, 0.007, 0.011, 0.014, 0.021mg/kg).

As the RASS will only be used if general agitation or sedation are reported, the number of participants with RASS performed, the reason for performance of the RASS, the time since injection when the RASS was administered, the RASS score, the resulting action taken (e.g., rescue drug administered, resolved or unresolved) will be presented by dose group and overall.

Signal neuropsychiatric events defined as DLTs (BPRS ≥40 or item score ≥4 at 48-hour post-dose evaluation) or symptoms (e.g., delirium, paranoia, and/or hallucinations) defined as adverse events will be noted and the affected participants' BPRS, C-SSRS, and RASS (if applicable) scores will be presented at each time point in relation to the determination of the event.

Change in BPRS scores from baseline (when BPRS≤25) will be compared for each dose level to placebo. Each time-point will be modeled separately. Changes in BPRS scores will be compared between each dose and the placebo group using a Wald test of coefficients from ANOVA.

Change in C-SSRS scores at SD 8 (from a baseline of zero) will be assessed. The proportion of individuals having a change in score from zero will be compared for each drug dosage level to the placebo group using Fisher's exact test. Scores for all participants receiving active Scop HBT will be compared to those receiving placebo.

6.14.7 Assessment of Cognitive Impairment

The DSST will be used to measure cognitive impairment due to Scop HBT. The raw score will be calculated from the difference in total number of trials attempted and the number of trials incorrect. Summary statistics for raw DSST scores (mean, median, min, max, standard deviation, 95% confidence intervals) will be presented over time by dose level. The proportion of individuals with declines in raw scores between baseline and 48 hours and baseline and Day 8 will be compared between active placebo and active Scop HBT using a Fisher's Exact Test. This test will be conducted once for all participants receiving active Scop HBT and all participants receiving placebo.

In addition, individual changes in DSST scores between baseline and 48 hours and SD 8 will be compared between each dosage cohort and placebo and for all active dosages and placebo. Equation 5 presents the model that will be used to compare DSST scores by cohort,

$$G(Y_i) = \beta_0 + \beta_1 \times I(D_i = 1) + \beta_2 \times I(D_i = 2) + \beta_3 \times I(D_i = 3) + \beta_4 \times I(D_i = 4) + \beta_5 \times I(D_i = 5) + \varepsilon_i \quad (5)$$

where Y_i,, is the change in DSST scores at 48 hours or SD 8, D_i is the dosage level for participant
i (1=0.005, 2=0.007, 3=0.011, 4=0.014, 5=0.021 mg/kg), β_0 is the change in DSST scores for placebo participants, and ε_i is the error term for each participant *i*. Wald tests will be used for the null hypotheses of no differences between active Scop HBT and placebo: $\beta_1 = 0$, $\beta_2 = 0$, $\beta_3 = 0$, $\beta_4 = 0$, $\beta_5 = 0$.

Equation 6 shows the model that will be used to test the null hypothesis of no differences between all levels of active Scop HBT compared to placebo

$$G(Y_i) = \beta_0 + \beta_1 \times I(D_i \in \{1,2,3,4,5\}) + \varepsilon_i \quad (6)$$

A Wald test will be used to test the null hypothesis that there are no significant differences in the change in DSST scores between active and placebo Scop HBT ($\beta_1 = 0$) in Eq. 6.

6.14.8 Assessment of Injection Sites

Descriptive statistics of injection site assessments will be reported. Mean, median, standard deviation, minimum, and maximum VAS scores will be presented for each time-point by dosing group (placebo, 0.005, 0.007, 0.011, 0.014, 0.021mg/kg).

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 timepoint, by dosage group.

Differences between placebo and active Scop HBT injection site VAS scores will be compared statistically by dosage level using three different ANOVA models corresponding to the first hour, next 4 hours, and 8 – 48 hours after injection. In the first model, VAS scores will be averaged over 10, 15, 30, & 45 minutes. In the second model, VAS scores will be averaged over 1, 1.5, 3, and 5-hour timepoints. The third model will include VAS scores averaged over 8, 12, 24, and 48-hour timepoints. VAS scores for active Scop HBT doses will be tested against scores for placebo using a one-sided alternative of higher scores for Scop HBT than placebo.

6.14.9 Medical History

Medical History data will not be tabulated but will be provided in a listing by cohort, dose level, and subject.

6.14.10 Concomitant Medications

Concomitant Medications will be coded using the World Health Organization (WHO) Drug dictionary, using Anatomical Therapeutic Chemical (ATC) classifications and WHO preferred terms. Concomitant Medications will not be tabulated but will be provided in a listing by cohort, dose level, and subject.

6.15 PHARMACOKINETIC ANALYSES

6.15.1 Plasma Pharmacokinetics

The estimation of pharmacokinetic parameters of interest is not described within this SAP. A separate PK report will detail methods and limitations of the estimation of PK parameters. However, PK parameters will be analyzed as part of this SAP.

PK parameters will be assessed for homoskedasticity prior to modeling using ANOVA. For parameters that vary by orders of magnitude across dose groups, a logarithmic transformation will be carried out prior to testing for homogeneity of variance. Otherwise a likelihood ratio test for homogeneity of variance will be carried out on the untransformed PK values or on transformed values, as appropriate. The tests for homogeneity of variance will exclude outlying values. If there are significant differences ($p<0.05$) in variances across dose groups, comparison of PK means across dose groups will be carried out based on a heterogeneous variance analysis of variance. Otherwise it will be carried out based on a homogeneous variance analysis of variance.

Dose-equivalency of five PK parameters (T_{max}, $t_{1/2}$, V_d/F, CL_F, MRT) will be tested using ANOVA. Models will adjust for sex of the subject. Equation 3 presents the model to be used for all ANOVA of PK parameters,

$$G(Y_i) = \beta_0 + \beta_1 \times I(D_i = 2) + \beta_2 \times I(D_i = 3) + \beta_3 \times I(D_i = 4) + \beta_4 \times I(D_i = 5) + \\ + \beta_5 Sex_i + \varepsilon_i \quad (8)$$

, where G is a link function (or identity), Y_i is the PK parameter of interest *i*, β_0 is the change in PK parameter for the placebo group, D_i is the dosage level *(1=0.005, 2=0.007, 3=0.011, 4=0.014, 5=0.021 mg/kg)*, and ε_i is an error term each for participant *i*. Models will control for the sex of the participantThe significance of the difference in parameters by dose level will be tested using a likelihood ratio test for the joint null hypothesis: H_0: $\beta_1 = \beta_2 = \beta_3 = \beta_4 = 0$. If bootstrapping is used, a null distribution will be generated using an F-statistic, as described previously. For parameters where dose-proportionality is assessed, the equivalency of each parameter with the next higher dose level will be tested, using the null hypotheses:

$$\beta_0 = \beta_0 + \beta_1 \; i.e. \; \beta_1 = 0$$
$$\beta_0 + \beta_1 = \beta_0 + \beta_2 + \; i.e. \; \beta_1 = \beta_2$$
$$\beta_2 = \beta_3 \quad (9)$$

$$\beta_3 = \beta_4$$
$$\beta_4 = \beta_5$$

Two PK parameters, C_{max} and AUC_{∞}, will also be used to test dose-proportionality. ANOVA models will compare C_{max}/Dose and AUC_{∞}/Dose across active dose levels. Joint significance will be tested using likelihood ratio tests. Individual doses will be compared to the next higher dose using Wald Tests of model parameters.

6.15.2 Urine Pharmacokinetics

The analysis of urine PK is exploratory and descriptive only. If available, urine concentrations and total quantities of Scopolamine in urine will be summarized by collection time window for each cohort. If metabolites of Scopolamine are analyzed, their concentrations and the ratio of Scopolamine to its metabolites will be calculated and presented descriptively as a function of collection window and dosing group. No hypothesis testing will be performed based on urine PK.

REFERENCES

None at this time.

Tables, Listings, and Figures

See separate shell document.

6.16 LIST OF TABLES

See separate shell document.

6.17 List of Listings

See separate shell document.

7. APPENDICES

None at this time.