BP-C-24-0001

A TWO-PERIOD, TWO-SEQUENCE, TWO-TREATMENT, SINGLE-DOSE CROSSOVER STUDY OF ATROPINE SULFATE OPHTHALMIC SOLUTION (1%) ADMINISTERED SUBLINGUALLY VERSUS ATROPINE SULFATE ADMINISTERED INTRAMUSCULARLY FOR BIOEQUIVALENCE DETERMINATION

Sublingual **A**tropine **B**io**e**quivalence by **R**oute of Administration (SABER)

Sponsor: Biomedical Advanced Research and Development Authority (BARDA)
200 Independence Ave.
Washington, DC 20201
ATTN: ASPR/BARDA

Version of Protocol: 1.0

Date of Protocol: 13 February 2024

CONFIDENTIAL

PROTOCOL APPROVAL - SPONSOR SIGNATORY

Study Title	A Two-period, Two-sequence, Two-treatment, Single-dose Crossover Study of Atropine Sulfate Ophthalmic Solution (1%) Administered Sublingually vs Atropine Sulfate Administered Intramuscularly for Bioequivalence Determination
Short Title	Sublingual Atropine Bioequivalence by Route of Administration (SABER)
Protocol Number	BP-C-24-0001
Protocol Version	v1.0
Protocol Date	13 February 2024

Protocol accepted and approved by:

[redacted]

Signature

Date

STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research. The Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11 (Electronic Records; Electronic Signatures), and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)
- The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice, and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Any additional Federal, State, and Local Regulations and Guidance

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) Good Clinical Practice (GCP) guidelines.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

2. SYNOPSIS

Name of Sponsor/Company: Biomedical Advanced Research and Development Authority (BARDA)

Name of Study Drug:

Test Drug: Atropine Sulfate Ophthalmic Solution, USP 1% (NDC 82260-0001-01)

Reference Drug: Atropine Sulfate Injection, USP 8 mg/20 mL (0.4 mg/mL) in a multidose vial presentation (NDC 63323–580-20)

Name of Active Ingredient: Atropine sulfate

Title of Study: A Two-period, Two-sequence, Two-treatment, Single-dose Crossover Study of Atropine Sulfate Ophthalmic Solution (1%) Administered Sublingually vs Atropine Sulfate Administered Intramuscularly for Bioequivalence Determination

Short Title: Sublingual Atropine Bioequivalence by Route of Administration (SABER)

Protocol Number: BP-C-24-0001

Version Number: 1.0

Study center(s): 1 (one)

Study period (years): 0.5 Estimated date first participant enrolled: April 2024 Estimated date last participant completed: August 2024	**Phase of development:** Phase 1

Study Objectives:

Primary Objective:

- To establish bioequivalence of Atropine Sulfate Ophthalmic Solution, USP 1% given sublingually (SL) vs intramuscular (IM) 8 mg/20 mL (0.4 mg/mL) atropine sulfate injection.

Secondary Objective:

- To compare the bioavailability of Atropine Sulfate Ophthalmic Solution, USP 1% given SL vs IM 8 mg/20 mL (0.4 mg/mL) atropine sulfate injection.

Methodology: This is a randomized, two-period, two-sequence, crossover study to assess the bioequivalence, bioavailability, and pharmacokinetics (PK) of a single dose of atropine administered SL or IM in healthy adult volunteers. Approximately 46 healthy male and non-pregnant female volunteers will be enrolled to obtain approximately 36 evaluable participants in the per protocol population. Additional participants may be randomized if participants are withdrawn prior to receiving one or both doses of study drug. Eligible participants will be randomized at a 1:1 ratio to receive one of two treatment dosing sequences (A or B) as depicted in the table below:

Study Design Scheme by Dosing Sequence

Dosing Sequence	**Targeted Number of Randomized Participants (N)**	**Targeted Number of Evaluable Participants (N)**	**Period 1 (Visit 1; Day 1)**	**Period 2 (Visit 2; Day 8)**
A	23	18	SL	IM
B	23	18	IM	SL

Volunteers will be screened for study participation from Days -14 to -3. After Screening on Day 1, eligible participants will be enrolled and will be randomized to receive one of two dosing sequences as presented in the table above. Once randomized, each participant will receive 2 doses of atropine separated by a wash out period of 6 ±1 days. During Visit 1 (Day 1) and Visit 2 (Day 8), participants will be administered SL or IM atropine, according to their randomly assigned dosing sequence. At each dosing visit, blood samples for PK will be collected at time 0 (pre-dose) and at 13 time points post-dose at 5, 10, 15, 20, 30, 45, 60, and 90 minutes and 2, 2.5, 4, 6, and 8 hours after dosing. Participants will be discharged from the clinic after the 8-hour blood sample collection. Participants will be followed for approximately 6 days after their last dose.

Number of participants (planned): Approximately 46 enrolled for 36 evaluable

Diagnosis and main criteria for inclusion: Healthy male and non-pregnant female participants aged 18 through 65 years, inclusive.

Eligibility criteria will be assessed at Screening and must be reviewed just prior to each dose of atropine. Criteria specified as only being evaluated at Screening or at Pre-dose Visits will be assessed only at those visits. If the participant no longer meets applicable eligibility criteria, the investigator, in consultation with the medical monitor in cases of uncertainty, must determine whether the participant should receive the atropine dose or be terminated early from study drug.

Participant Inclusion Criteria

1. Healthy male and non-pregnant female volunteers between the ages of 18 and 65 years, inclusive, at time of consent.
2. Willing and able to provide written informed consent.
3. Females who are of childbearing potential and are sexually active with a male partner must have used an adequate method of birth control for at least 2 months prior to Screening and must agree to continue using an adequate method of birth control from Screening through Follow-up (Day 15).
    a. A female of childbearing potential is defined as a post onset of menarche and premenopausal female capable of becoming pregnant. This does not include females who meet any of the following conditions: menopausal >2 years, tubal ligation >1 year, bilateral salpingo-oophorectomy, or hysterectomy.
    b. Adequate contraception is defined as a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label. Examples include oral contraceptives, injectable progestogen, implants of etonogestrel or levonorgestrel, estrogenic vaginal ring, percutaneous contraceptive patches, intrauterine device or intrauterine system, or male partner sterilization at least 6 months prior to the participant's Screening Visit.
4. In the judgment of the investigator, the participant is in good health, based on review of medical history and the results of Screening evaluation (including vital signs, physical examination, 12-lead electrocardiogram [ECG], and Screening laboratory assessments, performed no more than 14 days prior to randomization into the study).
5. Able to comply with the dosing instructions and available to complete the study Schedule of Assessments.

Participant Exclusion Criteria

1. Females who have a positive pregnancy test or who are breastfeeding.
2. Participants with thyroid disease as evidenced by a thyroid-stimulating hormone (TSH) <0.9 × lower limit of normal (LLN) or > 1.2 × upper limit of normal (ULN) at Screening (This Screening test will not be repeated prior to subsequent dosing).

3. Participants with aspartate aminotransferase (AST), alanine aminotransferase (ALT), or serum creatinine >1.5 × ULN at Screening. (These Screening tests will not be repeated prior to subsequent dosing.)
4. Have known human immunodeficiency virus (HIV), or acute or chronic hepatitis B or hepatitis C infection based on medical history; or test positive for any of these at Screening. Participants who have been effectively treated for hepatitis C, as evidenced by a negative hepatitis C RNA confirmation test and who no longer require antiviral therapy, are eligible for participation. (These Screening tests will not be repeated prior to subsequent dosing.)
5. Participants who took any prescription medications (with the exception of oral contraceptives or hormone replacement therapy) within 30 days of Screening. Prior to each dose, the investigator will review prohibited medication use and determine whether the participant should be terminated from further dosing.
6. Participants who took any over-the-counter medication/vitamins/herbal supplements in the last 72 hours prior to Screening. Prior to each dose, the investigator will review prohibited medication use and determine whether the participant should be terminated from further dosing.
7. Participants who are current smokers or are currently using any oral nicotine/oral tobacco product (e.g. snuff, chew, lozenges, nicotine gum, pouches) or electronic cigarette or vaping device (e.g., e-cigarette, mod, vape pen, JUUL, e-cigar, e-hookah, e-pipe, vape pods) or have used any of these products within 6 months prior to Screening.
8. Participants with glaucoma and/or history of ocular surgery (including Lasik™), ocular trauma, or congenital ocular disorder.
9. Participants with any history of heart disease, including but not limited to hypertension, coronary artery disease, arrhythmia (treated or untreated), congestive heart failure, pacemaker, history of vasovagal syncope, any supraventricular tachycardia, peripheral vascular disease, or claudication.
10. Participants with clinically significant arrhythmias or abnormal conduction; abnormal conduction is defined as a prolonged PR or QRS, or a QTc ≥450 msec for males or ≥470 msec for females.
11. Participants with a history of partial organic pyloric stenosis, chronic constipation, gastroparesis, or other gastrointestinal motility issues.
12. Participants with a history of xerostomia due to an underlying disease or previous radiation therapy to the head and neck.
13. Males with history of symptomatic prostatic hypertrophy; males or females with a history of urinary hesitancy or retention.
14. Participants with a blood pressure >140/90 mm Hg taken after the participant has been seated and resting for at least five minutes.
15. Participants with a history or current diagnosis of myasthenia gravis.
16. Participants who have donated blood within 8 weeks of Screening or intend to donate blood during the study period.
17. Participants with a history of drug or alcohol abuse in the last two years or evidence of a positive urine drug test at Screening. (This Screening test will not be repeated prior to subsequent dosing.)
18. Participants with a known sensitivity or prior adverse reaction to atropine.
19. Participants who have consumed alcohol within 24 hours prior to each Pre-dose Visit. (This will be assessed only at Visit 1 [Pre-dose] and Visit 2 [Pre-dose].)

20. Participants with any other condition that, in the opinion of the investigator, would pose a health risk to the participant if enrolled, would interfere with SL or IM administration of study drug, or would otherwise interfere with interpretation of study results.

Participants cannot be rescreened for exclusionary laboratory test results. Potentially exclusionary vital sign results may be repeated once. If a participant's repeat vitals remain exclusionary or the investigator determines that the repeat vital signs could pose a risk to participating in the study, then the participant will be excluded.

Test drug, dosage, and mode of administration: Atropine Sulfate Ophthalmic Solution USP, 1% (NDC 82260-0001-01), 1 mg (100 µL of a 1% w/v solution), administered SL by pipette with at least a 30 second dwell time without swallowing

Duration of treatment: Participants will receive two doses of atropine sulfate separated by approximately 7 days

Reference drug, dosage, and mode of administration: Atropine Sulfate Injection, USP 8 mg/20 mL (0.4 mg/mL) in a multidose vial presentation (NDC 63323–580-20), 1 mg (2.5 ml) administered by IM injection into the mid-anterolateral thigh

Criteria for evaluation: Pharmacokinetic parameters only (bioequivalence/bioavailability)

Study Endpoints

Primary Endpoints

The bioequivalence of atropine sulfate administered SL versus administered IM as measured by the following PK parameters:

- Area under the analyte concentration versus time curve to infinity (AUC_{∞})
- Area under the analyte concentration versus time curve to time of last quantifiable data point (AUC_t)

Secondary Endpoints

The relative bioavailability of atropine sulfate administered SL versus IM as measured by the following PK parameters:

- Area under the analyte concentration versus time curve to time 45, 60, 90, 120, 150, and 240 minutes (AUC_{45}, AUC_{60}, AUC_{90}, AUC_{120}, AUC_{150}, and AUC_{240}, respectively)
- Maximum measured plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Apparent terminal elimination half-life ($t_{1/2}$)
- Terminal elimination rate constant (λ_z)
- Volume of distribution (V_d/F)
- Total body clearance (CL/F)
- Absorption rate constant (K_a)

Statistical methods:

Analysis Plan

Statistical analyses will be performed using SAS® software Version 9.4 or later. Phoenix WinNonLin software Version 8.3 or later will be used to generate PK parameter estimates.

Descriptive statistics will be used to summarize participant characteristics and safety. These summaries will be presented overall and separately for each route of administration.

Pharmacokinetic parameter estimates will be summarized using descriptive statistics. Bioavailability of SL administration of atropine sulfate relative to that of IM atropine sulfate will be assessed based on ratios of least-square means and their associated 90% confidence intervals (CIs) generated from linear mixed models including terms for dosing sequence, route, and period as fixed effects, and subject nested within dosing sequence as a random effect. Bioequivalence will be considered met if the 90% CI of the ratio for AUC_∞ and AUC_t lie within 80.00 to 125.00%.

Additional details of the statistical analyses, methods, and data conventions will be described in the Statistical Analysis Plan (SAP).

Final Analyses

A clinical study report will be written to include all PK and safety data collected throughout the study. For the final analysis, the study database will be monitored, cleaned, and locked per associated study plans. Further details will be specified in the SAP.

Analysis Populations

PK Analysis Population

The PK analysis population will include all participants who are randomized, receive at least 1 study drug dose, and have PK samples collected for that period. Each participant's data will be analyzed according to the corresponding route of administration for the applicable period. The PK analysis population will be used for all PK analyses.

Per Protocol Population

The per protocol population will include all participants who are randomized, receive atropine via both routes of administration according to their randomized dosing sequence, and have PK samples collected for both periods. In addition, participants with major protocol deviations may be excluded if it is determined that the deviations affect the integrity of PK data. Each participant's data will be analyzed according to the corresponding route of administration for the applicable period. Primary and secondary analyses will be repeated in the per protocol population if it differs from the PK analysis population.

Safety Population

The safety population will include all participants who are randomized and receive at least 1 study drug dose. Each participant's data will be analyzed according to the corresponding route of administration for the applicable period. The safety population will be used for all safety displays.

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

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
anti-HCV	Hepatitis C antibody
ASPR	Administration for Strategic Preparedness and Response
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BARDA	Biomedical Advanced Research and Development Authority
BMI	Body mass index
CAPA	Corrective and Preventative Action
CFR	Code of Federal Regulations
CI	Confidence interval
CICP	Countermeasures Injury Compensation Program
CRU	Clinical research unit
CSN	Clinical Studies Network
CTCAE	Common Terminology Criteria for Adverse Events
DSMP	Data safety monitoring plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HHS	Health and Human Services
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular(ly)

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
IV	Intravenous
LFT	Liver function test
LLN	Lower limit of normal
MCM	Medical countermeasures
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NA	Nerve agent
NCI	National Cancer Institute
OTC	Over the counter
PK	Pharmacokinetic
POC	Point-of-care
PREP	Public Readiness and Emergency Preparedness
QA	Quality assurance
QC	Quality control
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SL	Sublingual(ly)
SME	Subject Matter Expert
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia

5. INTRODUCTION

5.1. Background

The Biomedical Advanced Research and Development Authority (BARDA) is tasked with, among other things, promoting and supporting the development of strategic medical countermeasures (MCMs) for the United States. Typically, this effort involves supporting novel drug development up to Food and Drug Administration (FDA) approval and inclusion into the Strategic National Stockpile. However, in the event of widespread nerve agent (NA) poisoning, pre-deployed MCMs are likely to be inadequate due to limited availability of community caches (Chempack), logistical challenges in bringing the resources to the site of treatment, depletion of the resources before all patients needing treatment receive it, and expiration or unavailability of approved MCMs and/or preferred delivery devices (auto-injectors).[1]

In response to this challenge, the Department of Health and Human Services (HHS) is investigating the bioavailability and pharmacokinetics (PK) of an alternative (sublingual [SL]) route of administration of atropine sulfate ophthalmic solution (1%) compared with the reference, atropine sulfate injected intramuscularly (IM).[2]

Atropine is an approved drug indicated for temporary blockade of severe or life-threatening muscarinic effects, symptomatic bradycardia, and to dilate the pupils to facilitate eye exams. Atropine is an antidote for organophosphorus or carbamate chemical warfare agent or pesticide poisoning, as well as the treatment of some (muscarinic) mushroom toxicity. Atropine is available in multiple dosing forms and is commonly administered by IM injection, intravenous (IV) injection, and as ocular drops. The ocular drop formulation is also given off-label SL for excessive drooling in multiple contexts, including maintenance of perioral hygiene in hospice patients, to alleviate hypersalivation caused by certain antipsychotic medications, to manage oral secretions/reduce ventilator-associated pneumonia risk in mechanically ventilated patients, and for excessive drooling in developmentally disabled children.[3-6]

This randomized, open-label, two-period, two-sequence, phase 1 study is designed to assess the bioequivalence, bioavailability, and PK of SL administered Atropine Sulfate Ophthalmic Solution, United States Pharmacopeia (USP) 1% (1 mg; test) compared to Atropine Sulfate Injection, USP administered IM (1 mg; reference) in healthy adult volunteers.

5.2. Study Rationale

Nerve agent toxicity requires the rapid administration of antimuscarinic MCMs to mitigate life-threatening bronchorrhea and seizures. Rapid administration of centrally acting doses of atropine and anticholinergic medications are most effective within 10 minutes of administration. Following IV administration of atropine, the heart rate increases within seconds, and the antisialagogue and central nervous system effects may take a few minutes to achieve maximum effect. In contrast, the IM route of atropine administration requires a very high dose before central antimuscarinic effects are seen, and the onset of action is delayed. Further, stockpiled NA MCM configurations (Chempack), containing drugs administered by auto-injector, are insufficient to treat large numbers of NA-poisoned patients in a timely manner. Ophthalmic atropine solution is generally available in the community and may provide a rapid, available source of effective medication in the event of an emergency.

Administration of atropine sulfate ophthalmic solution via the SL route may be an alternative means of delivering a rapid therapeutic dose of atropine to individuals exposed to NA while overcoming the stockpile supply deficits identified above.

The purpose of the current study is to assess the bioequivalence, bioavailability, and PK of SL administered Atropine Sulfate Ophthalmic Solution, USP 1% compared to Atropine Sulfate Injection, USP administered IM in healthy adult volunteers.

5.3. Previous Clinical Studies

Prior to conducting study BP-C-19010 (ClinicalTrials.gov Identifier: NCT04290039)[8], BARDA conducted an extensive literature review and identified 110 published English language articles involving the administration of atropine by SL, nasal, and oral routes. Eighteen studies were selected based on their relevance to the proposed clinical study and are summarized in Appendix 1. Included among these reports are 6 wherein hyoscyamine, the levo-enantiomer of atropine, was the active agent. A total of 470 participants were exposed to varying doses and regimens of SL atropine, including the ophthalmic formulation, or hyoscyamine in these reports. In several reports, atropine was administered SL on a regular regimen versus the single dose per timepoint as proposed in this study. No severe adverse reactions were reported, and the side effects observed were consistent with known anticholinergic effects previously observed with oral or parenteral administration, e.g., dry mouth. In one study of children in Brazil with cerebral palsy and drooling, side effects occurred in 4 of 33 (12%) patients. These side effects and their respective frequency were as follows: fever and flush (1), irritability (1), flush and irritability (1) and flush and angioedema (1).[5] Further characterization of these events was not provided. Norderyd et al. prospectively studied the effect of SL atropine in children and adolescents 5 through 18 years old with disabilities and excessive salivation (n = 23). During the course of the study, 1064 person-doses of atropine were administered to children without any reported adverse events (AEs).[3]

A study of SL injection of atropine is included here since it is a useful evaluation of atropine PK, and the atropine dose used was two-fold greater than the 1 mg dose to be used in the current study. Rajpal et al. evaluated 9 healthy male volunteers (mean age 20.8 ± 4.7 years, mean weight 59.67 ± 4.76 kg) administered a single SL injection of 2 mg atropine sulfate (in 0.1 mL).[7] Three of the participants had 99mTc-labeled diethylene triamine pentaacetic acid added to their injection to monitor the release rate of atropine sulfate. Within 10 minutes, 85% of the injected dose was released from the SL site of injection. This compared to only 24% released at 10 minutes from one participant who received IM atropine. The remaining six participants underwent blood sampling for PK and clinical monitoring for signs of atropinization (heart rate, pupil diameter, and mouth dryness). The peak serum concentration of SL atropine was 20 ng/mL at 15 minutes compared to peak serum concentrations of 6 to 8 ng/mL at 30 minutes following IM administration. All volunteers who received atropine by SL injection showed signs of atropinization by 10 minutes with peak intensity at 30 minutes and persistence of symptoms for nearly 60 minutes. The authors concluded that atropine administered by SL injection achieves clinically important serum levels more rapidly than by IM administration. Adverse events were not reported in this trial.

BARDA conducted, BP-C-19010, a randomized, 3-sequence, 3-period phase I crossover study to assess the bioavailability and PK of a single dose (0.5 mg and 1.0 mg) of 1% ophthalmic

atropine sulfate solution administered SL to 15 healthy adult volunteers.[8,9] The primary endpoint was evaluation of the bioavailability of each of the two SL doses against a 1.0 mg reference IV atropine dose. Secondary endpoints included the safety and tolerability (xerostomia scale) of atropine sulfate administered SL. Sublingual atropine was safe (no severe AEs or serious adverse events [SAEs] were reported with either dose) and well tolerated, with a single participant reaching maximum xerostomia on a single dosing day. The geometric mean AUC_∞ was 286.40, 493.81, and 816.47 min×ng/mL for the 0.5 mg and 1.0 mg SL doses and the 1.0 mg IV dose, respectively. Compared to IV administration, the 1.0 mg SL dose produced 0.60 (90% CI: 0.55-0.66) of the overall concentration of atropine over time (AUC_∞).

Based on the reported experience to date, the administration of atropine via the SL route appears to have an acceptable safety profile and does not significantly increase the risk associated with the use of the drug product as proposed.

6. STUDY OBJECTIVES

Table 2: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish bioequivalence of Atropine Sulfate Ophthalmic Solution, USP 1% given sublingually vs intramuscular 8 mg/20 mL (0.4 mg/mL) atropine sulfate injection.	• AUC_{∞} • AUC_t
Secondary	
To compare the bioavailability of Atropine Sulfate Ophthalmic Solution, USP 1% given sublingually vs intramuscular 8 mg/20 mL (0.4 mg/mL) atropine sulfate injection.	• AUC_{45}, AUC_{60}, AUC_{90}, AUC_{120}, AUC_{150}, AUC_{240} • C_{max} • t_{max} • $t_{1/2}$ • λ_z • Vd/F • CL/F • K_a

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, open-label, two-period, two-sequence, crossover study to assess the bioequivalence, bioavailability, and PK of a single dose of atropine administered SL or IM in healthy adult volunteers. Approximately 46 healthy male and non-pregnant female volunteers will be enrolled to obtain approximately 36 evaluable participants in the per protocol population. Additional participants may be randomized if participants are withdrawn prior to receiving one or both doses of study drug. Eligible participants will be randomized at a 1:1 ratio to receive one of two treatment dosing sequences (A or B) as depicted in Table 3.

Table 3: Study Design Scheme by Dosing Sequence

Dosing Sequence	Targeted Number of Randomized Participants (N)	Targeted Number of Evaluable Participants (N)	Period 1 (Visit 1; Day 1)	Period 2 (Visit 2; Day 8)
A	23	18	SL	IM
B	23	18	IM	SL

Figure 1 presents a diagram of the overall study design. Volunteers will be screened for study participation from Days -14 to -3. After Screening on Day 1, eligible participants will be enrolled and will be randomized to one of two treatment dosing sequences as presented in Table 3. Once randomized, each participant will receive 2 doses of atropine separated by a wash out period of 6 ±1 days. During Visit 1 (Day 1) and Visit 2 (Day 8), participants will be administered SL or IM atropine, according to their randomly assigned dosing sequence. At each dosing visit, blood samples for PK will be collected at time 0 (pre-dose) and at 13 time points post-dose at 5, 10, 15, 20, 30, 45, 60, and 90 minutes and 2, 2.5, 4, 6, and 8 hours after dosing. Participants will be discharged from the clinic after the 8-hour blood sample collection. Participants will be followed for approximately 6 days after their last dose.

At the Screening Visit, participants will receive instructions regarding preparation for dosing visits, and information about conduct during dosing visits. On the day of atropine administration, site staff will review eligibility criteria with each participant (except for those criteria specified as only being applicable at Screening; see Section 8.1). In addition to meeting eligibility criteria, participants will not be dosed with study drug until they meet the following pre-dose requirements:

1. Have fasted from food and drink for 2 hours prior to drug administration.
2. Have abstained from any other oral product that has the potential to interfere with SL atropine absorption (e.g., candy, chewing gum, mints, etc.) for 2 hours prior to study drug administration.

Following administration of study drug, participants:

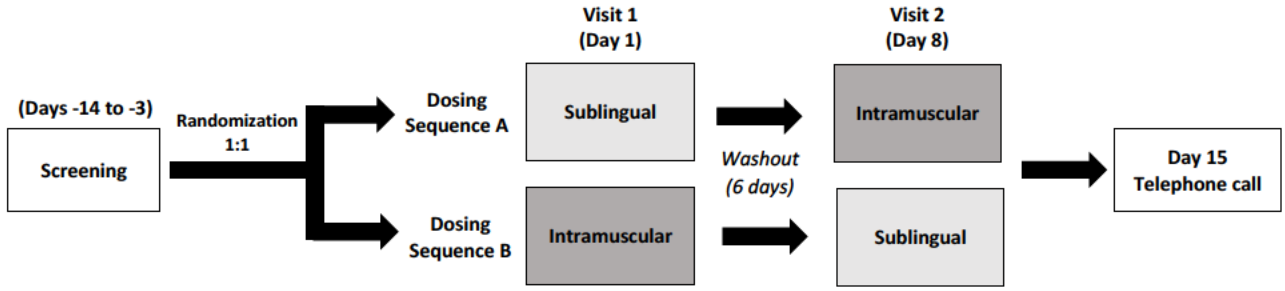
1. Will abstain from food and drink through 2 hours after drug administration or until the participant expresses their xerostomia is intolerable, whichever occurs first. After 2

hours, or if the participant reports intolerable xerostomia, water will be provided ad libitum.

2. Will be provided a meal/snack approximately 4 hours after drug administration.
3. Will have automated blood pressure and heart rate measurements recorded on the opposite arm from blood collection every 15 minutes for the first hour, every 20 minutes for the second hour, and every 30 minutes for the third and fourth hours, and thereafter as deemed clinically necessary by the investigator until the end of each visit.

Meal timing, activity levels, and general conditions in the clinical research unit will be as similar as possible for all study participants irrespective of dose and day.

Figure 1: Overall Study Design



7.2. Number of Participants

The proposed enrollment for this study is approximately 46 healthy male and non-pregnant female volunteers enrolled to obtain approximately 36 evaluable participants in the per protocol population.

7.3. Treatment Assignment

Each participant will receive two doses of atropine according to their assigned dosing sequence: one dose SL and one dose IM. The two doses will be given at Visit 1 (Day 1) and Visit 2 (Day 8). Participants will be randomized 1:1 across 2 dosing sequences as depicted in Table 3.

7.4. Individual Participant Dosing and Study Stopping Rules

7.4.1. Early Termination of Dosing for an Individual Participant

If a participant is confirmed pregnant, she will not receive further dosing of the study drug.

If a participant meets one or more of the criteria below, then the participant's dosing will be paused until the investigator has discussed the participant with the medical monitor and the BARDA Pharmacovigilance Subject Matter Expert (SME) and/or BARDA Medical Officer:

- Participant experiences any Grade 3 or higher AE (National Cancer Institute [NCI]-Common Terminology Criteria for Adverse Events [CTCAE] v5.0)[10] that, in the opinion of the investigator, is at least possibly related to the study drug.

- Participant experiences an AE that, in the opinion of the investigator, makes further dosing inadvisable because the AE causes functional impairment or because the AE requires a medical intervention or observation for safety.
- Participant no longer meets eligibility criteria in such a way that, in the judgment of the investigator, the safety of the participant may be compromised by continued participation or interpretation of the participant's subsequent study data are likely to be significantly compromised.

Once a participant has been reviewed by the medical monitor and the BARDA Pharmacovigilance SME and/or BARDA Medical Officer, they will recommend to either (1) continue dosing per the protocol or (2) discontinue further dosing of the participant.

Participants who do not complete both study drug doses for any reason will continue to be followed for safety for at least six days following the last dose. If a participant reports an AE judged at least possibly related to study drug, the event will be followed to resolution (with or without sequelae) or until considered stable by the investigator (in consultation with the medical monitor in situations of uncertainty).

The reason for early discontinuation of dosing will be captured in the electronic case report form (eCRF).

7.4.2. Study Pausing Rules

If the following criterion is met, further dosing of all participants will be paused.

- Two or more participants experience a grade 3 or higher AE in the same Medical Dictionary for Regulatory Activities (MedDRA) system organ class deemed at least possibly related to the study drug by the site investigator in consultation with the medical monitor.
- One grade 5 AE (death) deemed at least possibly related to the study drug by the site investigator in consultation with the medical monitor.

At that time, the medical monitor, and the BARDA Pharmacovigilance SME and/or BARDA Medical Officer will convene to discuss and review these cases. The site investigator may be present at these meetings to provide additional information. After this review, it may be decided to either continue to pause dosing pending review of additional data, resume dosing as specified in the protocol, modify the study, or terminate the study. As the trial sponsor, BARDA will make the final decision.

7.5. Criteria for Study Suspension or Termination

BARDA retains the right to suspend, modify, or terminate the study at any time. In case of premature termination or suspension and safety review of the study, Allucent will promptly inform the investigator of the termination or suspension of the study and the reason for termination or suspension, and the clinical site will inform the institutional review board (IRB).

This study may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

1. Determination of unexpected, significant, or unacceptable risk to participants

2. Insufficient compliance to protocol requirements
3. If required by regulatory authority(ies)

Study participants will be contacted, as applicable, and be informed of changes to their study visit schedule. The site investigator will assure appropriate follow-up for the participants, as necessary.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Selection of Study Population

This study will include all healthy adult male and non-pregnant female participants, between the ages of 18 and 65 years, inclusive, who meet all of the inclusion and none of the exclusion criteria. Eligibility criteria will be assessed at Screening and must be reviewed just prior to each dose of atropine. Criteria specified as only being evaluated at Screening or at Pre-dose Visits will be assessed only at those visits. If the participant no longer meets applicable eligibility criteria, the investigator, in consultation with the medical monitor in cases of uncertainty, must determine whether the participant should receive the atropine dose or be terminated early from study drug.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study or participant safety. Therefore, adherence to the criteria specified in the protocol is essential.

8.1.1. Participant Inclusion Criteria

1. Healthy male and nonpregnant female volunteers between the ages of 18 and 65 years, inclusive, at time of consent.
2. Willing and able to provide written informed consent.
3. Females who are of childbearing potential and are sexually active with a male partner must have used an adequate method of birth control for at least 2 months prior to Screening, and must agree to continue using an adequate method of birth control from Screening through Follow-up (Day 15)
    a. A female of childbearing potential is defined as a post onset of menarche and premenopausal female capable of becoming pregnant. This does not include females who meet any of the following conditions: menopausal >2 years, tubal ligation >1 year, bilateral salpingo-oophorectomy, or hysterectomy.
    b. Adequate contraception is defined as a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label. Examples include oral contraceptives, injectable progestogen, implants of etonogestrel or levonorgestrel, estrogenic vaginal ring, percutaneous contraceptive patches, intrauterine device or intrauterine system, or male partner sterilization at least 6 months prior to the participant's Screening Visit.
4. In the judgment of the investigator, the participant is in good health, based on review of medical history and the results of Screening evaluation (including vital signs, physical examination, 12-lead electrocardiogram [ECG], and Screening laboratory assessments, performed no more than 14 days prior to randomization into the study).
5. Able to comply with the dosing instructions and available to complete the study Schedule of Assessments (Appendix 2).

8.1.2. Participant Exclusion Criteria

1. Females who have a positive pregnancy test or who are breastfeeding.

2. Participants with thyroid disease as evidenced by a thyroid-stimulating hormone (TSH) < 0.9 × lower limit of normal (LLN) or > 1.2 × upper limit of normal (ULN) at Screening. (This Screening test will not be repeated prior to subsequent dosing.)
3. Participants with aspartate aminotransferase (AST), alanine aminotransferase (ALT), or serum creatinine > 1.5 × ULN at Screening. (These Screening tests will not be repeated prior to subsequent dosing.)
4. Have known human immunodeficiency virus (HIV), or acute or chronic hepatitis B or hepatitis C infection based on medical history; or test positive for any of these at Screening. Participants who have been effectively treated for hepatitis C, as evidenced by a negative hepatitis C RNA confirmation test and who no longer require antiviral therapy, are eligible for participation. (These Screening tests will not be repeated prior to subsequent dosing.)
5. Participants who took any prescription medications (with the exception of oral contraceptives or hormone replacement therapy) within 30 days of Screening. Prior to each dose, the investigator will review prohibited medication use and determine whether the participant should be terminated from further dosing.
6. Participants who took any over-the-counter medication/vitamins/herbal supplements in the last 72 hours prior to Screening. Prior to each dose, the investigator will review prohibited medication use and determine whether the participant should be terminated from further dosing.
7. Participants who are current smokers or are currently using any oral nicotine/oral tobacco product (e.g. snuff, chew, lozenges, nicotine gum, pouches) or electronic cigarette or vaping device (e.g., e-cigarette, mod, vape pen, JUUL, e-cigar, e-hookah, e-pipe, vape pods) or have used any of these products within 6 months prior to Screening.
8. Participants with glaucoma and/or history of ocular surgery (including Lasik^{TM}), ocular trauma, or congenital ocular disorder.
9. Participants with any history of heart disease, including but not limited to hypertension, coronary artery disease, arrhythmia (treated or untreated), congestive heart failure, pacemaker, history of vasovagal syncope, any supraventricular tachycardia, peripheral vascular disease, or claudication.
10. Participants with clinically significant arrhythmias or abnormal conduction; abnormal conduction is defined as a prolonged PR or QRS, or a QTc ≥ 450 msec for males or ≥ 470 msec for females.
11. Participants with a history of partial organic pyloric stenosis, chronic constipation, gastroparesis, or other gastrointestinal motility issues.
12. Participants with a history of xerostomia due to an underlying disease or previous radiation therapy to the head and neck.
13. Males with history of symptomatic prostatic hypertrophy; males or females with a history of urinary hesitancy or retention.
14. Participants with a blood pressure > 140/90 mm Hg taken after the participant has been seated and resting for at least five minutes.

15. Participants with a history or current diagnosis of myasthenia gravis.
16. Participants who have donated blood within 8 weeks of Screening or intend to donate blood during the study period.
17. Participants with a history of drug or alcohol abuse in the last two years or evidence of a positive urine drug test at Screening. (This Screening test will not be repeated prior to subsequent dosing.)
18. Participants with a known sensitivity or prior adverse reaction to atropine.
19. Participants who have consumed alcohol within 24 hours prior to each Pre-dose Visit. (This will be assessed only at Visit 1 [Pre-dose] and Visit 2 [Pre-dose].)
20. Participants with any other condition that, in the opinion of the investigator, would pose a health risk to the participant if enrolled, would interfere with SL or IM administration of study drug, or would otherwise interfere with interpretation of study results.

Participants cannot be rescreened for exclusionary laboratory test results. Potentially exclusionary vital sign results may be repeated once. If a participant's repeat vitals remain exclusionary or the investigator determines that the repeat vital signs could pose a risk to participating in the study, then the participant will be excluded.

8.2. Participant Withdrawal

8.2.1. Participant Withdrawal Criteria

Every participant has the right to refuse participation in the study (i.e., withdraw consent) at any time without providing any justification for withdrawal. A participant's participation must be terminated immediately upon his/her request, and the reason(s) for discontinuation documented accordingly in the corresponding eCRF.

Any participant who meets one or more of the following criteria will be removed from the study without prejudice:

- Participant request.
- Participant noncompliance, defined as refusal or inability to adhere to the study protocol or any other instances determined by the site investigator or BARDA.
- Participant lost to follow-up.
- Site investigator no longer believes participation is in the best interest of the participant.
- At request of BARDA or the IRB

For any participant who is withdrawn prior to completion of the Follow-up (Day 15) Visit, the Early Termination (ET) Visit assessments will be performed as outlined in the Schedule of Assessments (Appendix 2), when possible. The ET Visit may be conducted in clinic or by phone, as determined by the investigator.

8.2.2. Randomization of Additional Study Participants

In order to achieve the target number of evaluable participants within the per protocol analysis population, additional participants will be randomized to account for any participants who are randomized but do not receive the first dose of study drug.

If a participant is withdrawn from the clinical study after receipt of the first dose of study drug at Visit 1 and prior to completing the second dose of study drug at Visit 2, the participant will be removed from the per protocol population. Additional participants may be randomized to achieve the target number of evaluable participants within the per protocol analysis population.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Study Drug

9.1.1. Atropine Sulfate Ophthalmic Solution, USP 1%

Atropine Sulfate Ophthalmic Solution, USP 1% manufactured by Bausch & Lomb Americas Inc., is a sterile topical anti-muscarinic indicated for mydriasis, cycloplegia, and penalization of the healthy eye in the treatment of amblyopia.[11] Each mL of Atropine Sulfate Ophthalmic Solution USP, 1% contains the active ingredient atropine sulfate 10 mg, equivalent to 8.3 mg of atropine. Inactive ingredients include boric acid, hydroxypropyl methylcellulose, and water for injection, USP; hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0).

Atropine Sulfate Ophthalmic Solution, USP 1% will be supplied in 0.4 mL single-dose vials. Each vial will only be used to administer a single dose to a single participant.

9.1.2. Atropine Sulfate Injection, USP

Atropine sulfate injection, USP is a muscarinic antagonist indicated for temporary blockade of severe or life-threatening muscarinic effects, e.g., as an antisialagogue, as an antivagal agent, as an antidote for organophosphorus, carbamate, or muscarinic mushroom poisoning, and to treat symptomatic bradycardia.[12]

Atropine Sulfate Injection, USP, 8 mg/20 mL (0.4 mg/mL) manufactured by Fresenius Kabi is a sterile, nonpyrogenic, isotonic, clear solution of atropine sulfate in water for injection with sodium chloride sufficient to render the solution isotonic. Each mL contains atropine sulfate, 0.4 mg; benzyl alcohol, 9 mg; and sodium chloride 9 mg; it may also contain sulfuric acid for pH adjustment, pH 3.5 (3.0 to 3.8).

Atropine Sulfate Injection, USP will be supplied in 8 mg/20 mL multidose vials (0.4 mg/mL). Each vial will be used to administer multiple doses to multiple participants.

A summary of study drugs to be evaluated in this study is presented in Table 4.

Table 4: Summary of Study Drugs

	Study Drug	
Drug Name:	Atropine Sulfate Ophthalmic Solution, USP, 1%	Atropine Sulfate Injection
Route of Administration	SL	IM
Dosage Form:	1% USP solution	8 mg/20 mL (0.4 mg/mL) USP injectable solution
Unit Dose	100 µL (1.0 mg atropine sulfate)	2.5 mL (1.0 mg atropine sulfate)
Physical Description	Clear solution	Clear solution
Manufacturer	Bausch & Lomb Americas Inc.	Fresenius Kabi

9.2. Concomitant Medications

Any treatment, including all prescription drugs, herbal products, vitamins, minerals, and over-the-counter (OTC) medications administered from the time of consent through the end of study participation, is considered a concomitant medication. Concomitant medication use will be recorded in the eCRF and will include the medication name, dose, frequency, route of administration, and the dates of administration. Concomitant therapies will also be recorded on the applicable eCRF. Any changes, additions, and/or deletions in concomitant medications or therapies will be recorded in the participant's eCRF throughout the course of the participant's participation in the study.

If it is discovered that a participant is using a prohibited concomitant medication after he or she is enrolled in the study, the site investigator, in consultation with the medical monitor in cases of uncertainty, should determine the impact on the participant's participation. All instances of use of prohibited concomitant medications or therapies must be documented.

9.2.1. Prohibited and Permitted Concomitant Medications

The following concomitant medications are allowed during study participation:

- Contraceptive medications and estrogen or estrogen/progesterone hormone replacement therapy are permitted for female participants.
- Nonsteroidal anti-inflammatory drugs and acetaminophen are permitted for all participants.

Except for the permitted medications listed above, all other concomitant medications are prohibited from Screening until the end of study participation (i.e., after the Telephone Follow-

up Visit). In addition, all prescription medications are exclusionary if taken within 30 days prior to Screening, and prohibited until the end of study participation. All over-the-counter medications, vitamins, and herbal supplements are exclusionary if taken within 72 hours prior to Screening, and prohibited until the end of study participation.

9.3. Treatment Compliance

The study drug will be administered by an unblinded study staff member and thus is an observed compliance. Participant compliance will be determined by the number and percentage of participants who receive study drug at Visits 1 and 2 by dosing sequence. Any deviations from the dosing schedule outside the defined visit windows (Appendix 2) must be approved by BARDA and will be recorded.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Refer to Section 9.1 for detailed information regarding Atropine Sulfate Ophthalmic Solution, USP 1% and Atropine Sulfate Injection, USP.

10.2. Study Drug Packaging and Labeling

Study drug will be packaged and labeled according to applicable local and regulatory requirements.

10.3. Study Drug Storage

Study drug must be stored in a secure area (e.g., a locked room or locked cabinet), and protected from light and moisture. Atropine Sulfate Ophthalmic Solution, USP 1% and Atropine Sulfate Injection, USP should be kept at controlled room temperature between 20° and 25°C (68° to 77°F), inclusive. Atropine Sulfate Ophthalmic Solution, USP 1% is provided as 5 single-dose vials in foil pouches; vials should be stored as packaged until use. The temperature of the storage unit must be monitored, and documentation of proper storage must be maintained.

10.4. Study Drug Preparation and Administration

Study drug will be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit; it should not be administered if either condition exists. Study drug will not be administered if the seal is not intact immediately prior to taking the initial dose from each vial.

For SL administration, 100 µL of Atropine Sulfate Ophthalmic Solution, USP 1% will be administered SL by pipette to deliver 1.0 mg of atropine sulfate. Before administration of SL atropine, participants will be asked to swallow. Following administration, participants will be instructed to attempt not to swallow for 30 seconds and thereafter swallow as they normally would. Atropine Sulfate Ophthalmic Solution, USP 1% for SL administration will be provided in 0.4 mL single-dose vials, and each vial of atropine will only be used to administer a single dose.

For IM administration, 2.5 mL of Atropine Sulfate Injection, USP (8 mg/20 mL; 0.4 mg/mL) will be injected into the mid-anterolateral thigh to deliver 1.0 mg of atropine sulfate. Appropriate needle length for IM administration depends on age and body mass of the participant. The needle length should be sufficient to reach the muscle mass and prevent the atropine dose from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. For most adults receiving an intramuscular administration in the anterolateral thigh, a 1-1.5" needle inserted at a 90-degree angle to the skin should be utilized to ensure the IM dose is administered appropriately. Atropine Sulfate Injection, USP will be supplied in multi-dose vials. Multi-dose vials for IM administration will be dated and timed in the appropriate label areas upon initial puncture to indicate the first time of entry into the vial. No dose shall be administered from the opened vial after 24 hours of first entry (i.e., the beyond use date/time).

After initial use of single-dose vials for SL administration, or after the beyond use date/time of multi-dose vials for IM administration, the used vials should be maintained in a separate location from the unused vials until drug accountability has been reconciled.

10.5. Study Drug Accountability

The investigator is required to maintain adequate records of the disposition of the study drug, including the date and quantity of drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed. Records for receipt, storage, use, and disposition will be maintained by the study site. A study drug dispensing log will be kept current and will include identification of each participant and the date and quantity of study drug dispensed. All records regarding the disposition of the study drug will be available for inspection by the study monitor and BARDA.

10.6. Study Drug Handling and Disposal

After dosing has been completed for all participants, to satisfy regulatory requirements regarding accountability, all study drug will be reconciled and destroyed according to applicable regulations. Study drug will not be destroyed until authorized in writing by BARDA.

10.7. Randomization and Blinding

10.7.1. Randomization

Participants 18 through 65 years of age, inclusive, will be randomized 1:1 to one of two treatment dosing sequences (A or B) as specified in Table 3. The randomization schedule will be generated by the statistical team at Rho using a web-based randomization system.

10.7.2. Blinding

This study is not blinded.

11. ASSESSMENT OF PHARMACOKINETICS

Blood samples will be collected from each participant for PK assessments by a designated, qualified individual from the study research team. At Visit 1 (Day 1) and Visit 2 (Day 8), an indwelling venous catheter will be placed before dose administration for blood sample collection for serial determinations at the following times: 0 (pre-dose) and at 13 time points post-dose at 5, 10, 15, 20, 30, 45, 60, and 90 minutes, and 2, 2.5, 4, 6, and 8 hours. Ten (10) mL of whole blood will be collected into a sterile vacutainer containing ethylenediaminetetraacetic acid (EDTA) as a preservative for each sampling. Plasma will be stored frozen until analysis.

Pharmacokinetic samples will be analyzed by a bioanalytical facility approved by BARDA.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety will be evaluated utilizing the assessments defined in this section. If deemed clinically necessary, additional safety assessments not currently specified in the protocol may be performed at the discretion of the site investigator in consultation with the medical monitor and BARDA.

12.1.1. Demographic/Medical History

In order to define a baseline for potential AEs, the demographics and medical history of each participant will be collected at the Screening Visit.

12.1.2. Vital Signs

Vital sign measurements, including oral temperature, heart rate, respiratory rate, and diastolic and systolic blood pressure (after the participant is seated for at least 5 minutes), will be collected at Screening, Visit 1 (Day 1 Pre-dose), and Visit 2 (Day 8 Pre-dose) prior to any blood draws. Post-dose automated blood pressure and heart rate measurements will be recorded on the opposite arm from blood collection every 15 ± 5 minutes for the first hour, every 20 ± 5 minutes for the second hour, and every 30 ± 5 minutes for the third and fourth hours and thereafter as deemed clinically necessary by the investigator until the end of each visit. Vital signs may be repeated at an Unscheduled or Early Termination (ET) Visit per the investigator's discretion.

Respiratory rate, if regular, may be assessed over 30 seconds and doubled, but in no case will it be assessed over a period of less than 30 seconds. If the respiratory rate is irregular, it will be assessed over 60 seconds.

12.1.3. Weight and Height

Participant's height and weight will be measured at the Screening Visit. Body mass index (BMI) will be derived automatically from height and weight measurements in the electronic data capture system. Participant's weight will be assessed again at Visit 1 (Day 1 Pre-dose) and Visit 2 (Day 8 Pre-dose). Weight may be measured at an Unscheduled or ET Visit per the investigator's discretion.

12.1.4. Physical Examination

A physical examination will be performed at the Screening Visit to assess and confirm eligibility. The examination will include a general assessment of the skin, head, ears, eyes, nose, throat, neck, oral cavity, thyroid, lungs, heart, abdomen, lymph nodes, and musculoskeletal system/extremities, and a neurological (cranial nerve examination, including pupillary diameter, eye movements, and deep tendon reflexes) examination. A symptom-based physical examination may be performed at dosing visits, or at an Unscheduled or ET Visit per the investigator's discretion. In general, clinically significant abnormal findings are expected to be associated with an item recorded in the participant's medical history (when detected at Screening) or as an AE (when detected after Screening).

12.1.5. Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded and assessed at the Screening Visit, Visit 1 (Day 1 Pre-dose), and Visit 2 (Day 2 Pre-dose). Additionally, an ECG may be performed for any complaints of chest discomfort, lightheadedness, and/or palpitations per the investigator's discretion and repeated as needed during Visit 1 (Day 1 Post-dose) and Visit 2 (Day 2 Post-dose). ECGs may also be performed at an Unscheduled or ET Visit per the investigator's discretion. ECGs will be reviewed by a medically qualified individual to verify whether any abnormalities are clinically significant. In general, clinically significant abnormal ECGs are expected to be associated with an item recorded in the participant's medical history (when detected at Screening) or as an AE (when detected after Screening).

12.1.6. Clinical Laboratory Assessments

At the Screening Visit, venous blood and urine will be collected for all participants for Screening laboratory assessments. All clinical laboratory assessments provided in this section will be performed at Screening.

Clinical laboratory assessments may be repeated at an Unscheduled or ET Visit as clinically indicated per the investigator's discretion.

Samples will be analyzed by the local lab. The details for sample handling, processing, and shipping will be provided in the Laboratory Manual. Individual results will be sent to the clinical site, and the investigator will perform a clinical assessment of all laboratory data to assess eligibility and identify and document AEs as applicable.

The clinical laboratory assessments planned for this study are as follows:

12.1.6.1. Complete blood count with differential

Table 5 lists the parameters of the complete blood count with differential.

Table 5: Complete Blood Count with Differential

Red blood cells	**White blood cells**
Hematocrit	Basophils (% and absolute count)
Hemoglobin	Eosinophils (% and absolute count)
Red blood cell count	Lymphocytes (% and absolute count)
Platelets	Monocytes (% and absolute count)
Platelet count	Neutrophils (% and absolute count)
	White blood cell count

12.1.6.2. Serum Chemistry, Liver Function, and Thyroid-stimulating Hormone Assessments

The clinical chemistry, liver function, and TSH assessments planned for this study are provided in Table 6:

Table 6: Serum Chemistry, Liver Function, and TSH Assessments

• **Chem 7 panel** – Blood urea nitrogen (BUN) – Carbon dioxide – Creatinine – Glucose – Serum chloride – Serum potassium – Serum sodium	• **Liver function tests (LFTs);** – Aspartate aminotransferase (AST) – Alanine transaminase (ALT) – Alkaline phosphatase (ALP) – Direct bilirubin – Total bilirubin (fractionated for values for total bilirubin > ULN) • **Thyroid-stimulating hormone (TSH) with reflex to T4**

12.1.6.3. Virus Serology

At the Screening Visit, participant medical history will be reviewed for known human immunodeficiency virus (HIV) infection, and acute or chronic hepatitis B or hepatitis C infection. In addition, blood samples will be collected at the Screening Visit for HIV, hepatitis B surface antigen (HBsAg), and hepatitis C antibody (anti-HCV) tests.

12.1.6.4. Urine Drug Screen

A urine drug screen will be performed at the Screening Visit and will include tests for amphetamines, cocaine, tetrahydrocannabinol, methylenedioxymethamphetamine, and opiates.

12.1.6.5. Pregnancy Screen

At the Screening Visit, blood will be collected for a serum quantitative beta-human chorionic gonadotropin (beta-HCG) assay for female participants of childbearing potential. At Visit 1 (Day 1 Pre-dose) and Visit 2 (Day 8 Pre-dose), a urine point-of-care (POC) pregnancy test will be performed onsite for female participants of childbearing potential.

Additionally, a urine POC pregnancy test will be performed at any time during study participation if pregnancy is suspected.

12.1.7. Adverse Event Assessment

At all visits and phone contacts, including an ET or Unscheduled Visit, site staff will ask nonleading questions regarding the participant's health status (Section 12.3.1) and document any new or changed AEs. Adverse events occurring during washout periods (i.e., between Visit 1 and Visit 2, and between Visit 2 and the Telephone Follow-up Visit) should be collected at the next participant contact.

12.1.8. Concomitant Medication Assessment

Site staff will review concomitant medications (Section 9.2) at Screening, as well as Visit 1 (Day 1 Pre-dose) and Visit 2 (Day 8 Pre-dose) prior to administration of study drug. On Visit 1 (Day 1 Post-dose) and Visit 2 (Day 8 Post-dose), any medications or treatments administered to the

participant during attendance at the Clinical Research Unit (CRU) will also be recorded. Concomitant medications will also be reviewed during the Follow-Up telephone contact and at an Unscheduled or ET Visit.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related [21 Code of Federal Regulations [CFR] 312.32(a)]. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (Integrated Addendum to International Council for Harmonisation [ICH] E6[R1]: Guideline for Good Clinical Practice [GCP] E6[R2]).

Laboratory results and vital sign excursions of any magnitude will be defined as AEs if they are considered clinically significant by the site investigator. A lab or vital sign result should generally be considered clinically significant and an AE if, regardless of degree out of range, it has a reasonable probability of reflecting or contributing to a disturbance of homeostasis or pathological process or outcome.

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the event. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug [21 CFR 312.32(a)].

An AE or SAR is considered "unexpected" if it is not listed in the package inserts for the study drugs or is not listed at the specificity or severity that has been observed.

12.2.1.2. Serious Adverse Event (SAE)

An AE or SAR is considered "serious" if, in the view of either the site investigator or BARDA, it results in any of the following outcomes [21 CFR 312.32(a)]:

- Death
- Life-threatening adverse event that in the view of the site investigator or BARDA, places the participant at immediate risk of death. This does not, however, include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongs existing hospitalization. Planned hospitalizations will not be reported as SAEs unless categorized as medically important. Emergency room visits and observational admissions of under 24 hours, in themselves, do not qualify as SAEs.
- Results in persistent or significant disability/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 a serious adverse drug experience, when based on appropriate medical judgment, they may jeopardize the participant, or the participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.3. Collection, Recording, and Grading Severity of Adverse Events

12.3.1. Collection of Adverse Events

Adverse events of any type described above may be discovered through a variety of methods:

- Observing the participant
- Questioning the participant with standard nonleading questions to elicit any medically related changes in their well-being (e.g., Have you been hospitalized, had any accidents, used any new medications, or changed any medications [both prescription and OTC]?)
- Receiving an unsolicited complaint from the participant
- An abnormal value or result from a clinical (e.g., vital signs) or laboratory evaluation

12.3.2. Recording Adverse Events

Throughout the study, the investigator will record AEs on the eCRF. SAEs must be reported to Rho pharmacovigilance personnel within 1 business day of the site's awareness of the event. For the purposes of this study, any detrimental change in the participant's condition after signing informed consent and up to completion of the follow-up period after the last administration of study drug (i.e., through Follow-up [Day 15]) will be considered an AE and must be recorded. Treatment-emergent AEs are defined as AEs occurring after the participant receives at least one dose of atropine. AEs will be followed per the below criteria:

- AEs judged at least possibly related to study drug will be followed to resolution (with or without sequelae) or until considered stable by the investigator (in consultation with the medical monitor in situations of uncertainty).
- AEs judged unrelated to study drug will be followed to resolution (with or without sequelae) or, if not resolving, until considered stable by the investigator (in consultation with the medical monitor in situations of uncertainty), or until the end of the participant's study participation, whichever comes first.

12.3.3. Grading Severity of Adverse Events

The severity of AEs and SAEs will be graded as defined by criteria set forth in the NCI-CTCAE Manual Version 5.0. AEs will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild AE

Grade 2 = moderate AE

Grade 3 = severe AE

Grade 4 = life-threatening AE or urgent intervention indicated

Grade 5 = death

Events grade 1 or higher will be recorded on the appropriate AE eCRF for this study.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 12.2.1.2.

12.4. Relationship and Attribution to Study Drug

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE and must be provided for all AEs (serious and non-serious). The site investigator will assess and record the causality/relationship between the study drug and the AE.

BARDA's determination of attribution will be used for reporting to the IRB.

The relation and attribution of an AE to study drug will be determined using the descriptors and definitions provided in Table 7.

Table 7: Attribution of Adverse Events

Unrelated Categories	
Not Related	The AE is clearly not related to study drug.
Unlikely Related	The AE is unlikely related to study drug.
Related categories	
Possibly Related	The AE has a reasonable possibility to be related to study drug; there is evidence to suggest a causal relationship.
Probably Related	The AE is likely related to study drug.
Related	The AE is clearly related to study drug.

AE = adverse event

12.5. Reporting Safety Events to IRB

Once AEs and SAEs are recorded, Rho pharmacovigilance personnel will collaborate with appropriate personnel from BARDA and Allucent to process events and report events in a timely fashion to the IRB in accordance with applicable regulations and guidelines. Procedures for AE processing and reporting are detailed in the Data Safety Monitoring Plan (DSMP).

12.6. Pregnancy Reporting

This study includes pregnancy as safety data. Although pregnancy is not an SAE, information about any pregnancy in a female study participant should be reported to Rho pharmacovigilance personnel within 1 business day of the site's awareness of the event for tracking purposes.

Study dose administration will be discontinued for the pregnant participant. The investigator shall counsel the pregnant participant and discuss the risks of continuing with the pregnancy and

the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The pregnancy will be documented when identified and at its conclusion.

Should pregnancy result in a congenital abnormality, birth defect, miscarriage, or medically indicated abortion, an SAE must be submitted to Rho using the SAE reporting procedures described in Section 12.3.2.

12.7. Reporting Other Safety Information

Site investigators should promptly notify Rho, Allucent, BARDA, and the IRB when an unanticipated problem involving risks to participants or others, which is not otherwise reportable as an AE, is identified.

13. STATISTICS

13.1. Endpoints

Endpoints are summarized in Table 2 under Section 6.

The bioequivalence of atropine sulfate administered SL versus administered IM as measured by the following PK parameters using noncompartmental analysis (NCA) methods:

- Area under the analyte concentration versus time curve to infinity (AUC_{∞})
- Area under the analyte concentration versus time curve to time of last quantifiable data point (AUCt)

The relative bioavailability of atropine sulfate administered SL versus IM as measured by the following PK parameters using NCA methods:

- Area under the analyte concentration versus time curve to 45, 60, 90, 120, 150, and 240 minutes (AUC_{45}, AUC_{60}, AUC_{90}, AUC_{120}, AUC_{150}, and AUC_{240}, respectively)
- Maximum measured plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Apparent terminal elimination half-life ($t_{½}$)
- Terminal elimination rate constant (λz)
- Volume of distribution (V_d/F)
- Total body clearance (CL/F)
- Absorption rate constant (K_a)

13.1.1. Measures to Minimize Bias

Permuted block randomization will be performed centrally by designated Rho staff and will balance enrollment between treatment dosing sequences (see Section 10.7 for more details).

13.1.2. Analysis Plan

Statistical analyses will be performed using SAS® software Version 9.4 or later. Phoenix WinNonLin Version 8.3 software will be used to generate PK parameter estimates.

Descriptive statistics will be used to summarize participant characteristics and safety. These summaries will be presented overall and separately for each route of administration.

Details of the statistical analyses, methods, and data conventions will be described in the Statistical Analysis Plan (SAP).

13.1.2.1. Analysis Populations

13.1.2.1.1. PK Analysis Population

The PK analysis population will include all participants who are randomized, receive at least 1 study drug dose, and have PK samples collected for that period. Each participant's data will be

analyzed according to the corresponding route of administration for the applicable period. The PK analysis population will be used for all PK analyses.

13.1.2.1.2. Per Protocol Population

The per protocol population will include all participants who are randomized, receive atropine via both routes of administration according to their randomized dosing sequence, and have PK samples collected for both periods. In addition, participants with major protocol deviations may be excluded if it is determined that the deviations affect the integrity of PK data. Each participant's data will be analyzed according to the corresponding route of administration for the applicable period. Primary and secondary analyses will be repeated in the per protocol population if it differs from the PK analysis population.

13.1.2.1.3. Safety Population

The safety population will include all participants who are randomized and receive at least 1 study drug dose. Each participant's data will be analyzed according to the corresponding route of administration for the applicable period. The safety population will be used for all safety displays.

13.1.2.2. Primary Analysis

Pharmacokinetic parameters AUC_{∞} and AUC_t will be estimated for each participant and route using the noncompartmental method and will be summarized by route of administration using descriptive statistics.

Relative bioavailability of SL administration of atropine sulfate compared to that of IM atropine sulfate will be assessed based on ratios of least-square means and their associated 90% confidence intervals (CIs) generated from linear mixed models including terms for dosing sequence, route, and period as fixed effects, and subject nested within dosing sequence as a random effect. Bioequivalence will be considered met if the 90% CI of the ratio for AUC_{∞} and AUC_t lie within 80.00 and 125.00%.

Additional details of the statistical analyses, methods, and data conventions will be described in the Statistical Analysis Plan (SAP).

13.1.2.3. Secondary Analyses

The AUC_{45}, AUC_{60}, AUC_{90}, AUC_{120}, AUC_{150}, and AUC_{240}, C_{max}, $t_{max,}$ $t_{1/2}$, λ_z, V_d/F, CL/F, and K_a will also be estimated for each participant and route of administration using the noncompartmental method and will be summarized by route using descriptive statistics. Each parameter will be compared between routes, where applicable, using linear mixed models, including terms for dosing sequence, route, and period as fixed effects, and subject nested within sequence as a random effect in the model. Ratios of least-squares means and associated 90% CIs will be presented.

13.1.1.4. Interim Analysis

No interim analysis is planned for this study.

13.1.2.4. Safety Reviews

In the event a study pausing rule is met, the medical monitor and the BARDA Pharmacovigilance SME and/or BARDA Medical Officer will convene to discuss and review relevant cases. No pre-planned interim safety reviews will be conducted for this study.

13.1.2.5. Final Analysis

A clinical study report will be written to include all PK and safety data collected throughout the study. For the final analysis, the study database will be monitored, cleaned, and locked per associated study plans. Further details will be specified in the SAP.

13.1.2.6. Exploratory Analyses

No exploratory analyses are planned.

13.2. Sample Size Considerations

The target sample size for randomization for this study is approximately 46 participants, allowing for a 20% dropout rate that would result in approximately 36 evaluable participants (approximately 18 per dosing sequence) within the per protocol population. Additional participants may be randomized if participants are withdrawn prior to receiving one or both doses of study drug (Section 8.2.2).

The sample size was determined for an equivalence test of the ratio of means using two one-sided tests on data from a two-period cross-over design. In the previous PK study of SL administration of atropine (BP-C-19010),[8] the standard deviation for the dose-adjusted log10 difference in high (1.0 mg) versus low (0.5 mg) SL dosing for AUC_{∞} and C_{max} were 0.102 and 0.146, respectively. Since the intra-participant variability in PK parameters between SL and IM administration is unknown, the standard deviations were conservatively multiplied by a factor of 1.25 to determine power and sample size for this study. Corresponding coefficients of variance were estimated as 0.212 and 0.304 for AUC_{∞} and C_{max}, respectively. A sample size of 36 achieves greater than 99% power to test bioequivalence for AUC_{∞} and 86% power for C_{max} at the 0.05 significance level when the true ratio of means is 1.0 and the equivalence limits are 0.80 and 1.25. Even if the true ratio of means are within ±5% of 1.0, the study still maintains 96% and 77% power for AUC_{∞} and C_{max}, respectively.

13.3. Statistical Considerations

13.3.1. Covariates

Due to the small sample size and cross-over design of this study, analyses adjusted for additional covariates beyond those specified for the primary analysis are not planned.

13.3.2. Multicenter Studies

This is a single center study thus study data will be analyzed as a whole.

13.3.3. Multiple Comparisons and Multiplicity

No adjustments will be made for multiple comparisons.

13.3.4. Subgroup Analyses

Any subgroups requiring more consideration will be discussed in the SAP as needed.

13.3.5. Missing Data

Standard procedures will be used to ensure that the data are as complete and accurate as possible. All descriptive summaries will be based upon all available data, and no imputation will be done.

13.4. Procedures for Documenting Deviations from Planned Analyses

The principal features of the design of this study and of the plan for statistical analysis of the data are outlined in this protocol. Additional details will be included in the SAP before initiating analyses. Any changes to that plan will be documented in the final clinical study report and will be approved by BARDA before being initiated.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Inspection of Records

BARDA, its designees, other authorized representatives of BARDA, Rho or its designees, Allucent or its designees, representatives of the IRB, and/or regulatory agencies may inspect all source documents and records required to be maintained by the site investigator, including but not limited to, medical (office, clinic, or hospital) and pharmacy records for the participants in this study; eCRFs, IRB submissions and approvals, study drug accountability logs, study drug temperature monitoring logs, regulatory documents, correspondence, and all other essential documents. The clinical study site will permit site visits and access to (and when required by applicable law to copy) such records.

The site investigator also agrees to promptly notify BARDA and other authorized representatives of the sponsor of any inspections scheduled by any regulatory authority, or audits by other parties and promptly forward copies of any reports received to BARDA.

14.2. Institutional Review Board

A copy of the protocol, informed consent forms (ICFs), any other participant facing documents, and any proposed advertising/recruitment materials will be submitted to the IRB for written approval. Initial IRB approval and all materials approved by the IRB for this study, including the participant consent form and recruitment materials, must be maintained by the site investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance (QA) includes all the planned and systematic actions that are established to ensure that the clinical study is performed, and the data are generated, documented (recorded), and reported according to International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and local/regional regulatory standards.

To ensure the reliability of study data, the participating site(s) will have a plan in place to describe:

- routine internal quality control (QC) and QA activities for the purposes of measuring, documenting and reporting study conduct, protocol adherence, human subjects' protections, and reliability of the protocol-driven data collected;
- a process for addressing in a timely manner any data quality issues (i.e., collecting, recording and reporting data), systemic issues (i.e., protocol conduct, non-compliance, human subject protections), and implementation of corrective and preventative action (CAPA) procedures.

A quality assurance representative from BARDA (or designee), who is independent of and separated from routine monitoring, may periodically arrange audits of the clinical study by reviewing the data obtained and procedural aspects. These audits may include on site or remote audits and source data checks. Direct access to source documents is required for the purpose of these periodic audits.

15.1. Data Quality Assurance

Data collected at the study site will be entered accurately and contemporaneously by study staff into a 21 CFR 11-compliant, internet-based, remote data entry system, which is backed up nightly. Data will be provided using the participant's unique identification number, not name or initials; Rho will not collect personally identifying information such as the participant's name or social security number. Participants will provide demographic information such as biological sex at birth, race, ethnicity, and age. All elements of data entry (e.g., time, date, verbatim text, and the person performing the data entry) will be recorded within the remote data entry system's audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations. Data collected by the laboratories will be transferred electronically directly from the laboratory to Rho using standard secure data transfer procedures. The analysis datasets will incorporate data from both sources. Data collected by Rho will be held in the strictest confidence and are protected from access that could reveal personal information about any participant in the study.

Clinical data management and data cleaning procedures (e.g., resolving errors and inconsistencies in the data) will be performed in accordance with applicable Rho and/or BARDA standards and validation plans to ensure the integrity of the data. Adverse events (including SAEs) and concomitant medication terms will be coded using the MedDRA and the World Health Organization Drug dictionaries, respectively.

After study monitors verify the data and prior to the final study analysis, the investigator must sign each eCRF at the participant level to confirm the integrity of the data recorded.

After database lock, the study site will receive an electronic copy of all of their site-specific eCRF data as entered into the remote data entry system for the study, including full discrepancy and audit history. Additionally, all of the study's analysis datasets will be sent to BARDA electronically for storage. Rho will maintain a duplicate copy for its records and will upload a copy to the BARDA Clinical Studies Network (CSN) archive.

15.2. Study Monitoring

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently IRB/IEC approved protocol/amendment(s), ICH GCP, and applicable regulatory requirement(s). Clinical monitoring also verifies any critical study procedures are completed following specific instructions in ancillary documents referenced in the protocol.

Monitoring for this study will be performed by BARDA's authorized representatives at Allucent. Details of clinical site monitoring are documented in a monitoring plan. The monitoring plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, ICFs, medical and laboratory reports, site study drug storage records, training records, and protocol and GCP compliance. Site monitors will have access to the participating site facilities, study personnel, and all study documentation according to the monitoring plan. Study monitors will meet with site investigators to discuss any problems and outstanding issues, and will document site visit findings and discussions.

15.3. Protocol Deviations

15.3.1. Protocol Deviation Definition

A protocol deviation is any noncompliance with the IRB-approved study protocol, ICH GCP guidelines, or protocol-specific Manual(s) of Procedures (MOPs). Any deviation that affects the rights or safety of the participant or the integrity of the data will be considered a major protocol deviation. Prospective permission to deviate from protocol requirements, also known as protocol waivers or exemptions, will not be granted for this study.

15.3.2. Reporting and Managing Deviations

The site investigator has the responsibility to identify, document, and report deviations. Protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review. All deviations, regardless of the cause, must be documented in accordance with GCP. Documentation at a minimum, will include the date the deviation occurred, the date it was identified, a description of the deviation, whether the deviation resulted in an AE or SAE, and documentation of a corrective action plan. In addition, the site investigator will report noncompliance to the IRB/IEC, as applicable.

Rho, Allucent, and/or BARDA may request discussion with the site investigator to determine the effect of any major protocol deviation on a study participant and his/her further study participation, the effect of the deviation on the overall study, and corrective actions.

16. REGULATORY AND ETHICAL CONSIDERATIONS

16.1. Ethics Review

Before study initiation, the site will obtain IRB approval for this protocol; ICF(s); participant recruitment procedures; written information to be provided to participants; information about payments and compensation available to participants; and any other documents that the IRB may require to fulfill its responsibilities. Any amendments to the protocol will require IRB approval before implementation except for changes necessary to eliminate an immediate hazard to a participant.

IRB review and approval of protocol documents will occur at least annually throughout the enrollment and follow-up of participants, as per applicable regulations and the IRB.

The site investigator will promptly report all unanticipated problems involving risks to participants to the IRB.

The site investigator will notify the IRB of events such as deviations, SAEs, etc. as applicable to the IRB policy.

Participants may be compensated for their participation in this study. Compensation will be in accordance with the IRB's policies and procedures, and subject to IRB approval.

16.2. Ethical Conduct of the Study

The site investigator should conduct the study in accordance with this protocol, the Declaration of Helsinki, current ICH GCP guidelines, US 21 CFR Part 50 (Protection of Human Subjects), and Part 56 (Institutional Review Boards).

16.3. Written Informed Consent

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Potential participants will receive a concise and focused presentation of key information about the study, verbally and with a written consent form. The key information about the purpose of the study, the procedures and experimental aspects of the study, study interventions, study drugs, probability for random assignment to dosing schedules, risks and discomforts, the expected duration of the participant's participation in the trial, any expected benefits to the participant, and alternative treatments and procedures that may be available to the participant. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

Participants will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Participants will be informed of the anticipated financial expenses, if any, to the participant for participating in the study, as well as any anticipated prorated payments, if any, to the participant for participating in the study. They will be informed of whom to contact (e.g., the site investigator) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the

participant's participation in the study may be terminated. The participants will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the participant is otherwise entitled.

Participants will be informed that records identifying the participant will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the participant's identity will remain confidential. Participants will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Participants will be informed that the monitor(s), auditor(s), IRB, BARDA, and regulatory authority(ies) will be granted direct access to the participant's original medical records for verification of study procedures and/or data without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations, and that, by signing a written ICF, the participant is authorizing such access.

Participants will be allowed sufficient time to consider participation in this research study and have the opportunity to discuss this study with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

Participants will be informed of the Public Readiness and Emergency Preparedness Act (PREP Act) and the Countermeasures Injury Compensation Program (CICP) (Appendix 3).

Informed consent forms will be IRB-approved and participants will be asked to read and review the consent form. Participants must sign the ICF prior to starting any study procedures being done specifically for this study. Once signed, a copy of the ICF will be given to the participant(s) for their records.

New information will be communicated by the site investigator to participants who consent to participate in this study in accordance with IRB requirements. The informed consent document will be updated, and participants will be re-consented per IRB requirements, if necessary.

Using the ICF, participants who consent to participate in this study will be asked to consent to permission to be contacted with a request to participate in future clinical studies related to atropine administration.

17. DATA HANDLING AND RECORD KEEPING

17.1. Confidentiality

Participant confidentiality is strictly held in trust by the participating site investigators, their staff, and the sponsor(s) and their designees. This confidentiality is extended to cover clinical information relating to participants, test results of biological samples, and all other information generated during participation in the study. No identifiable information concerning participants in the study will be released to any unauthorized third party. Participant confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the site investigator, including but not limited to, medical (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

All source records including electronic data will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the site (including any electronic transmission of data) will be identified only by a coded number that cannot be linked to a participant.

17.2. Retention of Records

The site investigator should retain all documentation relating to the study (including but not limited to ICFs, source documentation, study drug records, eCRFs, and essential documents) for a period of 2 years after completion of the study.

If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

At study closure, the site investigator must inform BARDA, or designee, of the long-term storage location of the study's records. Following study closure, the site investigator must inform BARDA if that location changes (e.g., the site investigator leaves the institution where the study was conducted).

No study records will be destroyed without prior authorization from BARDA.

18. PUBLICATION POLICY

BARDA will be responsible for publication activities and for defining the manuscript/presentation development process, the number and order of authors, the publication/scientific meeting to which it will be submitted, and other related issues. BARDA has final approval authority over all such issues.

Data are the property of BARDA and cannot be published without prior authorization from BARDA, but data and publication thereof will not be unduly withheld.

The National Institutes of Health Public Access Policy will apply to this study.[13] ASPR-funded site investigators will be required to submit an electronic version of final, peer-reviewed manuscripts resulting from this study to the National Library of Medicine's PubMed Central upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication.

All applicable clinical trials supported by BARDA must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first participant. This will include a description of the clinical trial as required by US Law. This web site will not include information that can identify participants. Results information from those trials must be submitted no later than one year after the trial's primary completion date.

As required, the following will be posted on ClinicalTrials.gov: Protocol, ICF (that has been used to enroll participants), and SAP.

19. RESEARCH-RELATED INJURIES

For any potential research related injury, the site investigator or designee will assess the participant. The site investigator should then determine if an injury occurred as a direct result of the tests or treatments that are done for this study. As needed, referrals to appropriate health care facilities will be provided to the participant.

20. PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Table 8: Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
1.0	13 February 2024	N/A	Initial version

21. LIST OF REFERENCES

1. Calvano CJ, Enzenauer RW, Eisnor DL, Mazzoli RA. Atropine Eye Drops: A Proposed Field Expedient Substitute in the Absence of Atropine Autoinjectors. Journal of special operations medicine. 2017;17(3):81-3.
2. Schwartz MD, Sutter ME, Eisnor D, Kirk MA. Contingency medical countermeasures for mass nerve-agent exposure: use of pharmaceutical alternatives to community stockpiled antidotes. Disaster medicine and public health preparedness. 2019 Jun;13(3):605-12.
3. Norderyd J, Graf J, Marcusson A, Nilsson K, Sjöstrand E, Steinwall G, Ärleskog E, Bågesund M. Sublingual administration of atropine eyedrops in children with excessive drooling–a pilot study. International journal of paediatric dentistry. 2017 Jan;27(1):22-9.
4. De Simone GG, Eisenchlas JH, Junin M, Pereyra F, Brizuela R. Atropine drops for drooling: a randomized controlled trial. Palliative medicine. 2006 Oct;20(7):665-71.
5. Dias BLS, Fernandes AR, Maia HS Filho. Treatment of drooling with sublingual atropine sulfate in children and adolescents with cerebral palsy. Arquivos de neuro-psiquiatria. 2017 May;75(5):282-7.
6. Matos Santana TE, Capurso NA, Ranganathan M, Yoon G. Sublingual atropine in the treatment of clozapine-induced sialorrhea. Schizophrenia research. 2017 Apr;182:144-5.
7. Rajpal S, Ali R, Bhatnagar A, Bhandari SK, Mittal G. Clinical and bioavailability studies of sublingually administered atropine sulfate. The American journal of emergency medicine. 2010 Feb 1;28(2):143-50.
8. ClinicalTrials.gov [Internet]. NCT04290039: Sublingual vs IV Atropine Bioavailability Study. [updated 2023 June 22; cited 2024 Jan 23]. Available from: https://clinicaltrials.gov/study/NCT04290039
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11. Atropine Sulfate (Atropine Sulfate Solution); Atropine Sulfate Ophthalmic Solution, USP 1% [package insert]. Bridgewater, NJ: Bausch & Lomb Americas Inc.
12. Atropine Sulfate Injection, USP; [package insert]. Lake Zurich, IL. Fresenius Kabi.
13. National Institutes of Health [Internet]. Public Access Policy. [updated 2022 Aug 29; cited 2024 Jan 23]. Available from: https://publicaccess.nih.gov.

22. APPENDICES

APPENDIX 1. PUBLICATION REVIEW OF SUBLINGUAL ADMINISTRATION OF ATROPINE

Citation	Age of Population	Population type	Study Design	Primary Objective	Atropine Formulation	Atropine Dose Regimen (mg)	Duration of Atropine Rx.	Total N	Atropine Exposed N	Major Safety Findings
Antonello C, Tessier P. (1999). "Clozapine and sialorrhea: a new intervention for this bothersome and potentially dangerous side effect." J Psychiatry Neurosci. May;24 (3):250.	Adults	Chronic schizophrenia	Case reports	Treat clozapine-induced Hypersaliva-tion	1% ophthalmic solution	0.5 mg once daily	Not reported	3	3	"None of the patients reported any side effects."
Chaptini, L. A., et al. (2008). "Sublingual hyoscyamine spray as premedication for colonoscopy: a randomized double-blinded placebo-controlled trial." Am J Surg 196(1): 51-55.	Adults	Elective colonoscopy	Randomized double-blind, placebo controlled	Effect on colonoscopy quality and comfort	Hyoscyamine spray	0.25 mg	Single dose	100	50	"No significant difference in occurrence of side effects between the 2 groups." Vital signs comparable before, during and after procedure between the 2 groups.

Citation	Age of Population	Population type	Study Design	Primary Objective	Atropine Formulation	Atropine Dose Regimen (mg)	Duration of Atropine Rx.	Total N	Atropine Exposed N	Major Safety Findings
Comley C, Galletly C, Ash D. (2000). "Use of atropine eye drops for clozapine induced hypersalivation." Aust N Z J Psych. Dec;34(6):1033-4.	44 years	Chronic schizophrenia and associated depression	Case report	Treat clozapine-induced Hypersaliva-tion	1% ophthalmic solution	0.5 – 1.0 mg once daily	Not reported	1	1	"There have been no adverse effects from this treatment."
De Simone, G. G., et al. (2006). "Atropine drops for drooling: a randomized controlled trial." Palliat Med 20(7): 665-671.	Adults	Esophageal and gastric cancer and drooling	Double-blind, cross-over, randomized, placebo controlled	Effectiveness for drooling	0.5% ophthalmic solution	0.5 mg q6h	48 hours	22	21	No severe toxicity - no blurred vision, palpitations, heartburn, hesitancy, urinary retention. One patient discontinued for cognitive impairment thought due to severe chest infection.

Citation	Age of Population	Population type	Study Design	Primary Objective	Atropine Formulation	Atropine Dose Regimen (mg)	Duration of Atropine Rx.	Total N	Atropine Exposed N	Major Safety Findings
Dias, B. L. Set al. (2017). Treatment of drooling with sublingual atropine sulfate in children and adolescents with cerebral palsy. Arq Neuropsiquiatr, 75(5), 282-287.	2 – 17 years	Cerebral palsy, drooling	Open-label, non-controlled	Effectiveness for drooling	0.5% ophthalmic solution	0.125 mg thrice daily for weight 10-19 kg; 0.5 mg thrice daily for weight >= 20 kg	30 days	33	25	Side effects in 4/33 (12%): fever, flush, irritability, angioedema
Dumot, J. A., et al. (1998). Sublingual hyoscyamine for patient comfort during screening sigmoidoscopy: a randomized, double-blind, placebo-controlled clinical trial. Gastrointest Endosc, 48(3), 283-286.	25 – 83 years	Patients undergoing screening sigmoidoscopy	Double-blind, placebo controlled	Efficacy for comfort during screening sigmoidoscopy	Hyoscyamine 0.125 mg tablets	0.5 mg (2 tablets 10 min prior to sigmoidoscopy)	1 day	150	75	No treatment related adverse effects reported
Ghobrial, P. M., et al. (2014). Cine MR enterography grading of small bowel peristalsis: evaluation of the antiperistaltic effectiveness of sublingual hyoscyamine sulfate. Acad Radiol, 21(1), 86-91.	Not Described	Patients undergoing MRE	Open-label, non-controlled	Effect on peristalsis	Hyoscyamine 0.125 mg tablets	0.5 mg 1 hour before MRE	Single dose	92	92	Safety was not discussed

Citation	Age of Population	Population type	Study Design	Primary Objective	Atropine Formulation	Atropine Dose Regimen (mg)	Duration of Atropine Rx.	Total N	Atropine Exposed N	Major Safety Findings
Hyson, H. C., et al. (2002). "Sublingual atropine for sialorrhea secondary to parkinsonism: a pilot study." Mov Disord 17(6): 1318-1320.	62-82 years	Parkinson's disease/ Parkinsonism and drooling	Open-label, non-controlled	Effectiveness for drooling	1% ophthalmic solution	0.5 mg twice daily	1 week	7	7	No complaints of worsening constipation, blurred vision, dizziness, confusion;
Jones, J. B., & Dula, D. J. (1998). The efficacy of sublingual hyoscyamine sulfate and intravenous ketorolac tromethamine in the relief of ureteral colic. Am J Emerg Med, 16(6), 557-559.	18 years or older	Ureteral colic due to calculi	Randomized open-label, two-arm study	Effect on ureteral colic	Hyoscyamine sulfate	0.125 mg	Single dose	49	24	Safety was not discussed
Jones, J., et al. (2001). Sublingual hyoscyamine sulfate in combination with ketorolac tromethamine for ureteral colic: a randomized, double-blind, controlled trial. Ann Emerg Med, 37(2), 141-146.	18 years or older (44 years mean)	Ureteral colic	Double-blind, two-arm study	Effect on ureteral colic	Hyoscyamine sulfate	0.125 mg	Single dose	43	23	Safety was not discussed

Citation	Age of Population	Population type	Study Design	Primary Objective	Atropine Formulation	Atropine Dose Regimen (mg)	Duration of Atropine Rx.	Total N	Atropine Exposed N	Major Safety Findings
Lynch, C. R., et al. (2007). "Sublingual L-hyoscyamine for duodenal antimotility during ERCP: a prospective randomized double-blinded study." Gastrointest Endosc 66(4): 748-752.	Adults	Patients undergoing ERCP	Randomized double-blind, placebo controlled	Effect on glucagon needed during ERCP	Hyoscyamine	0.5 mg	Single dose	200	101	No significant difference between the two groups in incidence of adverse drug effects including nausea, vomiting, and xerostomia at 2 and 24 hours, tachycardia, hypotension, hypoxemia.
Matos Santana, T. E., et al. (2017). "Sublingual atropine in the treatment of clozapine-induced sialorrhea." Schizophr Res 182: 144-145.	Adults	Schizophrenia or schizoaffective disorder	Case reports	Effectiveness for clozapine-induced sialorrhea	1% ophthalmic solution	0.5-1.0 mg once to twice daily	> 1 week	3	3	"None of the patients reported any systemic side effects"

Citation	Age of Population	Population type	Study Design	Primary Objective	Atropine Formulation	Atropine Dose Regimen (mg)	Duration of Atropine Rx.	Total N	Atropine Exposed N	Major Safety Findings
Mustafa, F. A., et al. (2013). "Sublingual atropine for the treatment of severe and hyoscine-resistant clozapine-induced sialorrhea." Afr J Psychiatry (Johannesbg) 16(4): 242.	46 years	Adult with schizophrenia	Case report	Effectiveness for clozapine-induced sialorrhea	1% ophthalmic solution	0.5 mg up to three times daily	7 days	1	1	Safety was not discussed
Norderyd, J., et al. (2017). "Sublingual administration of atropine eyedrops in children with excessive drooling - a pilot study." Int J Paediatr Dent 27(1): 22-29.	5 - 18 years	Non-medically induced drooling associated with disability (CP, ASD, Down syndrome, etc.)	Open label, non-controlled	Effectiveness for drooling	1% ophthalmic solution	0.5 mg once to twice daily	8 weeks	26	19	Miction problems (3), obstipation (3), changed behavior (3)
Protus, B. M., et al. (2012). Evaluation of atropine 1% ophthalmic solution administered sublingually for the management of terminal respiratory secretions. Am J Hosp Palliat Care, 30(4), 388-392.	42 - 94 years	Adults, hospice terminal care	Retrospective chart review	Effect on respiratory secretions	1% ophthalmic solution	0.5 mg every 2 hours until effect	Varied by patient; range 1 hour to 6 days	22	22	No adverse effects reported

Citation	Age of Population	Population type	Study Design	Primary Objective	Atropine Formulation	Atropine Dose Regimen (mg)	Duration of Atropine Rx.	Total N	Atropine Exposed N	Major Safety Findings
Rapoport, A, (2010). "Sublingual Atropine Drops for the Treatment of Pediatric Sialorrhea.", J. of Pain and Symptom Management 40(5): 783-788.	14 years	MLD and excessive drooling	Case report	Effect on sialorrhea	0.5% ophthalmic solution	0.25 mg up to three times daily	2 weeks	1	1	Tongue fasciculation and dystonia developed after 2 weeks, determined to be due to metoclopramide. Sublingual atropine restarted without recurrence. No facial flushing, change in behavior, or tachycardia.
Rothrock, S.G, et al. (1993) Successful Resuscitation From Cardiac Arrest Using Sublingual Injection for Medication Delivery. Ann Emerg Med. 22(4):751-3.	7 months	Infant with cardio-pulmonary arrest	Case report	Effect in cardiac arrest	Not stated	0.15 mg (estimated 0.02 mg/kg)	Single dose	1	1	Safety was not discussed

Citation	Age of Population	Population type	Study Design	Primary Objective	Atropine Formulation	Atropine Dose Regimen (mg)	Duration of Atropine Rx.	Total N	Atropine Exposed N	Major Safety Findings
Sharma, A., et al. (2004). Intraoral application of atropine sulfate ophthalmic solution for clozapine-induced sialorrhea. Ann Pharmacother, 38(9), 1538.	55 years	Patient taking clozapine	Case report	Effectiveness for clozapine-induced sialorrhea	1% ophthalmic solution	1.0 mg twice daily	2 weeks	1	1	Clinician reported no adverse effects

ASD = autism spectrum disorder; CP = cerebral palsy; ERCP = endoscopic retrograde cholangiopancreatography; min = minute; MLD = metachromatic leukodystrophy; MRE = magnetic resonance enterography; q6h = every 6 hours; Rx = treatment

APPENDIX 2. SCHEDULE OF ASSESSMENTS

Study Visit	**Screening**	**Visit 1 [a]**		**Visit 2 [a]**		**Telephone Follow-up**	**ET [b]**	**Unscheduled**
Study Day	**Day -14 to -3**	**Day 1 Pre-dose (Baseline)**	**Day 1 Dosing**	**Day 8 Pre-dose (Baseline)**	**Day 8 Dosing**	**Day 15,-1/+7d**	**N/A**	**N/A**
Visit window based on actual dosing day	**N/A**	**N/A**		**V1+7d,±1**		**V2+7d,-1/+7**	**N/A**	**N/A**
Informed Consent	X							
Inclusion/Exclusion	X	X [c]		X [c]				
Randomization		X						
Demographic/Medical History	X							
Height, weight, BMI	X	X [d]		X [d]			X [d]	X [d]
Concomitant Medications	X	X	X	X	X	X	X	X
Physical Exam	X [e]	X [f]		X [f]			X [f]	X [f]
Vital Signs [g]	X	X	X	X	X		X	X
12-lead ECG	X	X	X [h]	X	X [h]		X [i]	X [i]
Urine drug screen [j]	X							
Serum quantitative beta-HCG assay	X							
HIV antibody, HBsAg, anti-HCV	X							
Laboratory Assessments [k]	X						X [l]	X [l]
Urine POC pregnancy test [m]		X		X			X [n]	X [n]
CRU admission		X		X				
Other pre-dose eligibility [o]		X		X				
Study drug administration			X		X			
Plasma PK [p]		X	X	X	X			
AEs	X	X	X	X	X	X	X	X
Discharge from CRU			X		X			

AE = adverse event; BMI = body mass index; CBC = complete blood count; CRU = clinical research unit; d = day; ECG = electrocardiogram; ET = early termination; HBsAg = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; N/A = not applicable; LFT=liver function test; PK = pharmacokinetic; POC = point-of-care; SL = sublingual; TSH = thyroid-stimulating hormone.

[a] Washouts of 6 ± 1 days will occur between visits. Adverse events and concomitant medications will be recorded for both washout periods.
[b] The ET Visit may be conducted in clinic or by phone as determined by the investigator.
[c] Eligibility criteria must be reviewed just prior to each dose of atropine, unless the criterion is specified as only being evaluated at Screening.
[d] Weight only will be measured at Visit 1 (Day 1 Pre-dose) and Visit 2 (Day 8 Pre-dose). Weight may also be measured at an ET or Unscheduled Visit per the investigator's discretion.
[e] All participants will undergo a physical examination at Screening. The examination will include a general assessment of the skin, head, ears, eyes, nose, throat, neck, oral cavity, thyroid, lungs, heart, abdomen, lymph nodes, and musculoskeletal system/extremities, and a neurological (cranial nerve examination, including pupillary diameter, eye movements, and deep tendon reflexes) examination.
[f] At Visit 1 (Day 1 Pre-dose), Visit 2 (Day 8 Pre-dose), ET, and Unscheduled visits, the investigator may perform symptom-based physical examinations at their discretion.
[g] Vital signs (heart rate, blood pressure, temperature, and respiratory rate) will be obtained prior to each dose of study drug. Post-dose automated blood pressure and heart rate measurements will be recorded on the opposite arm from blood collection every 15 ± 5 minutes for the first hour, every 20 ± 5 minutes for the second hour, and every 30 ± 5 minutes for the third and fourth hours, and thereafter as deemed clinically necessary by the investigator until the end of each visit. Vital signs may also be performed at an Unscheduled or ET Visit per the investigator's discretion.
[h] At Visit 1 (Post-dose) and Visit 2 (Post-dose), an ECG may be performed for any complaints of chest discomfort, lightheadedness, and/or palpitations per the investigator's discretion and repeated as needed.
[i] An ECG will be performed at an ET or Unscheduled Visit if deemed necessary by the investigator.
[j] Urine drug screen will include tests for amphetamines, cocaine, tetrahydrocannabinol, methylenedioxymethamphetamine, and opiates.
[k] Clinical laboratory assessments performed at the Screening Visit will include CBC with differential (red blood cell, total and differential white blood cell, hemoglobin, hematocrit, and platelet count), Chem 7 panel (blood urea nitrogen, total carbon dioxide, creatinine, glucose, chloride, potassium, sodium), liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin), and TSH with reflex to T4.
[l] Clinical laboratory assessments may be performed at an ET or Unscheduled Visit per the investigator's discretion.
[m] A urine POC pregnancy test will be conducted for all women of childbearing potential at Visit 1 (Day 1 Pre-dose) and Visit 2 (Day 8 Pre-dose). Results from all tests must be negative to proceed with dosing.
[n] A urine POC pregnancy test may be performed on females of childbearing potential at an ET or Unscheduled Visit if pregnancy is suspected.
[o] Participants must have fasted from food and drink for 2 hours prior to study drug administration, and must have abstained from any other oral product that has the potential to interfere with SL atropine absorption (e.g., candy, chewing gum, mints, etc.) for 2 hours prior to study drug administration.
[p] Blood samples for PK analysis will be taken at time 0 (pre-dose) and at 13 time points post-dose at 5, 10, 15, 20, 30, 45, 60, and 90 minutes and 2, 2.5, 4, 6, and 8 hours.

APPENDIX 3. PREP ACT

The following language applies only to Clinical Research Sites located in the United States.

Public Readiness and Emergency Preparedness Act

The drug atropine and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the U.S. Department of Health and Human Services under that Act. Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer or dispense study drug) are immune from liability from the administration, or use of a covered countermeasure, such as atropine. The PREP Act provides immunity for covered persons from liability, unless the injury was caused by willful misconduct.

The PREP Act also established the Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries or death that occur as the direct result of the administration or use of certain countermeasures. Any requests for compensation must be filed within one year of the administration or use of the covered countermeasure. Requests for Benefits must be made to the Health Resources and Services Administration's Countermeasures Injury Compensation Program (http://www.hrsa.gov/cicp/) by filing a Request for Benefits Form and all required medical records and supporting documentation. Additional information on filing a Request for Benefits is available on the CICP's website at http://www.hrsa.gov/cicp/. Compensation may then be available for reasonable and necessary medical benefits, lost wages and/or death benefits to eligible individuals for certain injuries in accordance with regulations published by the Secretary of HHS (found at 42 CFR part 110).

If an individual suffers a serious physical injury or death from the administration or use of a covered countermeasure in this study, the individual, the individual's legal or personal representative, the administrator/executor of a deceased individual's estate, or certain survivors may request benefits from the CICP. A serious physical injury means an injury that warranted hospitalization (whether or not the person was actually hospitalized) or that led to a significant loss of function or disability. The CICP is the payer of last resort. This means that it only covers expenses or provides benefits that other third-party payers (such as health insurance, the Department of Veterans Affairs, or Workers' Compensation programs) do not have an obligation to pay.

If the Secretary of HHS does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct and meets the other requirements for suit under the PREP Act. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a US Federal or a State court.