ARS PHARMACEUTICALS INC.

INVESTIGATIONAL NEW DRUG PROTOCOL

ARS-1 (INTRANASAL EPINEPHRINE)

PROTOCOL NUMBER EPI A01

[redacted]

A PHASE 2, SINGLE-DOSE, RANDOMIZED, ACTIVE AND PLACEBO CONTROLLED, CROSS-OVER STUDY OF THE SAFETY AND EFFICACY OF INTRANASAL EPINEPHRINE AFTER ADMINISTRATION OF ARS-1 OR ALBUTEROL IN SUBJECTS WITH PERSISTENT ASTHMA

SPONSOR:

ARS Pharmaceuticals Inc.

[redacted]

CONFIDENTIAL

KEY CONTACTS FOR THE STUDY

SPONSOR'S REPRESENTATIVES:

Sponsor Contact

[redacted]

Study Director

[redacted]

Study Medical Monitor

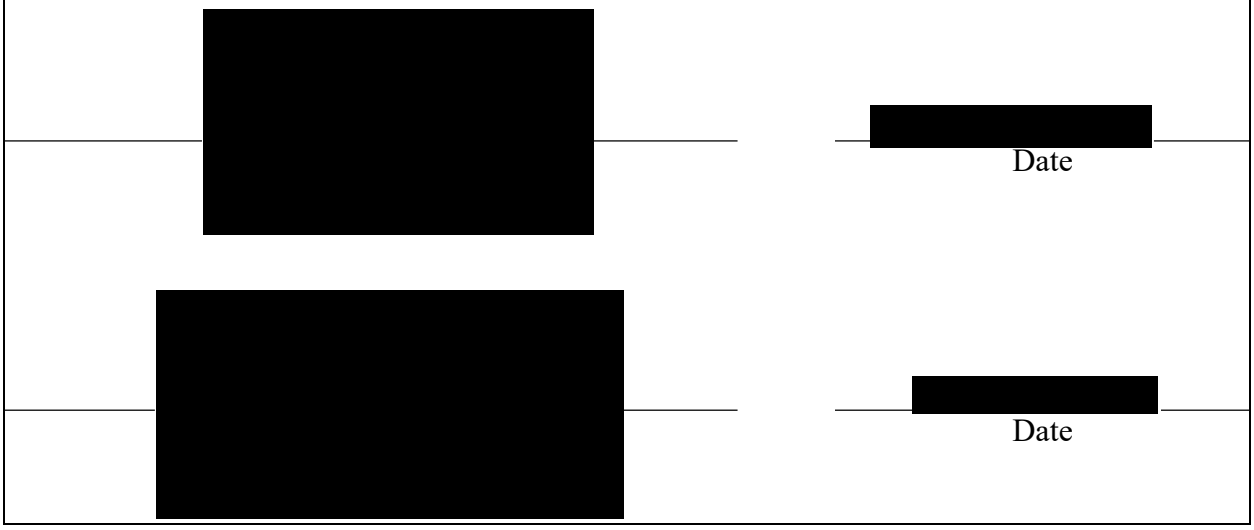
[redacted]

Serious Adverse Event Reporting

[redacted]

SPONSOR SIGNATURE PAGE

This protocol has been reviewed and approved by ARS Pharmaceuticals Inc. By my signature, I approve this document.



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADL	Assisted Daily Living
AE	adverse event
ALT	alanine aminotransferase
ARS	ARS Pharmaceuticals Inc.
ARS-1	epinephrine nasal spray suspension manufactured for ARS Pharmaceuticals Inc.
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{(0-t)}$	area under the plasma concentration-time curve to the final sample with a concentration ≥ LOQ
AUEC	area under the effect curves
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
BZK	benzalkonium chloride
CBC	complete blood cell count
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CO^2	carbon dioxide/bicarbonate
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events (v 5.0)
CV	coefficient of variation
DBP	diastolic blood pressure
DDM	dodecylmaltoside

ABBREVIATION	DEFINITION
ECG	electrocardiogram
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
E_{max}	maximum effect
FAS	Full Analysis Set
FDA	US Food and Drug Administration
$FEF_{25-75\%}$	Mid Forced Expiratory Flow Rates
FEV_1	forced expiratory volume in one second
FEV_3	forced expiratory volume in three seconds
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRAS	generally recognized as safe
HbSAg	Hepatitis B surface antigen
HIV	human immunodeficiency virus
HR	heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	inhaled corticosteroid
IFU	Instructions for Use
IM	intramuscular
IN	intranasal
IP	investigational (medicinal) product
IRB/EC	Institutional Review Board/Ethics Committee

ABBREVIATION	DEFINITION
ITT	Intent-to-Treat
kg	kilogram(s)
LABA	long acting β-agonists
LAMA	long-acting muscarinic antagonists
LDH	lactate dehydrogenase
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mcg	microgram
mg	milligram(s)
mITT	Modified Intent-to-Treat
mL	milliliter
PD	pharmacodynamics
PE	physical exam
PFT	pulmonary function testing
PK	pharmacokinetics
PR	pulse rate
QTcF	Fridericia's correction
RBC	red blood cell
SABA	short-acting β-agonists
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SOP	standard operating procedure
SVC	slow vital capacity
TEAE	treatment-emergent adverse event

ABBREVIATION	DEFINITION
T_{Emax}	time to maximum effect
t_{max}	time to maximum plasma concentration
µL	microliter
UDS	Unit Dose Sprayer
US/USA	United States of America
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary

INVESTIGATOR STATEMENT

I have read and understand the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines, all applicable government regulations, and the International Conference on Harmonisation Good Clinical Practice Guidelines E6 (ICH-GCP).

I will maintain accurate source documents from which data are transcribed onto case report forms and accurate drug accountability records that show the receipt and disposition of all study drugs.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study.

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form (ICF) prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/EC prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB-approved Informed Consent Form is obtained from each subject prior to initiation of any study procedures.

I will report (within 24 hours) any serious adverse event, regardless of relationship to study drug, or pregnancy that occurs during the course of the study, in accordance with the procedures described in Section 13.0 of the protocol. I will notify the Sponsor if I become aware that a partner of a study subject becomes pregnant while the subject was receiving this study drug.

I will submit all protocol inclusion/exclusion violations to the Medical Monitor for approval prior to enrollment of the subject in the study.

I will allow the Sponsor, ARS Pharmaceuticals Inc. (ARS) and its agents, as well as the United States (U.S.) Food and Drug Administration (FDA) and other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the Sponsor as soon as possible thereafter (no later than one week).

This protocol contains information that is proprietary to ARS. The information contained herein is provided for the purpose of conducting a clinical trial for ARS.

The contents of this protocol may be disclosed to study personnel under your supervision and to your IRB/EC. The contents of this protocol may not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without the prior written approval of ARS.

_____ _____

Investigator's Signature Date

PROTOCOL SYNOPSIS

<table>
<tr><td>Study Title</td><td>A Phase 2, Single-Dose, Randomized, Active and Placebo Controlled, Four-Period, Cross-Over Study of the Safety and Efficacy of Intranasal Epinephrine After Administration of ARS -1 or Albuterol in Subjects with Persistent Asthma (EPI A01)</td></tr>
<tr><td>Phase</td><td>Phase 2</td></tr>
<tr><td>Study Drug</td><td>ARS-1 (Intranasal [IN] Epinephrine)</td></tr>
<tr><td>Objectives</td><td>Intramuscular (IM) epinephrine injection is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis. Both IM and subcutaneous (SC) dosing of epinephrine is approved by the Food and Drug Administration (FDA) as efficacious in product labeling in the United States (US). IM epinephrine injections are used off-label for the treatment of bronchospasm refractory to albuterol and anticholinergic inhaler therapy but is frequently available to patients with asthma only in emergency room and urgent care settings. An epinephrine nasal spray (ARS-1) is being developed for patients as a needleless alternative route of epinephrine administration for the management of refractory asthma symptoms. Systemic exposure of epinephrine via nasal administration may also supplement inhaled or nebulized bronchodilators for the treatment of asthma symptoms.
The objectives and endpoints of this study are as below.
<table>
<tr><th>Objective</th><th>Endpoints</th></tr>
<tr><td colspan="2">Efficacy</td></tr>
<tr><td>To assess the effect of ARS-1 (1 milligram [mg] and 2 mg doses) versus Albuterol (180 microgram [mcg]) and placebo</td><td>[redacted]</td></tr>
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	• [redacted]
Safety	
To assess the safety and tolerability of ARS-1 in subjects with asthma after intranasal (IN) administration of epinephrine as compared to albuterol	• Adverse events (AEs) • Vital signs

Study Design

This is a Phase 2, single-dose, randomized, active and placebo controlled, crossover clinical study that will consist of a screening period and an open-label treatment period. Subjects with persistent asthma for >6 months with verification by medical records will be enrolled.

Each subject will be partially randomized to receive either a single treatment of ARS-1 nasal spray (1 mg or 2 mg dose), a single dose administration of albuterol (180 mcg) via inhaler, or placebo and then will be crossed over to receive other treatments.

Efficacy will be primarily assessed by pulmonary function testing (PFT) using MiniBox+ (pulmonary-function data calculator sold by PulmOne Advanced Medical Devices, Ltd.) at multiple timepoints after dosing study medications. A 7-day wash out between Treatment Periods will be used to ensure proper wash-out from medication effects.

Approximately 30 eligible male or female subjects 18 to 65 years of age with persistent asthma will be randomized to receive either ARS-1 (1 mg dose), ARS-1 (2 mg dose), albuterol (180 mcg single administration), or placebo in each Treatment Period according to the randomization sequences.

Screening/Run-in Period: Subjects who are diagnosed with persistent asthma will be screened to assess eligibility for the clinical trial. All subjects will undergo safety screening evaluations within 30 days prior to the first treatment. During the 14-day Run-in Period, which may take place while screening, subjects will undergo treatment washout from protocol-prohibited medications (see Table 8) while continuing their inhaled corticosteroid (ICS) maintenance asthma treatment, if applicable. [redacted]

Open-Label Treatment Periods: Subjects will return to the site for each Treatment Period. Each subject will be randomized per the sequences to receive one of the following treatments at each Treatment Period:

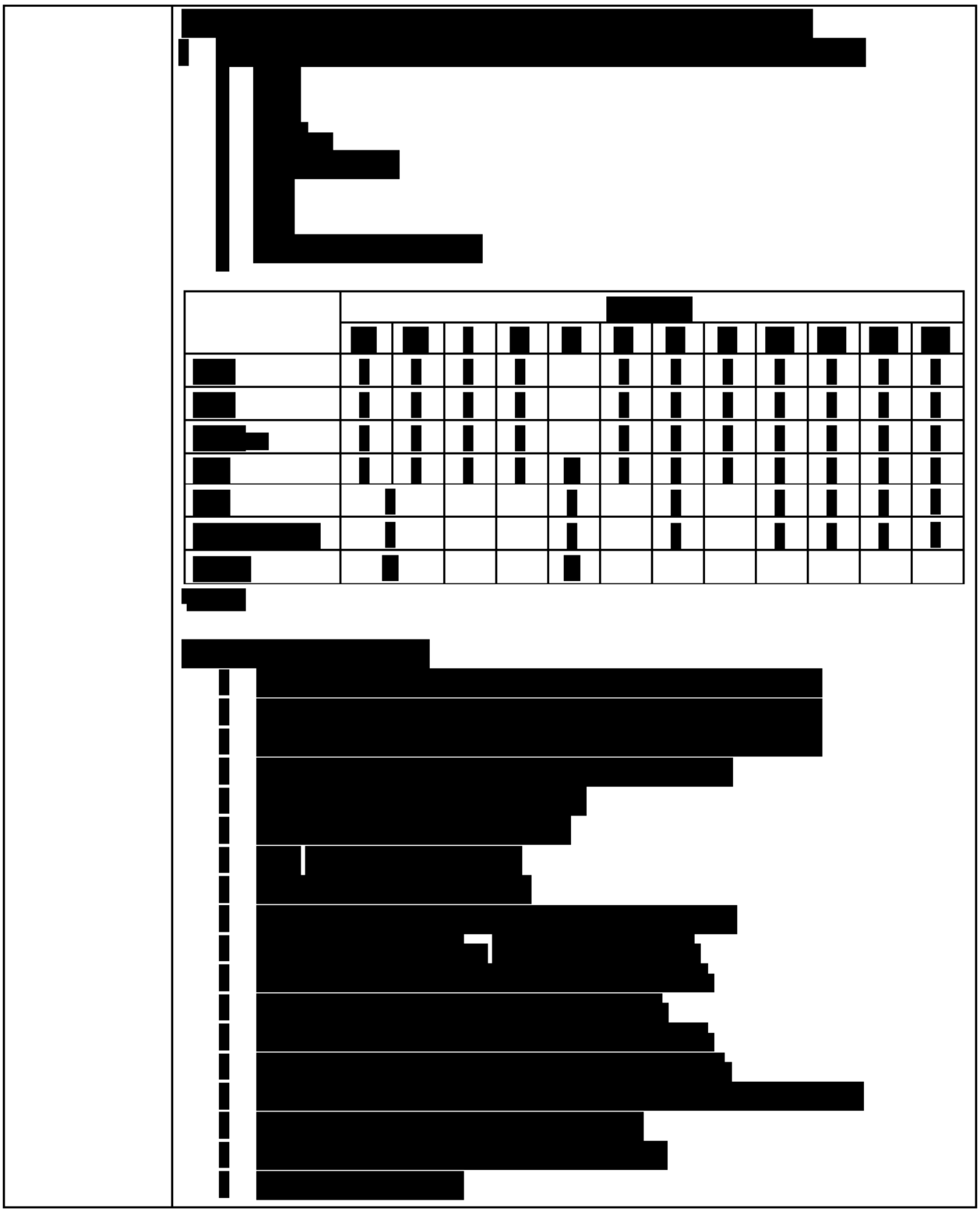
- 1 mg per 100 microliters (µL) dose of ARS-1,
- 2-mg per 100 µL dose of ARS-1,
- albuterol metered dose inhaler (MDI) (180 mcg), or
- placebo

[redacted]

	Subjects should remain in the clinic for at least 6 hours. Subjects will return to the site for subsequent Treatment Periods with a 7-day wash out period between each period. Follow-up phone calls will be done after 3 (+1) days from the last treatment to follow-up on AEs. If a subject receives rescue medications, that study period will be discontinued and the subject will be monitored for safety.
Sample Size	30 subjects (persistent asthma patients)
Study Population	Volunteers 18 to 65 years of age, diagnosed with persistent asthma
Main Inclusion Criteria	For a subject to be eligible for this study, he or she must meet **all** of the following criteria: 1. Is a male or female subject between the ages of 18 and 65 years, inclusive. 2. Asthma ($FEV_1 \geq 60\%$ predicted for age, height, and gender) that has been stable for at least four weeks prior to screening as defined by clinical history. 3. Reversible bronchoconstriction as verified by ≥15 % increase in FEV_1 within 30 minutes following inhalation of albuterol (180 mcg to 360 mcg). 4. Has body weight more than 30 kilogram (kg) and body mass index between 18 and 34 kg/m², inclusive. 5. Has no medical history of hypertension and cardiovascular disease in the last 10 years. Controlled hypertension without beta blocker confirmed by the Investigator is acceptable. 6. At screening, has stable vital signs in the following ranges (after 5 minutes of rest): • Systolic blood pressure (SBP) ≥90 and ≤140 mmHg • Diastolic blood pressure (DBP) ≥50 and ≤90 mmHg • Heart rate (HR) ≥45 and ≤100 beats per minute (bpm) *Note: Each blood pressure (BP) should be taken after at least 5 minutes rest in a chair with back supported, legs uncrossed, and upper arm bared (slight recline for comfort is permitted). If vital signs are out of range, the Investigator may obtain two additional readings, so that up to 3 consecutive assessments are made within 1 hour.* 7. If female of child-bearing potential, is not pregnant or breastfeeding based on the following: a. agree to the use of highly effective contraceptive methods for at least 2 weeks before baseline until 7 days after the last day of study drug and a negative urine pregnancy test at screening; or b. is of nonchildbearing potential defined as clinically infertile as the result of surgical sterilization (hysterectomy, bilateral tubal ligation, bilateral salpingectomy and/or bilateral oophorectomy); or c. is confirmed postmenopausal status (defined as either having amenorrhea for ≥ 12 consecutive months without another cause and documented serum follicle-stimulating hormone (FSH) level > 40 mIU/mL or another documented medical condition (e.g., was born without a uterus)). NOTE: The following are considered highly effective contraceptive methods: abstinence, hormonal oral contraceptives, injectables, and patches; intrauterine devices; double-barrier methods (synthetic condom, diaphragm, or cervical cap used with spermicidal foam, cream, or gel); Nexplanon contraceptive implant (if implanted within 3 years); and male partner sterilization. 8. If male (with or without vasectomy), agree to the use of highly effective contraceptive methods (as listed in Criterion #7 above) at screening until 7 days after the last day of study drug.

	9. Is able to communicate clearly with the Investigator and staff; able to read, complete questionnaires, and understand study procedures. 10. Is willing and able to provide written informed consent prior to participating in the study.
Main Exclusion Criteria	Subjects must **NOT** meet any of the following Exclusion criteria to be eligible for enrollment: 1. Has a history of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results. 2. Patients receiving the drugs listed in Table: Prohibited Medications (Table 8) should discontinue the medications from Run-in Period to the Treatment Period 4. 3. Patients receiving beta blocker due to potential interaction with the study drug. 4. Has prior nasal fractures, severe nasal injuries or history of nasal disorders (e.g., polyps, polyposis, recurrent epistasis [>1 nose bleed per month], clinically meaningful deviated septum, nasal piercing or any nasal passage abnormality based on the Investigator's judgement). 5. Has any clinically significant medical condition or physical exam (PE) finding as deemed inappropriate by the Investigator. 6. Has abnormal cardiovascular exam at screening including any prior history of myocardial infarction or clinically significant abnormal electrocardiogram (ECG) (e.g., second- or third-degree heart block, uncontrolled arrhythmia, QTcF [Fridericia's correction] interval >450 msec for male subjects and >470 msec for female subjects). 7. Has mucosal inflammatory disorders (e.g., pemphigus or Sjogren's syndrome or fungal sinusitis). 8. Has had significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening. 9. Has donated blood or had an acute loss of blood (>50 milliliter (mL)) during the 30 days before study drug administration or intends to donate blood or blood products within 30 days after the completion of the study. 10. Known hypersensitivity to any compound in the test product, or any other closely related compound (e.g., dihydropyridine-derived molecules). 11. Has participated in a clinical trial within 30 days prior to the first dose of study drug. Participation in an observational (non-interventional) study is not excluded as long as there are no scheduling conflicts with this study. 12. Has had treatment with any epinephrine or norepinephrine containing products within 7 days of Day -1. 13. At screening is positive for human immunodeficiency virus (HIV), Hepatitis B surface antigen (HbSAg), or Hepatitis C, or a positive urine screen for drugs of abuse or cotinine, or a positive saliva test for alcohol. 14. Has an immediate family member of the Investigator, or an employee of the study center, with direct involvement in the proposed study, or other studies under the direction of the Investigator or study center or is in a dependent relationship with a study center employee who is involved in the conduct of this study (e.g., spouse, parent, child, sibling), or may consent under duress.
Dosage and Administration of Study Drug	The ARS-1 dose of epinephrine by IN administration in this study is 1 mg and 2 mg per dose delivered in a volume of 100 µL aqueous solution. ARS-1 will be dosed using the Aptar Unit Dose Sprayer (UDS) that is the planned commercial product. The side (right or left) of the dosing will be alternated per randomization. Albuterol (180 mcg) will be administered from a commercially available MDI device.

	Placebo is saline to be administered by IN administration using the commercial sprayer device delivered in a volume of 100 µL aqueous solution. Placebo will be dosed using the Aptar UDS that is planned commercial device for ARS-1. [redacted].
Efficacy Assessments	[redacted]



Safety Analysis	AEs will be collected and reviewed to evaluate the safety and tolerability of ARS-1. AE collection will begin after dosing and continue for 5 hours after dosing. AEs may be either spontaneously reported or elicited during questioning and examination of a subject. AE information will be elicited at appropriate intervals by indirect questioning using a non-leading question. [redacted]
Statistical Analysis	[redacted]
Study Duration	It is planned that each subject will participate in the study for up to 54 days, which comprises a 30-day screening period and 24-day study period.
Study Centers	Up to Five (5) Centers

1.0 INTRODUCTION

1.1 Background

Asthma is a chronic heterogenous disease characterized by airway inflammation and narrowing of the bronchial tubes. Common respiratory symptoms include cough, wheeze, shortness of breath, rapid breathing, and chest tightness (1). There are two types of asthma, allergic, which is triggered by exposure to an allergen, and non-allergic, which is triggered by factors such as exercise, illness, stress, airborne irritants, extreme weather and certain medications (2). Severity is classified as intermittent, mild persistent, moderate persistent, or severe persistent (3). Asthma is one of the most common lung diseases in the United States (US), affecting an estimated 26 million Americans, including 20 million adults and 6 million children, which is approximately 1 in 12 people (2).

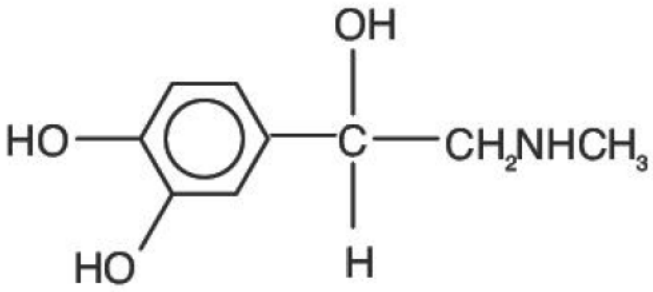
Patients often have periods of worsening symptoms and airway obstructions, known as exacerbations, attacks, or flare-ups, which can be fatal (4). Effective management of symptoms in patients with persistent asthma may be achieved with controller therapy, which intervenes in the inflammatory process to prevent the development of irreversible airway remodeling (3). However, as exacerbation triggers such as viruses, pollens, pollution, and poor adherence to controller therapies can be unpredictable, rescue medications are recommended in asthma management (3)(4)(5).

For asthma exacerbations, repeated administration of inhaled short-acting beta2-agonists (SABAs) is an effective and efficient way to achieve rapid reversal of airflow limitation (4). SABAs such as albuterol delivered by metered dose inhaler (MDI) are used as rescue medications for breakthrough symptoms and have been the first-line treatment for asthma for 50 years and provides immediate bronchodilation (3)(4).

Epinephrine has been used for the management of acute asthma for over 100 years (6)(7). Currently intramuscular (IM) epinephrine injections are used off-label for the treatment of bronchospasm refractory to albuterol and anticholinergic inhaler therapy but is frequently available to patients with asthma only in emergency room and urgent care settings (7)(8)(9)(10).

Epinephrine, illustrated in Figure 1 below, is a sympathomimetic catecholamine. Chemically, epinephrine is B-(3, 4dihydroxyphenyl)-a-methyl-aminoethanol. Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. It is a colorless to light yellow crystalline compound, insoluble in water. The formula is $C_9H_{13}NO_3$ and the molecular weight is 183.20442.

Figure 1: Epinephrine



ARS Pharmaceuticals, Inc. (ARS) is investigating ARS-1 for asthma patients as a needleless alternative route of epinephrine administration for the management of refractory asthma symptoms. Systemic exposure of epinephrine via nasal administration may also supplement inhaled or nebulized bronchodilators for the treatment of asthma symptoms outside hospital setting.

[redacted]

1.2 Clinical Experience with ARS-1 1.0 mg in Healthy Volunteers

ARS-1 1.0 milligram (mg) has been tested in in a series of PK studies to evaluate the bioavailability and bioequivalence of the IN formulation versus IM injections in both healthy volunteers and in volunteers with histories of seasonal allergies and rhinitis (Table 1).

Table 1: Summary of Individual Studies Included in the Integrated Pharmacokinetic Analysis

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

1.2.1

[redacted]

1.2.1.1

[redacted]

Figure 2: [redacted]

[redacted]

Table 2: [redacted]

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[redacted]				
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[redacted]

[redacted]

[redacted]

1.2.2.1 [redacted]

[redacted]

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Figure 3: [redacted]

Table 3: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

Figure 4: [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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Figure 5: [redacted]

Table 5: [redacted]

[redacted]			
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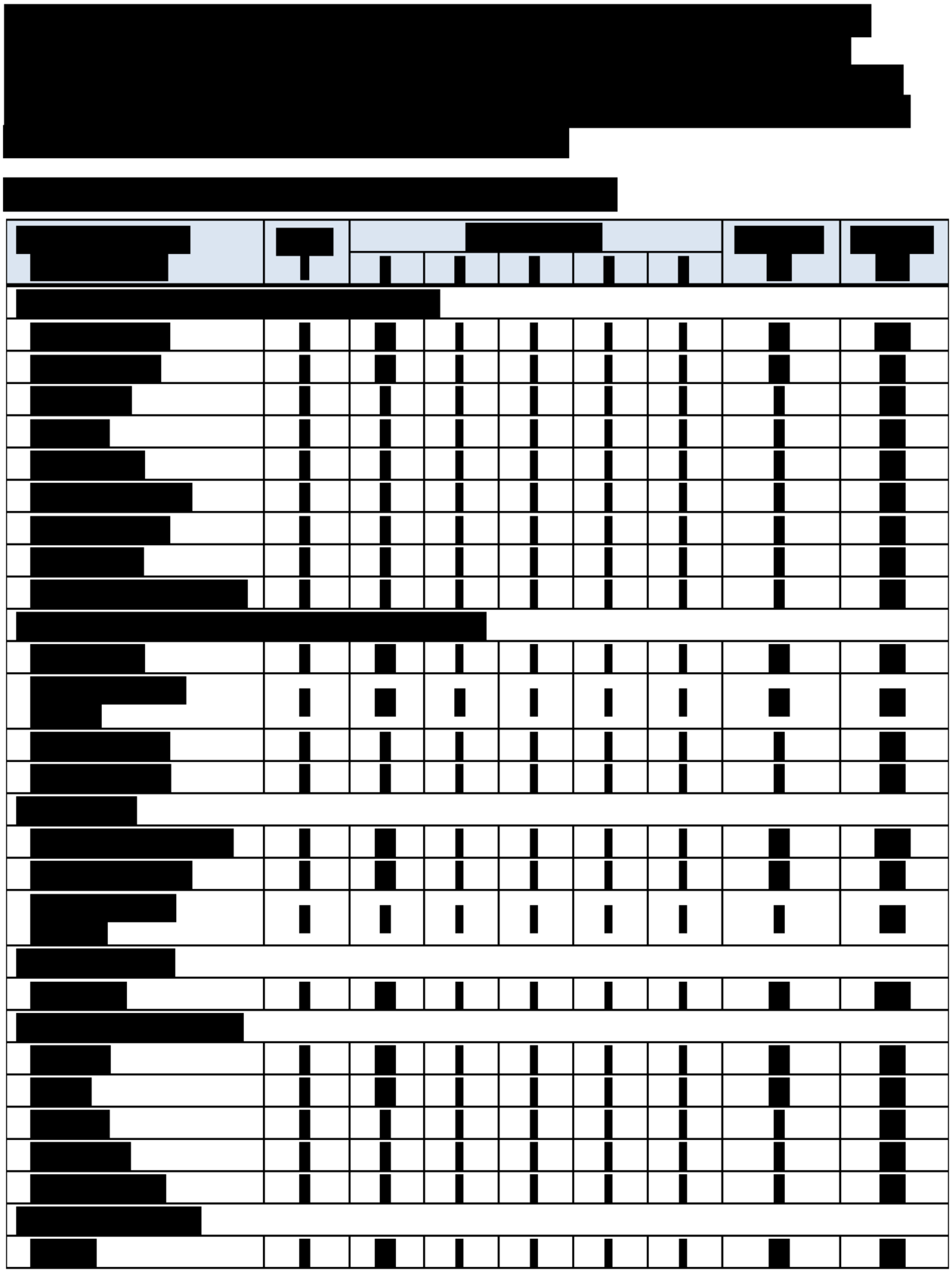
1.2.4 Safety

[redacted]

[redacted]



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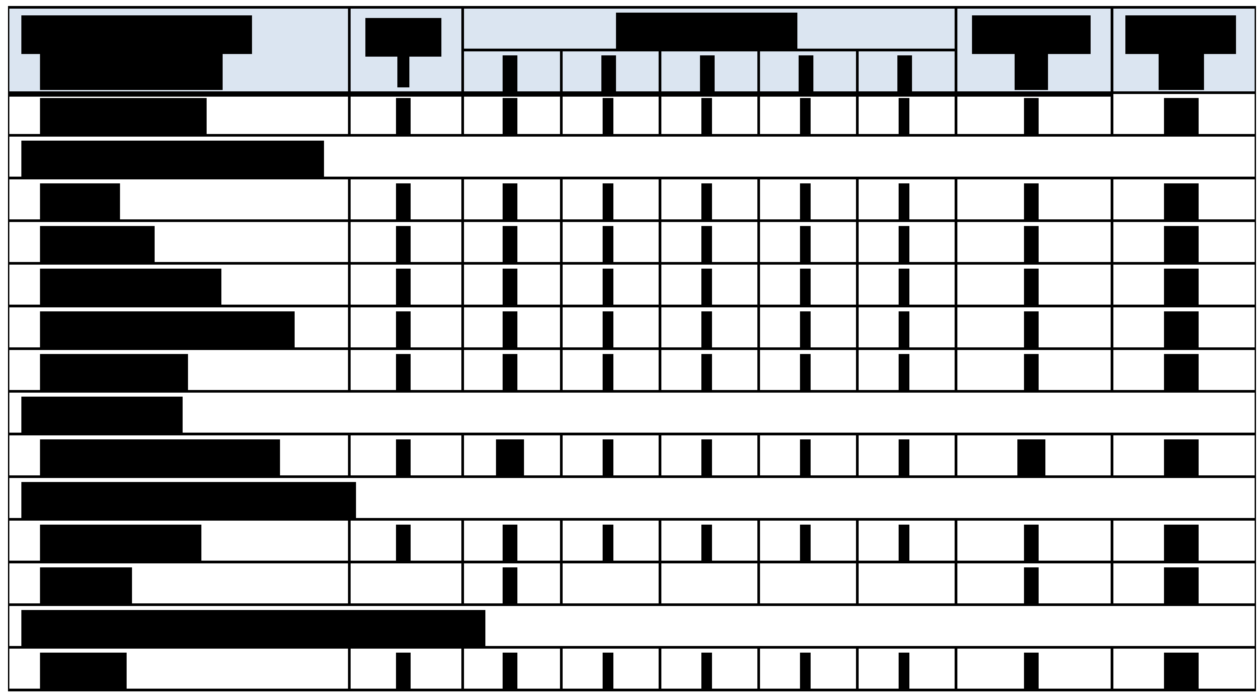

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1.2.4.2 [redacted]

[redacted]

1.3 Study Rationale

Both IM and SC dosing of epinephrine are approved by the FDA as efficacious in product labeling in the US.

An epinephrine nasal spray (ARS-1) is being developed for patients as a needleless alternative route of epinephrine administration for the management of refractory asthma symptoms.

In previous studies, a 10 mg/mL formulation of ARS-1 administered as a 0.1 mL spray (2 mg total epinephrine dose) gave pharmacokinetics that were similar to 0.3 to 0.5 mg injection products in the anterolateral thigh. The objective of this study is described in Section 2.0.

2.0 STUDY OBJECTIVES

2.1 Study Objectives

IM epinephrine injection is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis. Both IM and SC dosing of epinephrine is approved by the FDA as efficacious in product labeling in the US. IM epinephrine injections are used off-label for the treatment of bronchospasm refractory to albuterol and anticholinergic inhaler therapy but is frequently available to patients with asthma only in emergency room and urgent care settings. An epinephrine nasal spray is being developed for the management of refractory asthma symptoms. Systemic exposure of epinephrine via nasal administration may also supplement inhaled or nebulized bronchodilators for the treatment of asthma symptoms.

The objectives and endpoints of this study are as below.

Objective	Endpoints
Primary	
To assess the effect of ARS-1 (1 mg and 2 mg doses) versus Albuterol (180 microgram [mcg]) and placebo	[redacted]

	• [redacted]
Secondary	
To assess the safety and tolerability of ARS-1 in subjects with asthma after IN administration of epinephrine as compared to albuterol	• AEs • Vital signs

3.0 STUDY DESIGN

3.1 Description of Study Design

This is a Phase 2, single-dose, randomized, active and placebo controlled, crossover clinical study that will consist of a screening period and an open-label treatment period. Subjects with persistent asthma diagnosed for >6 months with verification by medical records will be enrolled.

Each subject will be partially randomized to receive either a single treatment of ARS-1 nasal spray (1 mg or 2 mg dose), a single dose administration of albuterol (180 mcg) via inhaler, or placebo and then will be crossed over to receive other treatments.

[redacted]

Approximately 30 eligible male or female subjects 18 to 65 years of age with persistent asthma will be randomized to receive either ARS-1 (1 mg dose), ARS-1 (2 mg dose), albuterol (180 mcg single administration), or placebo in each Treatment Period according to the randomization sequences.

Screening/Run-in Period: Subjects who are diagnosed with persistent asthma will be screened to assess eligibility for the clinical trial. All subjects will undergo safety screening evaluations within 30 days prior to the first treatment. During the 14-day Run-in Period, which may take place while screening, subjects will undergo treatment washout from protocol-prohibited medications (Table 8) while continuing their inhaled corticosteroid (ICS) maintenance asthma treatment, if applicable. [redacted]

Open-Label Treatment Periods: Subjects will return to the site for each Treatment Period. Each subject will be randomized per the sequences to receive one of the following treatments at each Treatment Period:

- 1 mg per 100 µL dose of ARS-1,
- 2 mg per 100 µL dose of ARS-1,
- albuterol MDI (180 mcg), or
- placebo

[redacted]

Subjects should remain in the clinic for at least 5 hours.

Subjects will return to the site for subsequent Treatment Periods with a 7-day wash out period between each period. Follow-up phone calls will be done after 3 (+1) days from the last treatment to follow-up on AEs.

If a subject receives rescue medications, that study period will be discontinued and the subject will be monitored for safety.

3.1.1 Randomization/Assignment to Study Drug

Thirty (30) subjects diagnosed with persistent asthma will be enrolled and randomized to receive one of the following treatments in each Treatment Period.

- 1 mg/100 µL dose of ARS-1,
- 2 mg/100 µL dose of ARS-1,
- albuterol MDI (180 mcg), or
- placebo

To ensure proper wash-out between the IN doses, each subject will be randomized to one of the following sequences:

- 1 mg ARS-1 IN : placebo : albuterol : 2 mg ARS-1 IN
- 2 mg ARS-1 IN : albuterol : placebo : 1 mg ARS-1 IN

The side (right or left) of dosing will be alternated per randomization.

Subjects will return to the site for subsequent Treatment Periods after a 7-day wash out period between each treatment.

3.2 Study Drugs

3.2.1 Test Product

ARS-1 is a solution formulation of epinephrine intended for nasal administration. [redacted] ARS-1 will be administered by IN administration using the commercial sprayer device at a dose of either 1 mg or 2 mg epinephrine per spray delivered in a volume of 100 µL aqueous solution. ARS-1 will be dosed using the Aptar Unit Dose Sprayer (UDS) that is the planned commercial product.

Albuterol (180 mcg) will be administered from a commercially available MDI device and will be sourced from a commercial supplier for this study.

Placebo is saline to be administered by IN administration using the commercial sprayer device delivered in a volume of 100 µL aqueous solution. Placebo will be dosed using the Aptar UDS that is planned commercial device ARS-1.

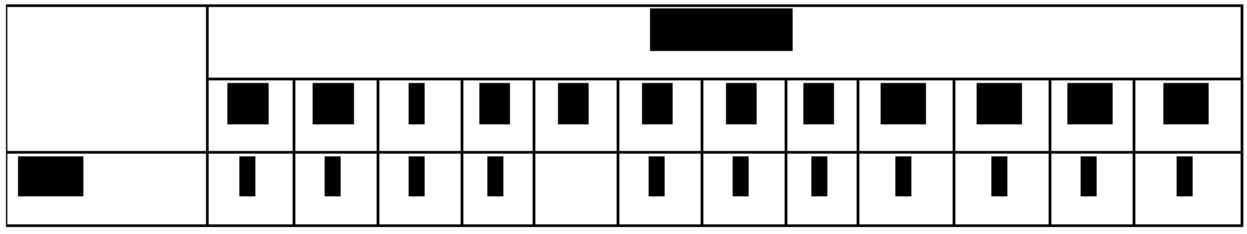
[redacted]

3.2.2 Dose and Dose Justification

[redacted]

3.3 Efficacy Assessment

[redacted]



[redacted]

[redacted]

[redacted]

3.4 Safety Assessments

Safety assessments include AEs and vital signs.

3.5 Concomitant Medications

3.5.1 Prior and Concomitant Medications

Prior medications are defined as medications that were taken within 30 days prior to initial dosing with study drug.

Concomitant medications are defined as medications taken any time after the start of dosing until discharge assessments.

3.5.2 Prohibited Concomitant Medications

No concomitant medications are permitted during the course of this study (except hormonal contraceptives).

3.6 Prohibited Medications

Subjects will undergo treatment washout from protocol-prohibited medications while continuing their ICS maintenance asthma treatment, if applicable. The following medications, but not limited to, will be prohibited before the reversibility test at screening and through the 14-day Run-in Period to the Treatment Period 4.

Table 8: [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]

3.7 Procedures for Monitoring Subject Compliance

Subjects will be in the clinical trial site from the day of each Treatment Period and will remain in the unit for at least 5 hours to complete efficacy assessments and safety assessments. Each Treatment Period will be separated a minimum 7-day wash out period.

4.0 STUDY POPULATION

The study population will be male or female volunteers age 18 to 65 years diagnosed with persistent asthma who have consented to participate in this study.

4.1 Inclusion Criteria

For a subject to be eligible for this study, he or she must meet **all** of the following criteria:

1. Is a male or female subject between the ages of 18 and 65 years, inclusive.

2. Asthma (FEV_1 ≥60% predicted for age, height, and gender) that has been stable for at least four weeks prior to screening as defined by clinical history.

3. Reversible bronchoconstriction as verified by ≥15% increase in FEV_1 within 30 minutes following inhalation of albuterol (180 mcg to 360 mcg).

4. Has body weight more than 30 kg and body mass index between 18 and 34 kg/m^2, inclusive.

5. Has no medical history of hypertension and cardiovascular disease in the last 10 years. Controlled hypertension without beta blocker confirmed by the Investigator is acceptable.

6. At screening, has stable vital signs in the following ranges (after 5 minutes of rest):

   - Systolic blood pressure (SBP) ≥90 and ≤140 mmHg
   - Diastolic blood pressure (DBP) ≥50 and ≤90 mmHg
   - Heart rate (HR) ≥45 and ≤100 bpm

   Note: Each BP should be taken after at least 5 minutes rest in a chair with back supported, legs uncrossed, and upper arm bared (slight recline for comfort is permitted). If vital signs are out of range, the Investigator may obtain two additional readings, so that up to 3 consecutive assessments are made within 1 hour.

7. If female of child-bearing potential, is not pregnant or breastfeeding based on the following:

   a. agree to the use of highly effective contraceptive methods for at least 2 weeks before baseline until 7 days after the last day of study drug and a negative urine pregnancy test at screening; or
   b. is of nonchildbearing potential defined as clinically infertile as the result of surgical sterilization (hysterectomy, bilateral tubal ligation, bilateral salpingectomy and/or bilateral oophorectomy); or
   c. is confirmed postmenopausal status (defined as either having amenorrhea for ≥ 12 consecutive months without another cause and documented serum follicle-stimulating

hormone (FSH) level > 40 mIU/mL or another documented medical condition (e.g., was born without a uterus)).

NOTE: The following are considered highly effective contraceptive methods: abstinence, hormonal oral contraceptives, injectables, and patches; intrauterine devices; double-barrier methods (synthetic condom, diaphragm, or cervical cap used with spermicidal foam, cream, or gel); Nexplanon contraceptive implant (if implanted within 3 years); and male partner sterilization.

8. If male (with or without vasectomy), agree to the use of highly effective contraceptive methods (as listed in Criterion #7 above) at screening until 7 days after the last day of study drug.

9. Is able to communicate clearly with the Investigator and staff; able to read, complete questionnaires, and understand study procedures.

10. Is willing and able to provide written informed consent prior to participating in the study.

4.2 Exclusion Criteria

Subjects must **NOT** meet any of the following Exclusion criteria to be eligible for enrollment:

1. Has a history of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results.

2. Patients receiving the drugs listed in the Table: Prohibited Medications (Table 8) should discontinue the medications from the Run-in Period to the Treatment Period 4.

3. Patients receiving beta blocker due to potential interaction with the study drug.

4. Has prior nasal fractures, severe nasal injuries or history of nasal disorders (e.g., polyps, polyposis, recurrent epistasis [>1 nose bleed per month], clinically meaningful deviated septum, nasal piercing or any nasal passage abnormality based on the Investigator's judgement).

5. Has any clinically significant medical condition or physical exam (PE) finding as deemed inappropriate by the Investigator.

6. Has abnormal cardiovascular exam at screening including any prior history of myocardial infarction or clinically significant abnormal ECG (e.g., second- or third-degree heart block, uncontrolled arrhythmia, QTcF [Fridericia's correction] interval >450 msec for male subjects and >470 msec for female subjects).

7. Has mucosal inflammatory disorders (e.g., pemphigus or Sjogren's syndrome or fungal sinusitis).

8. Has had significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening.

9. Has donated blood or had an acute loss of blood (>50 mL) during the 30 days before study drug administration or intends to donate blood or blood products within 30 days after the completion of the study.

10. Known hypersensitivity to any compound in the test product, or any other closely related compound (e.g., dihydropyridine-derived molecules).

11. Has participated in a clinical trial within 30 days prior to the first dose of study drug. Participation in an observational (non-interventional) study is not excluded as long as there are no scheduling conflicts with this study.

12. Has had treatment with any epinephrine or norepinephrine containing products within 7 days of Day -1.

13. At screening is positive for human immunodeficiency virus (HIV), Hepatitis B surface antigen (HbSAg), or Hepatitis C, or a positive urine screen for drugs of abuse or cotinine or a positive saliva test for alcohol.

14. Has an immediate family member of the Investigator, or an employee of the study center, with direct involvement in the proposed study, or other studies under the direction of the Investigator or study center or is in a dependent relationship with a study center employee who is involved in the conduct of this study (e.g., spouse, parent, child, sibling), or may consent under duress.

4.3 Stopping or Suspending the Study

If the trial is prematurely terminated or suspended for any reason, the Investigator/Institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies).

In addition, if the Investigator or the Sponsor terminates or suspends a trial,

- the Investigator should inform the institution where applicable, and the Investigator/Institution should promptly inform the Institutional Review Board/Ethics Committee (IRB/IEC) (and the Sponsor, if applicable) and should provide the Sponsor and/or the IRB/IEC a detailed written explanation of the termination or suspension.

- the Sponsor should promptly inform the Investigators/Institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension.

5.0 SCREENING/RUN-IN ASSESSMENTS

5.1 Complete or Targeted Physical Examination

The Investigator will perform a complete PE at screening. Targeted PEs will be performed at pre-dose each Treatment Period. Results will be recorded on the appropriate page of the electronic case report form (eCRF).

5.2 Medical History

A medical history will be obtained at screening and confirmed at Day 0 pre-dose. Medical history will include demographic data (age, sex, race/ethnicity, etc.).

5.3 Vital Signs

Vital signs (BP, pulse rate [PR], respiratory rate, and temperature) are to be obtained at screening and pre-dose and post-dose each Treatment Period.

5.4 Height and Weight

Height will be reported in centimeters at screening. Body weight will be reported in kilograms at screening.

5.5 ECG

Subjects will be in a sitting or slightly reclined position and kept comfortable for a standard (after resting for at least 5 minutes) 12-lead ECG that will be performed in triplicate by a trained technician at screening.

All ECGs are obtained in triplicate. ECG assessments will be conducted by taking a 10 second reading in triplicate, each 1 to 2 minutes apart for screening and baseline and within the window before and after dosing. Subjects will be in a sitting or slightly reclined position and kept comfortable.

ECGs will be assessed by the Investigator, Sub-Investigator or a cardiologist. The ECG report must be reviewed, signed, and dated by the Investigator or cardiologist. The original ECG results will be kept on file at the site as source documentation.

5.6 Clinical Laboratory Evaluations

Blood samples and urine specimens for laboratory evaluation will be collected at screening per Schedule of Study Procedures (Appendix A).

Urine samples will be collected at screening for amphetamines, barbiturates, benzodiazepine metabolites, cocaine metabolites, methadone, opiate metabolites, phencyclidine, marijuana metabolites, and cotinine. For alcohol, saliva test will be utilized.

The presence of HIV antibody, HbSAg, and Hepatitis C antibody will be assessed at screening.

5.6.1 Hematology

Complete blood cell count (CBC) will include a standard red blood cell (RBC), hemoglobin, hematocrit, white blood cell (WBC) with differential, and platelet count.

5.6.2 Serum Chemistry

Comprehensive metabolic panel will include serum alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, calcium, phosphorus, chloride, sodium, potassium, blood urea nitrogen (BUN), creatinine, total bilirubin, albumin, total protein, amylase, bicarbonate/carbon dioxide (CO_2), uric acid, and lactate dehydrogenase (LDH).

5.6.3 Coagulation

Coagulation will include PT and aPTT.

5.6.4 Urinalysis

Urinalysis will include pH, specific gravity, glucose, protein, ketones, blood and a detailed microscopic analysis. Microscopic analysis will be performed and will include the following: WBC, RBC and bacteria.

5.6.5 Pregnancy Tests

A urine pregnancy test will be administered to females of childbearing potential at screening.

5.6.6 [redacted]

[redacted]

[redacted]

6.0 EFFICACY

6.1 [redacted]

[redacted]

- [redacted]

6.2 Patient Satisfaction Score

A horizontal line of 100-mm long will be used before discharge at each Treatment Period to assess the patient satisfaction score.

Patients will be queried with the following question, “Are you satisfied with the treatment?” to rate their satisfaction. At each end of the horizontal line, there are descriptors representing extremes of satisfaction (i.e., no satisfaction and extreme satisfaction). The patients will rate their satisfaction by making a vertical mark on the 100-mm line. The measurement in millimeters will be converted to the same number of points ranging from 0 to 100 points.

7.0 PHARMACOKINETICS

No PK measures will be assessed during this study.

8.0 PHARMACODYNAMICS

No PD measures will be assessed during this study.

9.0 SAFETY ASSESSMENTS

9.1 Collection of Adverse Events Data

Data regarding TEAEs will be collected in this study. TEAEs are events that are not present at baseline, or if present at baseline, have worsened in severity. AEs will be assessed while the subjects are in the study. AEs assessed by the Investigator as related to study drug and “ongoing” at discharge will be monitored by the Investigator until resolved or until the subject is deemed “lost to follow-up”.

Epinephrine is expected to increase the BP and HR transiently as part of the efficacy. BP increased and HR increased will not be considered as an AE unless such event requires treatment. A symptom reported by subjects and considered as an AE will be reported as an AE.

Any AEs reported by the subject or noted by the Investigator or his/her designee will be recorded on the eCRF regardless of the Investigator opinion of causality. The following information will be recorded for each AE: description of the event, date and time of onset, date and time of resolution, severity, causal relationship to study drug, outcome, action taken with the study drug and any treatment given.

All abnormal changes from baseline will be collected, graded with regards to severity or clinical significance, assessed for causal relationship and recorded on the eCRF.

Refer Section 13.0 for further detail.

9.2 Complete or Targeted Physical Examination

The Investigator will perform a complete PE at screening. Targeted PEs will be performed pre-dose in each Treatment Period. Results will be recorded on the appropriate page of the eCRF.

9.3 Vital Signs

[redacted]

The Investigator will assess vital signs on an ongoing basis and make sure the BP is within normal limit before study drug dosing.

10.0 STUDY VISITS AND PROCEDURES

Refer to Appendix A for the Schedule of Study Procedures.

10.1 Screening/Run-In (Days -30 to -1)

The Investigator or his/her approved designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign the Informed Consent Form (ICF). Written informed consent must be provided by the potential study participant prior to initiation of any screening evaluations or other study-related procedures. The signature date and the name of the individual at the site who obtained the informed consent will be recorded in the subject's medical record.

After written informed consent is obtained, the subject will be assigned a screening number and will undergo the designated screening procedures listed in Appendix A. The Investigator, Sub-Investigator or delegate will assess the results of these screening evaluations to determine eligibility for entry into the study according to the inclusion/exclusion criteria listed in Section 4.0.

All subjects will undergo safety screening evaluations within 30 days prior to the first treatment. During the 14-day Run-in Period, which may take place while screening, subjects will undergo treatment washout from protocol-prohibited medications (Table 8) while continuing their ICS maintenance asthma treatment, if applicable. [redacted]

Screening evaluations may be performed up to 30 days in advance of dosing but must be completed at least one (1) day prior to Day 0.

The following study evaluations and procedures are required to determine eligibility:

- Obtain and record a medical history, including demographics, prior medications, and concomitant medications.
- Complete PE
- Vital signs
- Height and weight measurements
- Blood and serum samples for the following laboratory evaluations:
    - Hematology
    - Serum chemistry
    - Coagulation
    - HIV antibody
    - Hepatitis screening
- Urinalysis, urine drug, alcohol and cotinine screen (Saliva test for alcohol may be utilized)
- Urine pregnancy test
- AEs
- 12-lead ECG (performed in triplicate)
- Albuterol reversibility test
- FEV_1
- Discontinue protocol-prohibited medications (Run-in Period)

10.2 Pre-dose Evaluations (Days 0, 7, 14, and 21)

Pre-dose assessments on Days 0, 7, 14, and 21 include the following:

- Admission to clinical site
- Confirm eligibility (Day 0 only)
- Targeted PE
- Vital signs
- Concomitant medication
- AEs

- Discontinue protocol-prohibited medications
- [redacted]

10.3 Drug Administration

Each subject will randomly receive each of the following treatments:

- a single dose of ARS-1 (1 mg),
- a single dose of ARS-1 (2 mg),
- albuterol MDI (180 mcg),
- placebo.

ARS-1 and placebo will be dosed according to the IFU (Appendix B). The side (right or left) of the dosing will be alternated per randomization.

Albuterol will be administered per its IFU.

The calendar date and 24-hour clock time of all doses will be recorded on the eCRF.

10.4 Post-dose Evaluations (Days 0, 7, 14, and 21)

Post-dose assessments on Days 0, 7, 14, and 21 include the following:

- Vital signs
- Concomitant medication
- AEs
- Discontinue protocol-prohibited medications
- [redacted]
- Patient satisfaction score

If a subject receives rescue medications, that study period will be discontinued and the subject will be monitored for safety.

10.5 Discharge Assessment (Days 0, 7, 14, and 21) and Follow-up Call (Day 24)

Within two (2) hours of collection of the efficacy assessments at 300 minutes in each Treatment Period, all subjects will undergo vital sign measurements for the discharge assessment. In addition, AEs and concomitant medication will also be recorded.

A follow-up phone call will be conducted 3 (+1) days (Day 24) from the last treatment period to follow-up on AEs.

11.0 PREMATURE DISCONTINUATION FROM STUDY

A premature discontinuation from study will occur when a subject who signed informed consent ceases participation in this study, regardless of circumstances, prior to completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- Failure to meet inclusion/exclusion criteria before receiving first dose of study drug has been administered
- Death
- Significant safety event that in the opinion of the Investigator warrants discontinuation
- Lost to follow-up after every attempt has been made to contact the subject, including sending a registered letter
- Subject withdraws consent

The Principal Investigator and the Institutional Review Board/Ethics Committee (IRB/EC) reserve the right to prematurely terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to prematurely terminate the study at any time for administrative reasons.

12.0 PRODUCT SPECIFICATIONS

12.1 Description

[redacted]

The drug product will be manufactured as the final commercial product in an Aptar UDS.

12.2 Formulation, Packaging, and Labeling

ARS-1 will be prepared by Renaissance, the commercial supplier for ARS-1, for this study as 10 mg/mL and 20 mg/mL formulations. ARS-1 will be filled into a commercially available Aptar UDS that will deliver an exact volume of 100 µL of ARS-1 solution. The sprayer does not require priming and can be used in any orientation.

12.3 Receipt, Storage and Stability of ARS-1

ARS-1 filled into Aptar UDS devices may be held at room temperature (15-25 °C) in a secure location until dosing.

12.4 Administration of Study Drug

Refer Section 10.3.

12.5 Ordering and Distribution of Study Drug

ARS-1 and placebo will be manufactured by Renaissance Pharmaceuticals for this study under full Good Manufacturing Practice (GMP) conditions.

Albuterol will be sourced from a US commercial supplier for this study.

12.6 Accountability of Study Drugs

All study drugs received, dispensed, and returned must be accounted for in the study drug Dispensing Log, including:

- Subject number and initials
- Date study drug was dispensed
- Quantity dispensed
- Quantity returned
- Quantity wasted, as applicable

All study drug received and dispensed by the Investigator will be inventoried and accounted for throughout the study. The study drug must be stored in a restricted area with limited access. Contents of the study drug containers must not be combined. Used sprayers will be accounted for and disposed appropriately.

The Investigator must maintain an accurate, up to date Dispensing Log for all study drugs supplied by the Sponsor. Study drug dispensed for all subjects must be recorded on the Drug Accountability Form. The study drug Dispensing Log and remaining drug inventory will be reviewed at each monitoring visit by the Sponsor-designated clinical monitor.

The study drug supplied for this study is for use only in subjects properly consented and enrolled into this protocol. Study drugs must be kept in a secure location physically separated from standard clinic or office drug supplies.

13.0 SAFETY MONITORING AND ADVERSE EVENTS

13.1 Adverse Events

Data regarding TEAEs will be collected in this study. TEAEs are events that are not present at baseline, or if present at baseline, have worsened in severity.

Definition of Adverse Events and Adverse Drug Reactions:

AEs in the eCRF will be classified according to the most recent FDA definitions and in a manner consistent with International Conference on Harmonization (ICH) guidelines. As such the following definitions will be used:

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product (IP) or other protocol-imposed intervention, regardless of attribution. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (e.g., worsening of asthma). A laboratory abnormality will be reported on the “Adverse Event” case report forms only if it is associated with clinical sequelae or requires therapeutic intervention.

Epinephrine is expected to increase the BP and HR transiently as part of the efficacy. BP increased and HR increased will not be considered as an AE unless such event requires treatment. A symptom reported by subjects and considered as an AE will be reported as an AE.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 (Appendix C).

AEs will be taken during Run-in Period, at pre-dose (as baseline) and for 5 hours post dose on each treatment day. Subjects will have a follow up phone call 3 (+1) days after the last treatment period to follow-up on AEs.

If an AE remains unresolved at discharge, the subject will be followed, at the Investigator's discretion, until resolution of the event or until the subject is deemed "lost to follow-up". AEs assessed by the Investigator as related to study drug and "ongoing" at discharge will be monitored by the Investigator until resolved or until the subject is deemed "lost to follow-up". SAEs must be followed until resolution by the PI, even if this extends beyond the study-reporting period. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

The Investigator will assess AEs for severity, relationship to IP, and as to whether the event meets one or more of the definitions of an SAE. The assessments will be recorded on the source documents and AE case report form (CRF), using the categories defined below.

Causality Category	Description
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. For the purpose of this protocol, the term unlikely will be considered not related to study medication and an "Adverse Event".
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. For the purpose of this protocol, an event that has possible relationship to study medication will be defined as a "Suspected Adverse Drug Reaction".
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. For the purpose of this protocol, an event that has probable relationship to study medication will be defined as an "Adverse Drug Reaction".

In order to classify adverse events and diseases, preferred terms will be assigned by the Sponsor or its designee to the original terms entered on the CRF, using MedDRA.

For those AEs that are not described on the CTCAE v 5.0 (Appendix C), such AEs will be graded on a 5-point scale (mild, moderate, severe, life-threatening, death) and reported as indicated on the CRF. Intensity of such an AE is defined as follows:

Table 9: Severity Assessment Terminology for Reporting Adverse Events (CTCAE v 5.0)

Grade	Common Term	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Assisted Daily Living (ADL).
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care

Grade	Common Term	Description
		ADL.
4	Life-Threatening	Life-threatening consequences; urgent intervention indicated.
5	Death	Death related to AE

13.2 Serious Adverse Events

According to the ICH Guidelines for Good Clinical Practice (E6), an SAE is any untoward medical occurrence during the course of a clinical investigation that is characterized by one or more of the following:

- Results in death
- Is life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events

Hospitalization admissions scheduled prior to the study are not considered SAEs unless the hospitalization is prolonged due to an AE. However, such hospitalization should be documented in the Investigator's comment in the eCRF. Hospitalizations for scheduled treatment of a preexisting condition that has not worsened or hospitalization for fewer than 24 hours does not meet the category of "New or prolonged hospitalization".

13.3 Pregnancy Reporting

Although not an SAE, exposure to study drug during pregnancy, even if no AE is reported in the mother, should be reported within 24 hours.

13.3.1 Reporting Requirements for Serious Adverse Events

All SAEs must be reported to the Sponsor by the Investigator, study coordinator, other designated study personnel, or clinical research associate within 24 hours of notification of the SAE. To report such events, an SAE form must be completed by the Investigator and sent within 24 hours by email or fax with relevant information.

Within the 48 hours following the initial report, the Investigator must provide further information on the SAE if available. This should include a copy of the completed SAE form, and any other

information that will assist the understanding of the event. Significant new information on ongoing SAEs should be provided promptly as a follow-up.

The Investigator also must report all SAEs promptly to the appropriate IRB/EC as required by the institution within 24 hours or 48 hours if on weekend/holiday.

[redacted]

13.3.2 Recording of Serious Adverse Events

All SAE information must be recorded on the SAE form provided by the Sponsor. Additional follow-up information (e.g., test results, autopsy, and discharge summary) must be obtained to supplement the SAE report form. A copy of all initial and follow-up reports must be filed with the subject's eCRF.

14.0 STATISTICAL CONSIDERATIONS

14.1 Sample Size Determination

The sample size is based on practical consideration. It is assumed that approximately 30 patients to crossover will be adequate to detect signals of clinical efficacy of ARS-1.

14.2 Analysis Data Sets

Data Analysis Set	Definition	Analysis
Intent-To-Treat (ITT) analysis set	Subjects who are randomized and received at least one treatment. Subjects will be analyzed per randomization scheme.	Demographics Primary efficacy

Modified ITT (mITT) analysis set	A subset of the ITT analysis set that includes subjects who received treatment and have post-treatment efficacy data from at least two treatments.	Efficacy
Safety analysis set	Subjects who are randomized and received at least one treatment. Subjects will be analyzed based on the treatment received at each treatment period.	Safety

14.3 Efficacy Data Analyses

14.3.1 Primary Efficacy Analyses

[redacted]

Superiority comparison of ARS-1 1 mg vs. placebo, ARS-1 1 mg vs. albuterol MDI 180 mcg, ARS-1 2 mg vs. placebo, ARS-1 2 mg vs. albuterol MDI 180 mcg, and albuterol MDI 180 mcg vs. placebo will be tested at the 2 sided 0.05 significance level. If both ARS-1 1 and 2 mg are statistically superior to placebo or albuterol MDI 180 mcg, comparison between the ARS-1 doses will be conducted.

There will be no adjustments for multiplicity; hence all analyses will be viewed as exploratory and hypothesis generating, rather than confirmatory.

14.3.2 Secondary Efficacy Analyses

Secondary analysis will be conducted using the similar method as that of the primary analyses.

The peak FEV_1 will be the largest FEV_1 value measured up to 300 minutes.

14.3.3 Other Efficacy Analyses

Baseline-adjusted FEV_1 and peak change in baseline-adjusted FEV_1 will be compared at each timepoint.

Time to peak Baseline-adjusted FEV_1 is the time to reach the largest FEV_1 during the 5 hours.

≥15% increase in FEV_1 is the 15% increase from the baseline FEV_1.

14.4 Safety Data Analysis

Safety variables to be monitored include AEs and vital signs.

AE assessment will be taken during Run-in Period, at pre-dose (as baseline) and for the 5-hour evaluation period after dosing. AEs will also be solicited at the follow up telephone call. AEs occurring during Run-in Period and at baseline will be summarized separately without dose assignment.

Safety data will be summarized using descriptive statistics.

The incidence and severity of AEs reported during the study and their relationship to study drug will be tabulated. AEs will be coded using MedDRA™ and will be presented by body system. The incidence of laboratory abnormalities as determined by CTCAE v 5.0 will be summarized for each dose cohort and time point.

The World Health Organization Drug Dictionary (WHODD) will be used to classify prior and concomitant medications by therapeutic class and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class by dose cohort.

15.0 DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

15.1 Data Collection and Reporting

An eCRF will be completed for each subject who receives at least one dose of study drug. All entries on the eCRF must be supported by original source documentation (e.g., laboratory reports, medical records) maintained at the investigational site.

The Investigator will make all safety assessments (AEs and vital signs) on an ongoing basis. The Investigator is required to review all entries on the eCRF and sign at appropriate time intervals.

15.2 Study Monitoring

All aspects of the study will be monitored carefully by the Sponsor's designees with respect to current Good Clinical Practice (GCP) and Standard Operating Procedures (SOP) for compliance with applicable government regulations. It is the responsibility of the Investigator to provide all study records, including eCRFs, source documents, etc., for review and source document verification by the clinical monitor.

All eCRFs will be 100% source verified against corresponding source documentation (e.g., office and clinical laboratory records) for each subject. Clinical monitors will evaluate

periodically the progress of the study, including the verification of appropriate consent form procedures, review of drug accountability and preparation procedures, adherence to dosing procedures, and the verification of the accuracy and completeness of eCRFs. Clinical monitors will also ensure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

15.3 Audit and Inspection

The Sponsor or representative may conduct audits at the trial site(s). Audits will include, but are not limited to, protocol compliance, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The Investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may inspect the trial site during or after the trial. The Investigator should contact the Sponsor immediately if this occurs and must fully cooperate with the inspections conducted at a reasonable time in a reasonable manner.

15.4 Deviation from Clinical Trial Protocol

Deviations from the protocol are to be avoided. If a deviation occurs, the Investigator must promptly report the deviation to the study monitor.

The Investigator (or designee) will record any failure to follow the protocol because of any other medical unavoidable reason to avoid the subject's urgent risk and record a document as soon as possible stating this and the reason. It must be submitted to the Sponsor and the director of the study site.

15.5 Retention of Records

The Investigator must retain all study records required by ARS and by the applicable regulations in a secure and safe facility. The Investigator must notify ARS of any change in the location, disposition or custody of the study files. The Investigator/Institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained until whichever is the later day in the following: (1) At least the date of approval for the drug or (2) the date when three (3) years have passed since the discontinuation or completion of the study. No records relating to this study should be disposed of without the written approval of ARS. It is the responsibility of ARS to inform the Investigator/Institution as to when these documents no longer need to be retained.

15.6 Data Disclosure and Subject Confidentiality

Subject medical information and video recordings obtained as a result of this study is considered confidential and used only for study evaluation purposes. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor clinical monitor (or designee), and the IRB/EC.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain subject confidentiality. All records will be kept in a locked and secured area. All computer entry and networking programs will be identifiable only by coded numbers. Clinical information will not be released without written permission from the subject, except as necessary for monitoring by the IRB, the FDA, or the study Sponsor.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate, to obtain patents in the Sponsor's name covering any of the foregoing.

The results of this study will be published under the direction of the Sponsor. Results will not be published without prior review and approval by the Sponsor and Study Investigator.

16.0 PROTECTION OF HUMAN SUBJECTS

16.1 Basic Principles

The study will be conducted in accordance with the relevant regulatory requirements, this protocol, and ethical principles that are consisted with the GCP guideline developed by the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use. This clinical trial will also be conducted in compliance with Declaration of Helsinki, protocol, Standard specified in the relevant local regulations. Prior to initiation of the study, the Investigator and the Sponsor should obtain approval from the IRB/IEC on this protocol and any further amendments, and the subject information and informed consent form.

Any suspected serious breaches must be immediately reported to the Sponsor. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety of the subjects or the scientific value of the study.

Personnel involved in the study will be qualified by education, training, and experience to perform their respective tasks.

16.2 Institutional Review Board/Ethics Committee

The Investigator or designee agrees to provide the IRB/EC with all appropriate material, including a copy of the ICF. The study will not be initiated until the Investigator obtains written approval of the research plan and the ICF from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor. The Sponsor ensures that the IRB/EC complies with the requirements set forth in 21 CFR Part 56 (Code of Federal Regulations).

16.3 Informed Consent

The Investigator is responsible for:

• Explain the subject of the study, the risks and benefits expected from participating in the study, and that the participation is voluntary so that the subject can understand.

• Obtain informed consent to participate in the trial from the subject by signing or signing the consent form and entering the date before starting the study procedure and study drugs.

• Properly answer questions from subjects at any time during the trial and if new information that can affect the subject's intention to continue the trial is obtained while the subject is participating in the trial, the information is promptly communicated to the subject.

• Give a copy of the written consent form to the study participants and keep one copy at the study site.

16.4 Subject Health Injury and Insurance

In general, if a subject is health-injured as a direct result of the investigational products, the Sponsor or its contracted insurance company will pay for reasonable and necessary medical treatment for the health-injury. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the Sponsor should comply with such laws or regulations. Where applicable, the Sponsor will arrange for specific insurance coverage. If health damage occurred to a subject participating in the clinical trial due to the willful or gross negligence of Investigator’s site, indemnification will be discussed based on the contract with the site. The indemnification for the health damage and the payment to subjects will be described in the ICF.

16.5 Completion of the Study

If the clinical trial is completed at the study site, the Investigator will notify the director of the study site that the trial has been completed and provide an approximate summary in writing. The director of the study site will promptly notify the IRB/EC and the Sponsor in writing about the completion.

17.0 REFERENCE LIST

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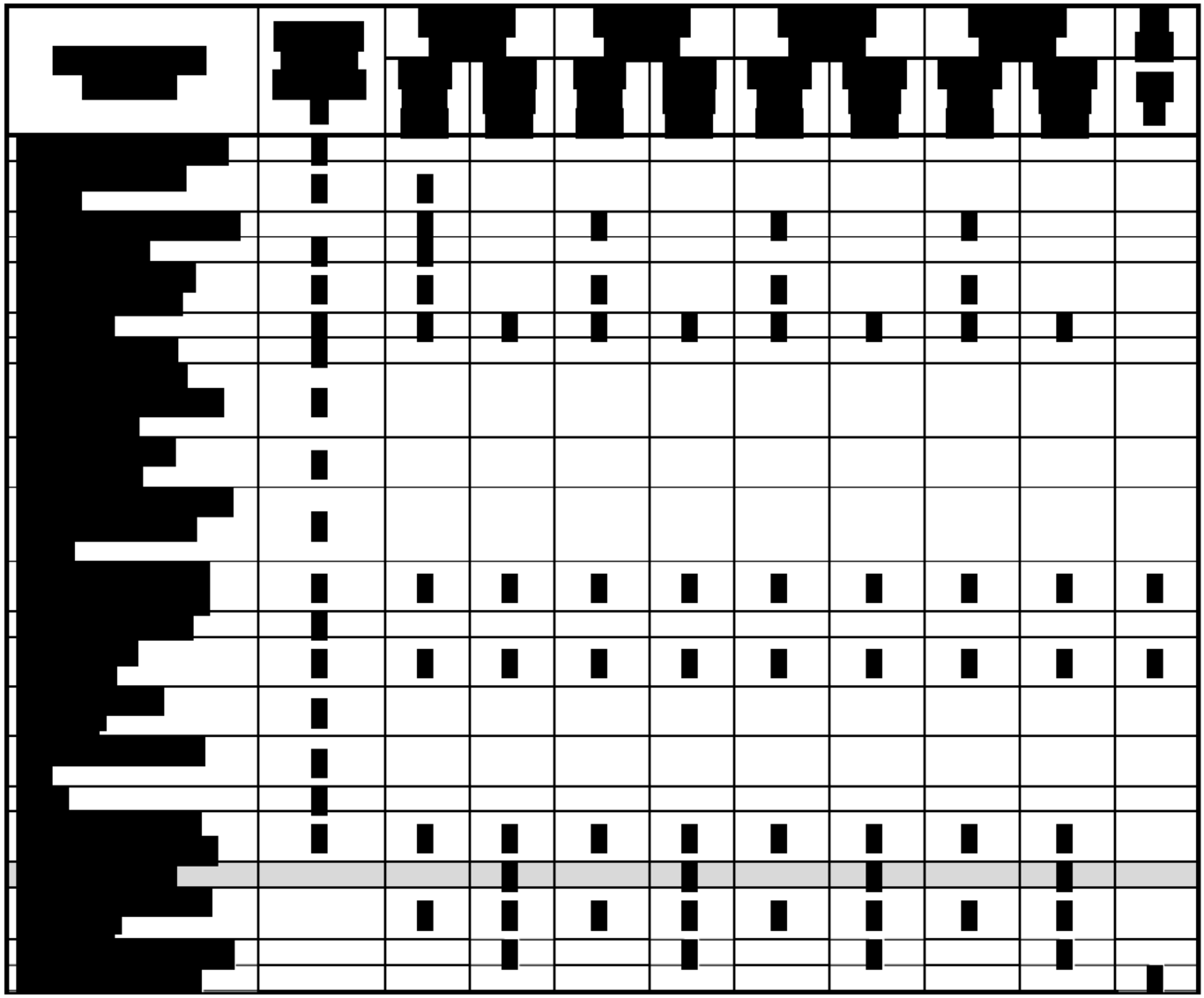
Appendix A: Schedule of Study Procedures

Table: [redacted]



c. [redacted]

Appendix B: [redacted]

Appendix C: Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf