UNIVERSITY OF SASKATCHEWAN

PARTICIPANT INFORMATION SHEET and CONSENT DOCUMENT

Title:	A Randomized, Double-blind, Placebo-controlled Phase 2a Study of ARO-RAGE Inhalation Solution to Assess Efficacy on Small Airway Dysfunction in Allergen-Induced Mild Asthma
Protocol Number:	ARORAGE-2001
Sponsor:	Arrowhead Pharmaceuticals, Inc.
Principal Investigator: **(Study Doctor)**	Brianne Philipenko, MD, FRCPC Division of Respirology, Critical Care and Sleep Medicine University of Saskatchewan 103 Hospital Drive, Saskatoon, SK S7N 0W8 306-380-6777
Sub-Investigators:	Beth Davis, PhD Don Cockcroft, MD, FRCPC
24-hour EMERGENCY Telephone Contact:	RUH Switchboard – call 306-655-1000 and ask for the doctor on call or call 911

1. INTRODUCTION

You are being invited to take part in the research study because you are at least 18 years of age but less than 66 years of age and you have a diagnosis of allergic asthma. A person who takes part in a research study is called a research participant.

This document explains the tests and treatments involved in this study. Knowing what is involved will help you decide if you want to take part in this investigational research. Participation in this research is voluntary. It is up to you to decide whether to take part or not. Even if you do decide to take part, you are free to end your participation in this study at any time without needing to give an explanation. Choosing not to take part, or to stop taking part, will not impact your current health care and/or academic status and/or employment. If you don't wish to take part, you don't have to.

Arrowhead Pharmaceuticals, Inc. is funding this research study and will be referred to as the "Sponsor." The study doctor will not receive any personal financial benefit for conducting the study. The costs of your Study Doctor's fees for clinic evaluations, procedures, and tests required to be done for research purposes will be paid for by Arrowhead Pharmaceuticals, Inc. The University of Saskatchewan will receive some financial compensation to offset research associated costs.

No member of the research team will receive a personal financial benefit from your involvement in this research study.

Please read this information carefully. Ask questions about anything you don't understand or want to know more about. Before deciding whether or not to take part, you may also want to talk about the research study with other people, such as family, friends, or healthcare providers. Feel free to do this.

If you decide you want to take part in the research study, you will be asked to sign the consent section of this document. By signing and dating this consent form you are telling us that you:

- Understand what you have read
- Consent to take part in the research study

- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a signed and dated copy of this form to keep.

2. HOW LONG WILL I BE IN THIS STUDY AND HOW MANY PARTICIPANTS WILL BE IN THIS STUDY?

If you choose to participate in this study, your participation will last approximately 17 weeks and will require at least 10 visits to the research lab.

This study will be conducted at 6 academic respiratory research sites in Canada. The study plans to enrol thirty-six (36) participants in the study. We plan to enroll 2-3 participants at this site.

3. WHAT IS THE PURPOSE OF THIS RESEARCH?

This research study will evaluate ARO-RAGE (also called the study drug) as a possible treatment for asthma. ARO-RAGE is an investigational drug. An investigational drug is one that is not approved by Health Canada; however, Health Canada has approved the use of ARO-RAGE in this research study.

Asthma is a chronic respiratory disease characterized by narrowing of the airways, the tubes which carry air into the lungs, causing symptoms of wheezing, shortness of breath, chest tightness and/or cough. This narrowing of the airways is often due to chronic inflammation. Treatments for asthma include bronchodilator or rescue inhalers (e.g. Ventolin®), anti-inflammatory inhalers (e.g. Pulmicort®) and combination inhalers which combine a bronchodilator and an anti-inflammatory medication in a single inhaler (e.g. Symbicort®). Other treatments are available for more severe or poorly controlled asthma. Despite available treatments, some individuals with asthma are still poorly controlled and research is needed to investigate potential new treatments.

ARO-RAGE is being developed to treat patients with asthma by reducing expression of the RAGE (receptor for advanced glycation end products) protein in the lung. ARO-RAGE is designed to prevent the body, specifically the epithelial cells of the lung, from making RAGE by blocking the signal that would normally lead to RAGE production. Since RAGE is an important driver of inflammation in the airway, it is possible that ARO-RAGE will decrease inflammation in patients with asthma. Decreased inflammation may then result in better airflow, improved symptoms, and fewer disease exacerbations.

4. WHAT DOES PARTICIPATION IN THIS RESEARCH INVOLVE?

You will be participating in a randomized, double-blind, placebo-controlled research study. Randomization is where people are put into groups and each group is given a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance and there is an equal chance (50:50 chance - like the flip of a coin) of being assigned to either group. If you are eligible to participate in the study and have provided consent, you will be assigned to 1 of 2 treatment groups. You will be randomized to receive either ARO-RAGE or placebo. A placebo is a substance that looks like the study drug but does not contain any active ingredients (i.e. should have no effect on what is being studied). Using a placebo treatment as a comparator is the best way to be confident that any effects observed with the active treatment (i.e. ARO-RAGE) can be attributed to ARO-RAGE. If you receive placebo, your response to allergen exposure is anticipated to be similar to what you would experience in the real world. What might differ from real world allergen exposure, is that you will not be allowed to use any medication to treat your response. However, your response will be closely monitored and appropriate medication will be provided in the event of an emergency. Also remember that your participation is voluntary and you may withdraw from the study at any time.
The treatment will be administered on two occasions via inhalation from a nebulizer. Double-blind means that neither you nor the study doctor can choose or will know what treatment you receive. However, in medical emergencies your study doctor can find out which treatment you are receiving.

Your study doctor and/or research team will describe your treatment schedule. This consent form has details that outline the various tests and procedures to be performed.

Study Visits
There are five visit types as follows:

- Screening Period
- Baseline Screening Period
- Treatment Period
- Challenge Assessments
- Safety Follow up Period / End of Study Visit.

The study treatment, (ARO-RAGE) or placebo, is a ready-to-use solution administered by inhalation using a nebulizer. The nebulizer being used in this study is the Investigational eFlow Nebulizer System. This device is not licensed for use in Canada but has been authorized by Health Canada as an investigational device for this study.

The study drug will only be administered at the hospital or clinic under the supervision of the study doctor and/or site staff on dosing day visits. On dosing days, you may leave the hospital or clinic after a minimum of two (2) hours after the study drug is administered and once all assessments are completed, unless your study doctor determines additional monitoring is needed for safety reasons. You will return to the clinical facility for outpatient visits. There are no planned overnight visits.

Screening Phase
After signing this consent form, you will be asked to undergo certain tests and procedures to determine if you are eligible to take part in this study.

SCREENING - VISIT 1	
Screening visit Day -28 to Day -16 **Approx. 2 hours**	You will be asked to sign this consent form and then the following assessments will be performed: • You will be asked questions about your demographics, medical history, medications you are taking and any therapies you are receiving and have taken 30 days prior to this screening visit. • A complete physical examination will be performed. This will include examination of your head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; axillary lymph nodes (armpit lymph nodes); and neurological system (brain and spinal cord) and musculoskeletal system (bones and muscle) . • Your height and weight will be measured. • Your vital signs (blood pressure, heart rate, respiratory (breathing) rate, temperature, blood oxygen levels) will be measured. • An electrocardiogram (ECG) will be performed to measure the electrical activity of your heart. • Blood samples (10mL or 2 teaspoons) will be collected to assess your general health. • A urine sample will be collected to assess your general health. • Blood samples (15mL or 1 Tablespoon) will be collected for testing for HIV, Hepatitis B and C and Quantiferon Testing. Quantiferon testing is looking to see if you have ever been exposed, or currently have tuberculous (TB). It is important to understand that a positive screening test does not necessarily mean you have the disease. Should you receive a positive screening result for HIV or either Hepatitis B or C, the study doctor will assist in arranging subsequent medical care. HIV, Hepatitis B and Hepatitis C are all "notifiable diseases" which means that it is required by law to notify government health authorities of any new cases. • A urine pregnancy test will be performed if you are a female of childbearing potential. • A blood test for hormone levels will be performed if you are a female who is post-menopausal. • A skin test will be done to identify what allergens you are sensitive to (e.g. cat, grass, house dust mite). • Oscillometry testing. Oscillometry is a breathing test that requires you to breathe normally through a filter/mouthpiece attached to a device that measures airflow. The test assesses how well your lungs and airways are working. The test will be completed at all visits except Visit 10. • A breathing test called spirometry will be performed to assess how well your lungs work by measuring how much air you are able to inhale and exhale. Spirometry will be performed at all visits. Spirometry is a simple, safe test performed routinely in people with all types of lung disease, including asthma. While wearing nose clips, you inhale as much air as you can via a mouthpiece/filter attached to a handheld device. After inhaling as much air as you can, you exhale forcefully for as long as you can (i.e. until your lungs are empty) and then you inhale fully again. You will need to repeat this test a few times to ensure the measurements are accurate and consistent. • A lung function test called "diffusing capacity for carbon monoxide" (DLCO) will be performed 2 times during the study. This test measures how well your lungs get oxygen into your blood stream. During this test, you will inhale a very small amount of carbon monoxide, then hold your breath, and finally

	exhale quickly. You will need to repeat this test to ensure the measurements are accurate and consistent. • Collection of any adverse event information from time of signing the consent. An adverse event is any unexpected or unwanted change in your health that happens during the study. Your screening window may be extended by up to 4 weeks, if necessary. Your study doctor will inform you if that is required. Some screening procedures may also need to be repeated, your study doctor will discuss these with you should any repeated testing be required.
A decision about whether you are eligible to continue with screening for the study will be made when the results of the assessments noted above are available.	

SCREENING– VISIT 2	
Baseline Screening visit - Day -15 **Approx. 2.5 hours**	• You will be asked questions about the medications you are taking and any therapies you are receiving and have taken since your last visit. • You will also be asked about adverse events (i.e. whether you have experienced any negative or unusual health problems) • Your vital signs will be measured. • A blood sample (5mL or 1 teaspoon) will be collected to measure RAGE levels in your blood. • A urine sample will be collected to assess your general health. • A urine pregnancy test will be performed if you are a female of childbearing potential. • A skin titration test will be done. This test is similar to the skin prick test but instead of many allergens, increasing concentrations of an allergen identified at Visit 1 will be tested to help us determine the dose of allergen to use for the allergen inhalation challenge. • Oscillometry will be completed. • Spirometry will be performed. • You will undergo a procedure called sputum induction. This procedure will occur at least 10 times throughout the study. During this procedure, you will inhale increasing concentrations (3%, 5% and 7%) of hypertonic saline (i.e. salty water) aerosolized by nebulization. Inhaling hypertonic saline helps to produce/mobilize mucus (i.e. sputum) from the airways which will be collected by having you huff/cough/spit the mucus into a sterile cup. The sample is then processed and analyzed and provides information about airway inflammation. • You will also undergo methacholine challenge testing. This test is used routinely by doctors to assist in diagnosing asthma. Methacholine challenge testing involves the inhalation of aerosolized methacholine, a known bronchoconstrictor that may cause your airways to narrow. After completing spirometry you will inhale 0.5mL aerosolized saline. You will be required to wear nose clips during the inhalations. Spirometry is performed again at 30 and 90 seconds after the inhalation. The process will repeat with increasing doubling doses of methacholine every 5 minutes until the amount of air you are able to exhale is reduced by at least 20%.

SCREENING – VISIT 3	
Baseline Screening visit Day -14 **Approx. 9 hours**	• Information regarding adverse events will be collected. • Your vital signs will be measured. • An allergen inhalation challenge will be conducted. This test involves spirometry and inhaling increases doses of an allergen (e.g. cat, grass, house dust mite) until your lung function decreases by at least 20%. Spirometry is measured at pre-defined timepoints throughout the test and up to 7 hours after the last inhalation of allergen. After the final spirometry measurement, 200 mcg of bronchodilator (salbutamol) will be administered to relieve any induced bronchoconstriction. • Spirometry and Oscillometry testing will be completed. These tests will be repeated multiple times similar to spirometry testing (i.e. pre-defined timepoints up to 7 hours). • Sputum induction will be performed.

SCREENING – VISIT 4	
Baseline Screening visit Day -13 **Approx. 2.5 hours**	• Information regarding adverse events will be collected. • Vital signs will be measured. • Oscillometry testing will be completed. • Spirometry will be performed. • Sputum induction will be performed. • You will undergo methacholine challenge testing.
A decision about whether you can take part will be made when all your screening results are available.	

Baseline Screening Period, Treatment Period, Follow- up Period & End of Study (EOS)/Early Discontinuation

If you are found eligible to participate, then the following required tests and procedures to be performed are shown in the tables below. If you miss a visit, you may be asked to come in for an unscheduled visit to complete some or all of the missed tests and procedures. Your doctor may also ask you to come to clinic for an unscheduled visit if they consider it necessary.

TREATMENT – VISITS 5 AND 6	
Clinic Visit Day 1 and Day 29 - Dosing **Approx. 5 hours**	**<u>Visit 5 (Day 1) and Visit 6 (Day 29) – Dosing</u>** • You will be asked questions about your health, medications, and therapies since your last visit. • Your vital signs will be measured. • A urine pregnancy test will be performed if you are a female of childbearing potential. • An ECG will be performed. This test will be completed both before and after you receive your dose of the study drug. • A urine sample will be collected to perform routine clinical laboratory tests. • Blood samples (24mL or 1.6 Tablespoons at each visit) will be collected:

	○ to perform routine clinical laboratory tests (i.e. like tests your family doctor would request to assess your overall health) ○ to measure how much study drug is in your blood requires two draws, one prior to dosing and the other one hour after dosing ○ to check if your body has made antibodies to the study drug ○ to measure levels of RAGE protein • Oscillometry testing will be completed. • Spirometry testing will be performed. One test will be completed before you receive the study drug, and another will be performed after you receive study drug. • You will undergo methacholine challenge testing (Visit 5 only). • Nebulized study drug (ARO-RAGE or placebo) will be administered via inhalation. • You will be required to remain in the lab for safety purposes for 2 hours after receiving ARO-RAGE

CHALLENGE ASSESSMENTS– VISITS 7 to 9	
Clinic Visit Day 57 **Approx. 2.5 hours**	**<u>Challenge assessments – Visit 7 (day 57)</u>** • You will be asked questions about your health, medications, and therapies including any adverse events. • Your vital signs will be measured. • Blood samples (20mL or 1.3 Tablespoons) will be collected to: ○ perform routine clinical laboratory tests. ○ to measure levels of RAGE. • A urine sample will be collected to perform routine clinical laboratory tests • Sputum induction will be performed. • Oscillometry testing will be completed. • Spirometry will be performed. • A methacholine challenge test will be conducted.
Clinic Visit Day 58 **Approx. 9 hours**	**<u>Challenge assessments – Visit 8 (day 58)</u>** • You will be asked questions about any adverse events. • Your vital signs will be measured. • An allergen inhalation challenge will be conducted. • Oscillometry testing and spirometry will be performed.
Clinic Visit Day 59 **Approx. 2.5 hours**	**<u>Challenge assessments – Visit 9 (day 59)</u>** • You will be asked questions about any adverse events. • Your vital signs will be measured. • Oscillometry testing will be completed. • Spirometry will be performed. • Sputum induction will be performed for biomarker measurements • You will undergo a methacholine challenge test.

SAFETY FOLLOW UP PERIOD / END OF STUDY VISIT – VISIT 10	
Safety Follow Up Period Day 89 **Approx. 1 hour**	**<u>End of Study or early discontinuation visit</u>** • You will be asked questions about your health, medications, and therapies since your last visit including any adverse events. • Your vital signs will be measured. • Your weight will be measured. • A physical examination will be performed. • A urine sample will be collected to perform routine clinical laboratory tests and a pregnancy test if you are a female of childbearing potential. • Blood samples (20mL or 1.3 Tablespoons) will be collected to: ○ perform routine clinical laboratory tests. ○ measure the level of RAGE in your blood. ○ check if your body has any antibodies to the study drug. • DLCO will be measured. • Spirometry will be performed.
Please tell the study staff if you have any unusual symptoms at any time during the study. You will be closely monitored for any side effects, and you should report any changes in the way you feel to your study doctor.	

Optional future research sub-study

There is also an optional sub-study associated with this study. This optional sub-study relates to leftover biological samples (blood, urine and sputum). If you are willing, the Sponsor would like to store your leftover biological samples for future research. You do not need to consent to this optional sub-study to participate in this research. Additional information is provided in Section 11.

5. WHAT DO I HAVE TO DO?

It is important that you carefully take into consideration the impact that participating in this research study may have on your lifestyle. It is important that you attend all study visits and commit to all the required procedures. If you participate in this study, you will be expected to:

- attend the clinic visits and undergo the required study procedures.
- not take part in any other studies while you are taking part in this study.
- inform your study doctor about any health problems, accidents or medical interventions that happen while you are in the study, even if you think it is not important.
- inform your study doctor before you start any new medication or stop any medication that you are already taking. This includes prescribed or over the counter products, even if used short term.
- not donate any blood or blood products following the first dose of study drug through the end of study.
- not drive or operate machinery until you know how the study treatment affects you.
- withhold certain medications that should not be taken prior to study procedures, such as antihistamines and anti-inflammatory medications. Your study doctor will review the list of medications, and the duration to withhold them with you.
- fast from caffeinated food and drinks at least 4 hours prior to the procedure on the days the induced sputum procedure, Oscillometry and/or spirometry is performed.
- not drink more than 7 units of alcoholic drinks per week (1 unit of alcohol = 1 glass of wine (150 mL), approximately one-half pint of beer (360 mL) or 45 mL of 40% alcohol).

- not smoke tobacco, marijuana, or use e-cigarettes (vape) at any time while you are taking part in the study. You must also inform your study doctor about any use of recreational drugs, non-prescription medications, or herbal supplements when you first give your consent to join the study. If your use of any of these substances changes during the study, you must let your study doctor know right away.
- Female participants of childbearing potential must agree to use a method of highly effective contraception during this study and for 90 days following the end of study or for 90 days following the last dose of the study drug, whichever is later. Female participants who use hormonal contraceptives as highly effective contraception must be stable on the medication for at least 1 menstrual cycle prior to Study Day 1. Otherwise, the method of highly effective contraception must be initiated at least 28 days prior to Study Day 1.Use of a condom must begin following signing of informed consent.
- Male participants with female partners of childbearing potential or whose partner is pregnant must agree to use a condom during the study and for at least 90 days after end of study (EOS) or the last dose of investigational product (IP), whichever is later. Use of a condom must begin following signing of informed consent.
- If a male participant (or male partner of a female participant who is of childbearing potential) is known to be infertile or has had a vasectomy, a condom is not required. You should not change your method of highly effective contraception during the study.
- advise your study doctor of any planned surgery.
- inform the study doctor if you decide not to continue in the study.

If you decide to participate in this research study, it is a good idea for you to inform your family physician of your participation. In addition, the study doctor may need to consult with your family physician regarding your health and medications. Contacting your family physician can only occur with your permission. You can indicate your willingness or not on the signature page of this document whether to have the study doctor or another member of the research team contact your family physician.

Following all these instructions is important not only for your safety but also to ensure the data collected are accurate.

6. WHAT ARE THE ALTERNATIVES TO PARTICIPATION?

You do not have to participate in this study to receive treatment for your asthma. Your current asthma treatment and how you treat your asthma are ultimately decisions and discussions made between you and your family doctor or respiratory specialist. The alternative to participating in this study is not to participate.

7. WHAT ARE THE POSSIBLE BENEFITS TO YOU FOR PARTICIPATING?

You may or may not benefit by taking part in this research study. There is no guarantee that you will receive direct benefit from this research study. The information developed from this research study may be used to further develop ARO-RAGE which may help people with asthma in the future.

The knowledge gained from this study may lead to new discoveries, which could lead to the approval of a new drug and ultimately benefit the Sponsor financially but there will be no financial benefit to you from these discoveries.

8. REIMBURSEMENT AND COST

The study drug is provided at no cost to you, your private medical insurance (if any), or the public health insurance plan. You will still have to pay for the costs of your regular medical care that are not part of this study.

9. COST AND COMPENSATION

You will receive an honorarium up to $1250 for completing the study. Payments will be made in three instalments. If you withdraw from the study early, you will receive partial payment (pro-rata payment) according to the following schedule:

- $50 for completion of Visit 1
- $100/visit for completion of Visits 2, 4, 7, 9
- $200/visit for completion of Visits 3, 8
- $100 for completion of Visit 5
- $150 for completion of Visit 6
- $150 for completion of Visit 10

The honorarium you receive is tax reportable. You will need to provide your social insurance number and the University will issue you a T4 for tax purposes. Any personal information collected as a record of the honorarium will be stored separately from the data for 7 years for auditing purposes. If you are withdrawn from the study for medical or non-medical reasons, or if you decide to withdraw from the study, you will be reimbursed for the study visits you have completed as per the amounts indicated above.

If you are required to return following the final study visit for follow up or for repeat lab testing, you will be paid $50 per additional visit.

10. WHAT ARE THE POSSIBLE RISKS AND DISADVANTAGES OF TAKING PART?

Medical treatments may cause side effects. You may experience none, some or all of the side effects listed below. These may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. You will be closely monitored throughout the study for the development of any side effects.

There is always a risk of some unexpected serious, life-threatening side effects occurring following the administration of a new experimental treatment. You will be monitored closely for any side effects and you must tell the study doctor or study staff about any new or unusual symptoms you experience.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your participation in this study. Your study doctor will discuss the best way of managing any side effects with you.

Complaints/side effects associated with the study drug

ARO-RAGE has been tested in research studies involving healthy volunteers and individuals with asthma. As of 08 May 2025, 92 people have received ARO-RAGE Inhalation Solution and some side effects have been reported as outlined below. These side effects may or may not be related to or caused by ARO-RAGE. Complaints reported in $\geq$10% (i.e. very common) of study participants receiving the study drug in the following studies were:

Healthy Volunteer Single Ascending Dose study:

- Headache (27%)
- Upper respiratory tract infection (20%)
- COVID-19 (17%)
- Post procedural (bronchoscopy) complication (10%)
- Post procedural fever (10%)
- Procedural pain (10%)

Health Volunteer Multiple Ascending Dose study:

- COVID-19 (32%)
- Upper respiratory tract infection (25%)

- Sore throat (21%)
- Headache (11%)
- Tiredness (11%)

Mild–to-Moderate Asthma Multiple Ascending Dose study:

- Upper respiratory tract infection (26%)
- Headache (26%)
- Asthma (11%)
- Back pain (11%)
- COVID-19 (11%)
- Chest comfort (11%)
- Dizziness (11%)
- Gastroenteritis or stomach upset (11%)
- Blood in urine (11%)
- Urinary tract infection (11%)

High FeNO Asthma Multiple Ascending Dose study:

- Elevated blood creatine phosphokinase (27%) – an increase in a protein produced by the body that can occur when skeletal muscle tissue is broken down/damaged as occurs with intense exercise. Common symptoms include muscle pain, weakness, cramps and fatigue.
- Upper respiratory tract infection (20%)
- Asthma (13%)
- Headache (13%)

As with any drug, an allergic reaction is possible. A serious allergic reaction can be life-threatening. Some symptoms of allergic reactions are:

- Rash
- Wheezing, or difficulty breathing
- Dizziness or fainting
- Swelling around the mouth, throat or eyes
- A fast pulse and / or a drop in blood pressure
- Sweating

This research study includes regular laboratory measurements and assessments to help identify any possible risks that might develop during your participation in this research study. The safety data of each participant in this study will be closely monitored by the study doctor and the Sponsor for signs or symptoms related to these or other possible risks.

Allergen Inhalation Challenge

Inhaling allergen may lead to cough, chest tightness, wheezing, and difficulty breathing (i.e. may produce similar symptoms to what you experience when exposed to allergen in a real world setting). The test is carried out in a way to minimize the danger of a severe asthmatic reaction; however, there is still a very small possibility that a severe reaction could occur, including anaphylaxis. Qualified medical personnel will be available to provide appropriate medical treatment should anaphylaxis or a severe reaction occur.

Blood Draw

Blood will be drawn from a vein in your arm. There may be some slight discomfort involved in taking blood with a needle. There is a small risk that a clot will form in the vein, which usually resolves untreated in a few weeks. There is a small risk of infection, although the use of antiseptic solutions prior to insertion of the

needle minimizes this risk. There is also the possibility of bruising and discomfort around the blood collection site, although this is generally minor and resolves untreated within a few days.

During the study, the estimated total blood volume to be collected will be up to approximately 127mL (about 1/2 cup).

Electrocardiogram (ECG)

An ECG is a medical test that records the electrical activity of your heart and will be performed at 3 visits by attaching several leads or electrodes to your chest, wrists and ankles. You may develop a mild rash or skin irritation where the electrodes are attached. If any paste or gel is used to attach the electrodes, you may have an allergic reaction to it. This irritation usually goes away once the patches are removed, without requiring treatment.

Spirometry

You may feel dizzy or light-headed from breathing in deeply and you may cough from forcefully exhaling.

While spirometry is a low-risk procedure, people with certain heart conditions, or who have had recent major surgeries of the brain, eye, nose, chest, or abdomen may be at increased risk when performing spirometry. You will not be able to participate in this study or undergo spirometry tests if you have these risk factors or have had recent surgeries of the brain, eye, nose or abdomen.

Prior to a study visit involving a spirometry test, your study doctor will advise you to withhold using your asthma rescue medication for at least 8 hours (i.e. withhold short acting bronchodilator medication like Ventolin®). This is because asthma medications can affect your spirometry test results. In the event of a medical emergency that requires use of your rescue inhaler, you should use your inhaler and contact study staff to reschedule or postpone your visit.

Oscillometry

You may experience slight discomfort due to the positioning of your head, neck and cheek.

Methacholine Inhalation Tests

During this procedure, you could experience cough, chest tightness, wheezing, and difficulty breathing. Symptoms, if they occur, are mild and resolve following the inhalation of a bronchodilator medication which will be provided to you. The test is carried out in a way to minimize the danger of severe airway narrowing; however, should this occur, treatment with a bronchodilator to reverse airway narrowing will be available.

Skin Testing

If you are sensitive to one or more of the allergens placed on your arm, a raised bump referred to as a wheal will develop. These bumps will be itchy and redness of the skin surrounding the wheal may appear. These effects will normally resolve within 1 to 2 hours. More prolonged or severe swelling can occur and may be treated with an oral antihistamine, topical corticosteroid cream, and/or an ice pack. Severe allergic reactions from allergy testing are very rare but can result in a decline in blood pressure and difficulty breathing, and can be potentially fatal. Study staff will be monitoring you during this time and treatment will be provided if necessary.

Diffusing Capacity for Carbon Monoxide (DLCO)

You may feel a bit winded afterwards.

Induced Sputum

Sputum induction has been performed in many previous studies and has been shown to be a low-risk procedure, even in those participants with asthma. However, inhaling salt water can irritate your airways and cause symptoms like coughing. In some cases, sputum induction has the potential to narrow your

airways and temporarily decrease your lung function, resulting in shortness of breath. Your lung function will be checked following each inhalation of saltwater to monitor if airway narrowing is occurring. If your lung function drops significantly and/or if you develop troubling symptoms as a result of the procedure, the procedure will be stopped and study staff will provide you with asthma medication.

Pregnancy

The effects of ARO-RAGE on the unborn child and on the newborn baby are not known. Because of this, it is important that research study participants are not pregnant or breast-feeding and do not become pregnant during the course of the research study and for 90 days after the end of the study or last dose. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding.

The long-term effects of the study treatment on fertility are also unknown. This means that it is unknown if treatment with these medications will affect your ability to have children in the future.

If you are an individual of child-bearing potential and you become pregnant or if your partner is of child-bearing potential and becomes pregnant you should tell the study doctor immediately.

For participants of child-bearing potential:

A individual of child-bearing potential is any pre-menopausal female who may become pregnant. If you are unsure if this applies to you, please check with the study doctor before you start the study treatment. Females who are post-menopausal will have a blood hormone test to confirm menopausal status.

Female participants of the study of childbearing potential must agree to use a highly effective method of contraception during the duration of this study until at least 90 days after the end of study or your last dose, whichever is later.

Male participants of the study with female partners of childbearing potential or whose partner is pregnant must agree to use a condom during the duration of this study and for at least 90 days after end of study or your last dose, whichever is later.

Participants who use hormonal contraceptives as highly effective contraception must be stable on the medication for ≥ 1 menstrual cycle prior to Study Day 1. Use of a condom must begin at the time of signing this consent form. While it is recommended to stay on your current contraception plan for the duration of the study, we ask that you please discuss with the study doctor if you are planning n changing your method of contraceptive during participation in this study.

The following are acceptable highly effective methods of contraception (to be used in addition to a condom):

- Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation (via oral, intravaginal, or transdermal [through the skin] administration)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (via oral, injectable, implantable, or transdermal administration)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing systems (IUSs).
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence
- Progestogen-only oral agents that do not reliably inhibit ovulation (e.g., norethindrone/norethisterone) and/or have a failure rate exceeding 1% when used consistently and correctly are not considered highly effective methods.

True sexual abstinence for the duration of the study and for at least 90 days following your last study visit or after the last dose of IP, whichever is later, is an acceptable method of contraception only when in line with the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not considered "true" abstinence and are not acceptable methods of contraception.

If you are unsure which method of birth control you are using (or want to start using) and whether it is acceptable for this research study, please ask the study doctor for more information.

You must also agree not to donate eggs for 90 days from the last study drug administration or 90 days after the end of study (whichever is later).

If you do become pregnant during the study or within 90 days after your last dose of study medication or after the end of study, you must tell the study doctor as soon as possible. If you become pregnant during the study, you will not receive any more doses of the study medication, but you may continue to have study assessments. You will be invited to give optional consent to allow access to information regarding the outcome of the pregnancy and the well-being of the baby for the purpose of determining any effects from the study. If you agree to the optional pregnancy consent, the study doctor will follow-up on your pregnancy and the health of your child for 1 year after giving birth.

<u>For participants of non-child bearing potential:</u>

If you are a sexually active male and have a partner who is of child-bearing potential (meaning a female who may become pregnant) **it is very important that you use appropriate birth control** (contraception) whilst taking the study drug during your participation in this research study.

Male participants of the study with female partners of childbearing potential or whose partner is pregnant must agree to use a condom during the duration of this study and for at least 90 days after end of study or your last dose, whichever is later. Use of a condom must begin at the time of signing of informed consent If a male participant (or male partner of a female participant who is of childbearing potential) is known to be infertile or has had a vasectomy, a condom is not required.

You are responsible for informing your partner of the possible risks to an unborn child of the study drug you will be taking in this research study.

If your partner becomes pregnant during your participation in this research study or within 90 days following your last study visit, you must report this to the study doctor as soon as possible. Your partner will be asked to sign an optional consent form for the collection of her pregnancy information and the health of the child. If she agrees to the optional pregnancy consent, the health of your child will be followed up on for 1 year after birth.

You must also agree not to donate sperm during the study and for 90 days from the last study drug administration or 90 days after the end of study (whichever is later).

11. WHAT WILL HAPPEN TO MY TEST SAMPLES?

Numerous biological samples (i.e. blood, urine and sputum) will be collected from you as part of this research study. Some of these samples will be transferred to laboratories used by the Sponsor for this research study.

The laboratories (and location) include:

- **Medpace Reference Laboratories,** Ohio, USA
- **Charles River Laboratories,** Quebec, Canada
- **Keystone Bioanalytical,** PA, USA

- **Arrowhead Pharmaceuticals,** WI, USA
- **McMaster University Laboratory,** Ontario, Canada
- **EPL Archives,** VA, USA
- **MEU,** Manchester, UK

All samples collected will be coded or de-identified; labelled only with a unique study number and your year of birth but will not include your name or other personal details that could identify you.

Your sample may be stored for up to 25 years after the end of the study or at least 2 years after the last approval of a marketing application or formal discontinuation of clinical development of the study drug, whichever comes last. The biological samples will be sent to a central laboratory(ies) selected by the Sponsor. The data obtained from these samples will be stored by Arrowhead Pharmaceuticals, Inc. or the laboratory that performs the testing and if you agree to participate in the Optional Future Research substudy, leftover samples collected from the study may be used for future research.

Optional future research sub-study
The Sponsor would like to use any leftover biological samples collected for this study for future scientific research. This is called biobanking. The goal of biobanking is to allow for more research to be done that may lead to new discoveries and ultimately improve people's health. The Sponsor may also send the samples to current or future collaborators for future research performed pursuant to this consent. Your biological samples will be stored for up to 25 years by the laboratories to which they are sent.

These locations include:
- **Arrowhead Pharmaceuticals,** WI, USA
- **Medpace Reference Laboratories,** Ohio, USA
- **EPL Archives,** VA, USA

Agreeing to future use is optional. You can still participate in this study without participating in the optional sub-study. Your willingness (or not) to participate in this optional sub-study will be captured on the signature page of this document.

Right now, we don't know exactly what research may be done in the future using your de-identified data and leftover biological samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and the study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

12. WHAT IF NEW INFORMATION ARISES DURING THIS RESEARCH STUDY?

During the course of this research study, we may learn more information or discover new findings that could be important to you. This includes information that might cause you to change your mind about being in the research study. If such information becomes available, your study doctor or other study staff will notify you as soon as possible and discuss with you whether you want to continue in the research study. If you decide to withdraw, please inform your study doctor or other study staff immediately to discuss the withdrawal process.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research study. If this happens, the study doctor will explain the reasons and arrange an end of treatment visit.

13. CAN I HAVE OTHER TREATMENTS DURING THIS RESEARCH STUDY?

While you are participating in this research study, you may not be able to take some or all of the medications or treatments you have been taking before participation or you may need to withhold certain medications

before study visits. It is important to tell your study doctor and the study staff about any treatments or medications you are currently using, including over-the-counter medications, vitamins or herbal remedies. You should also tell your study doctor about any changes to these during your participation in the research study. Your study doctor will explain to you which treatments or medications need to be stopped for the time you are involved in the research study. Importantly, you will be required to withhold the use of bronchodilator (e.g. Ventolin®) for at least 8 hours prior to every study visit. In the event of a medical emergency, you should use the bronchodilator or any other medication needed and then contact study staff as soon as possible to discuss next steps.

14. WHAT IF I WITHDRAW FROM THIS RESEARCH STUDY?

Your participation in this research is voluntary. You may withdraw from this study at any time. You do not have to provide a reason. Your future medical care, employment or academic status will not be affected.
If you choose to enter the study and then decide to withdraw at a later time, all data collected about you will be retained for analysis.

If you decide to withdraw consent and stop your participation in the study, please contact your study doctor or another study staff member who will tell you what you should do before leaving the research study. You may be asked to return to the clinic for a follow-up visit for safety reasons.

15. CAN I BE ASKED TO LEAVE THE STUDY?

The study doctor may take you off the study if:
• Your health changes, and the study is no longer in your best interest, or you are unable to tolerate the study treatment.
• New information becomes available, and the study is no longer in your best interest.
• You are unable to complete all required study procedures.
• The study is stopped by Health Canada, the University of Saskatchewan Biomedical Research Ethics Board (REB) or the study Sponsor, Arrowhead Pharmaceuticals, Inc.

16. WHAT HAPPENS WHEN THE STUDY ENDS?

The study drug ARO-RAGE will not be available to you after your participation in this research study has finished as ARO-RAGE is not an approved treatment for asthma.

The results of the study will be available in aggregate form (i.e. you will not be identified) at http://www.clinicaltrials.gov searchable using the number NCT07241546. Study results will only be available once all participants have completed the study and the data are analyzed. Results are anticipated to be available in late 2027.

The Investigators and the study Sponsor intend to publish the study results in a scientific journal and may present the aggregate data at future relevant conferences/workshops or meetings but your identity will not be disclosed.

You can indicate how you would like to obtain the study results on the signature page of this document.

17. PRIVACY AND CONFIDENTIALITY

In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected.

Your study records will be identified by using your participant ID number. They will be kept for 15 years in a secure area such as a locked file cabinet and office at the University of Saskatchewan.
Tissue samples and results of the study without your name or other information that could identify you will be sent to the Sponsor and companies noted in section 11 above and combined with information from other participants for analysis.

No information that discloses your identity will be released or published without your specific consent to the disclosure, or as required by law. Rarely, your study documents may be obtained by courts of law. Some authorities have a duty to check your study and medical records to make sure all the information is correct. Your study and medical records may be inspected in the presence of the investigator or their qualified designate by representatives of the study Sponsor, the University of Saskatchewan Biomedical Research Ethics Board, Health Canada, and possibly governmental agencies in other countries such as the United States Food and Drug Administration (FDA), European Medicines Agency (EMA), and other national health agencies that regulate this research where the study medication may be considered for approval.

If you decide to withdraw from this study, your study and medical records will be made available to these agencies. However, they will only look at your records up to the date of your withdrawal, except where the reporting of side effects associated with the study medication is required. You may ask the study doctor to see and copy your personal health information related to the study. You may also ask the study doctor to correct any study related information about you that is wrong. In the case of a blinded study, you may have to wait until the end of the study to see your study records to protect the integrity of the study.

The results of this study may be presented in a scientific meeting or published, but your identity will not be disclosed. For your own safety, it is strongly recommended that your family physician be informed of your participation in this study. With your permission, they will be informed and may be consulted regarding your health and treatment.

18. WHAT HAPPENS IF SOMETHING GOES WRONG

In the case of a medical emergency related to the study, you should seek immediate care and, as soon as possible, notify the study doctor. Inform the medical staff you are participating in a clinical study. Necessary medical treatment will be made available at no cost to you. By signing this document, you do not waive any of your legal rights against the Sponsor, investigators, or anyone else.

19. FURTHER INFORMATION AND WHO TO CONTACT

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this study or if you have any medical problems which may be related to your involvement in the study (for example, any side effects), you can contact the Principal study doctor as described on page 1 of this document or any of the following people:

Clinical contact person

Name	*Brianne Philipenko*
Position	*Principal Investigator*
Telephone	*306-380-6777*
Email	*bsp943@mail.usask.ca*

If you have any complaints or concerns about your rights as a research participant and/or your experiences while participating in this study, contact:

Reviewing EC approving this research and contact details

Reviewing EC name	*University of Saskatchewan Biomedical Research Ethics Board*
Contact	*Chair of the University of Saskatchewan Biomedical Research Ethics Board*
Telephone	*306-966-2975 or toll free 1-888-966-2975*
Email	*ethics.office@usask.ca*

All research in Canada involving humans is reviewed by an independent group of people called a Research Ethics Board. The ethical aspects of this research study have been reviewed by The University of Saskatchewan Biomedical Research Ethics Board.

CONSENT FORM

Title:	A Randomized, Double-blind, Placebo-controlled Phase 2a Study of ARO-RAGE Inhalation Solution to Assess Efficacy on Small Airway Dysfunction in Allergen-Induced Mild Asthma
Protocol Number:	ARORAGE-2001
Sponsor:	Arrowhead Pharmaceuticals, Inc.
Principal Investigator: (Study Doctor)	Brianne Philipenko
Address:	Room 346 Ellis Hall, 103 Hospital Drive, Saskatoon, SK, S7N 0W8
Telephone:	**306-380-6777**

Please let study staff know if you require an interpreter.

CONSENT STATEMENT

- **I have read (or someone has read to me) the information in this consent form.**
- **I understand the purpose and procedures and the possible risks and benefits of the study.**
- **I understand that this study may not provide any benefits to me.**
- **I have been informed that the alternative to participating in this study is not to participate.**
- **I was given sufficient time to think about participating in this study.**
- **I had the opportunity to ask questions and have received satisfactory answers.**
- **I understand that I am free to withdraw from this study at any time for any reason and I understand that the decision to stop taking part will not affect my future medical care, employment or academic status.**
- **I agree to follow the study doctor's instructions and will tell the study doctor as soon as possible if I feel I have had any unexpected or unusual symptoms.**
- **I give permission for the collection, use and disclosure of my personal health information for the research purposes, as described in this consent form.**
- **I understand that by signing this document I do not waive any of my legal rights.**
- **I will be given a signed and dated copy of this consent form.**
- **I agree to participate in the optional sub-study regarding storage of my leftover biological samples for future research use. ❑ Yes ❑ No**

- **My family physician can be informed about my participation in this study, and, if required, consulted regarding my health and treatment.**

  ❑ Yes, you may contact my primary care physician. Name:

  ❑ No, please do not contact my primary care physician

  ❑ I do not have a primary care physician.

_____(initial) Please send me a lay summary of the study results when available. Provide contact information (e.g. email; phone; street address): _____

_____(initial) Please send me a copy of the journal publication if/when available. Provide contact information (e.g. email; phone; street address): _____

_____(initial) I will access the study results by contacting the study site or visiting http://www.clinicaltrials.gov.

Statement by Participant	I hereby consent to take part in this study. I understand that I will receive a signed copy of this consent form for my records. _____ (full name) _____ (signature) __ __ / __ __ __ / __ __ __ __ (Date DD/MMM/YYYY) Time: _____

Witness Signature (if applicable) ** **Tick if Not applicable** ☐

I confirm that the Information Sheet and Informed Consent Form, and any other written information, was accurately explained to, and apparently understood by, the participant. I confirm that informed consent was freely given by the participant.

_____ (full name)

_____ (signature)

__ __ / __ __ __ / __ __ __ __ (Date DD/MMM/YYYY)

**A witness signs when the Information Sheet and Informed Consent Form has been read to the participant – (i) in addition to the participant or (ii) in lieu of the participant – for participants who are legally capable of providing consent but unable to read, or unable to read and write.

Statement by Consenter (Investigator/designee)

I have discussed this study with the above named participant. The participant appeared to fully understand the information provided about the study.

_____ (full name)

_____ (signature)

_____ (study role)

__ __ / __ __ __ / __ __ __ __ (Date DD/MMM/YYYY)