Main Participant Information Sheet/Consent Form

USC Clinical Trials

Title	Arrowhead Pharmaceuticals, Inc. / A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Mixed Dyslipidemia
Protocol Number	AROAPOC3-2002
Global Sponsor	Arrowhead Pharmaceuticals, Inc.
Local Project	Arrowhead Australia Pty Ltd
Principal Investigator	Dr Nischal Sahai
Location	USC Clinical Trials L1, 19-31 Dickson Rd, Morayfield, QLD, 4506

Part 1 What does my participation involve?

This Participant Information and Consent Form is 27 pages long, please make sure you have all the pages of this document.

1 Introduction

You are invited to take part in the above named research project because you have mixed dyslipidaemia (increased blood levels of cholesterol and triglycerides which are types of fats) . The research project is testing a potential new treatment for mixed dyslipidaemia. The new drug is called ARO-APOC3 (also called the study drug), which is administered by injection. ARO-APOC3 has previously been tested in healthy volunteers and participants with dyslipidaemia (elevated levels of triglycerides or cholesterol).

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research project.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend, or your local doctor. If English is not your first language and you require an interpreter, one will be provided for you.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read.
- Consent to take part in the research project.
- 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 copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

You are invited to take part in this research project because you have a history of dyslipidaemia. Mixed dyslipidaemia refers to raised levels of cholesterol combined with elevated triglycerides. If you have this disease, it means you have higher-than-normal levels of cholesterol, triglycerides, and other lipids in your blood. Mixed dyslipidaemia can lead to heart disease and other serious conditions.

ARO-APOC3 (known as the study drug) is being developed to treat mixed dyslipidaemia by blocking the expression of a protein called Apolipoprotein C3 (ApoC-III). ApoC-III is involved in the regulation of triglycerides and cholesterol in the blood and stops them from being broken down. Reducing the expression of this protein is expected to result in a reduction of triglyceride and cholesterol levels in the blood and in the liver.

While ARO-APOC3 has already been tested in healthy volunteers and patients, the side effects in people with elevated cholesterol and triglycerides is still being studied.

ARO-APOC3 is an experimental drug and is one that is currently being tested and has not been approved for use by Regulatory Authorities such as the Therapeutic Goods Administration (TGA) in Australia and the Food and Drug Administration (FDA) in America. Experimental drugs may be tested in research studies such as this one.

The purpose of this study is to test three different dose levels of ARO-APOC3 in approximately 320 participants with mixed dyslipidaemia.

The intention is to test the safety and tolerability of ARO-APOC3, as well as the pharmacokinetics (PK - how your body uses the study drug) and pharmacodynamics (PD - how the study drug affects your body) of the study drug. We are doing this study to find out:

- Does the study drug have any side-effects and is it well tolerated when given as multiple doses?
- How much of the study drug gets into the blood stream, and how long does the body take to get rid of it?
- Which of the three dose levels will best decrease the level of triglycerides and cholesterol and other types of fat in the blood compared to a placebo, or dummy injection?

3 What does participation in this research involve?

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group 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 (random). You will be assigned at random (like a coin toss) to receive one of three dose levels of ARO-APOC3 (10mg, 25mg or 50mg) or placebo. Study participants randomized to the 50mg dose will also be randomized to receive the second dose on either Week 12 or Week 24. A placebo is a substance not containing the active agent under study. It will be administered to some participants to compare the effects of the active agent that will be administered to other participants. The placebo looks similar to the study drug, but it is not. You will have a 3 in 4 (75%) chance of receiving ARO-APOC3 and a 1 in 4 (25%) chance of receiving placebo.

You will be participating in a double-blind study. This means that neither you nor your Study Doctor will know which study treatment (ARO-APOC3 or placebo) you are receiving. However, in certain circumstances, your Study Doctor can find out which treatment you are receiving, if necessary. This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoid Study Doctors or participants jumping to conclusions.

STUDY PROCEDURES

You must be willing to attend all the scheduled visits to the site. Various procedures will be performed each time you visit the site.

Your study doctor might need to repeat any of these procedures at times other than those specified below if he/she feels it is necessary for your safety.

If you agree to take part in this research project, no research project-related procedures can start until this consent form is signed and dated.

Three different dose levels of the ARO-APOC3 will be tested in this study. Once the Study Doctor confirms you are eligible to participate, the study drug or placebo will be administered by subcutaneous (under the skin) injection at Day 1 and at either Week 12 or Week 24. The dose of study drug (or placebo) that you are assigned to receive during the study will be chosen randomly on Day 1.

After signing the informed consent form, you will undergo screening evaluations to determine whether you are eligible to participate in the study. The Screening period may last up to 6 weeks to complete and may require that you visit the study centre up to 3 separate occasions. At most study visits (except for the very first Screening visit), you will need to arrive at the study clinic in a **fasted-state (no food or drink other than water for at least 10 hours).**

The details of the study and tests performed are shown in the table below. During the screening period, assessments will be done to check whether the study is suitable for you.The day you have your first dose of ARO-APOC3 or placebo is called Study Day 1 and all other days are counted backward or forward from Day 1. The duration of the study is approximately 54 weeks from screening to the Week 48 End-of-Study visit.

SCREENING	
Screening Period (Day -42 to Day -1)	The entire Screening Period for this study may take up to 6 weeks to complete and may require two or three separate visits to the study clinic (Screening Visits 1, 2, and 3). At the Study Doctor's discretion, the assessments at Screening Visit 1 and Screening Visit 2 may be combined. If Screening Visits 1 and 2 are combined, then you must be in a fasted state (no food other than water) for at **least 10 hours** prior to collection of screening blood samples. Your Study Doctor will discuss this with you.
Screening Visit 1 (Day -42 to Day -21) Approximately 3 hours *(Fasting not required)*	At the first Screening visit, the following will occur: • After a discussion with the Study Doctor to make sure that you fully understand the purpose and procedures required of this trial and have had all of your questions answered, you will be asked to give your informed consent. After signing the informed consent form: • You will be asked questions about your diet, health, demographics, medical history, and medications; including questions about recreational drugs, alcohol, and tobacco use. • The Study Doctor will assess your risk for cardiovascular disease and whether you are on or should be on an appropriate lipid lowering medication. • The Study Doctor will discuss a healthy diet based upon your diagnosis and individual medical needs. • Your Study Doctor will need to confirm that you have been on a stable diet for at least 2 weeks and are on stable medications prior to completing the assessments required at Screening Visit 2. Therefore, it is very important to tell the Study Doctor about all medications you are taking so that he/she can confirm you are eligible to complete the Screening Visit 2 assessments. Physical examination - your overall health will be assessed which may include assessment of your general appearance, head, neck, ears, eyes, nose, throat, skin, abdomen, cardiovascular system, respiratory system, extremities, musculoskeletal system and neurological status. • Height and weight • Vital signs (blood pressure, heart rate, breathing rate, temperature) • Blood and urine samples will be collected to test for the following: - Tests to assess your general health

	- Hormone test, if you are a female who may be post-menopausal - Blood samples for testing for Hepatitis B and C. If a positive result is found for Hepatitis B or C, your Study Doctor may inform the local public health authorities, if required by law. - Urine sample to assess general health - Urine pregnancy test (females of childbearing potential) You will be asked to maintain a stable diet and remain on a stable medication regimen for the remainder of the Screening period. You will be contacted by the Study Doctor after he/she has received your laboratory results.
Screening Visit 2 (Day -35 to Day -21) Approximately 2 hours *(At least 10-hr fasted state)*	If your Study Doctor confirms you are eligible to continue to the 2nd Screening visit assessments, you will be asked to arrive in the clinic after having fasted (no food or drink other than water) for **at least 10 hours** before the study visit. At the 2nd Screening visit, the following will occur: • Your Study Doctor will ask questions about your diet, health, and medications; including questions about recreational drugs, alcohol, and tobacco use. • The Study Doctor will discuss a healthy diet based on your diagnosis and individual medical needs and confirm that your diet has been stable for at least two weeks prior to the visit. • You will be asked about the medications you are taking and whether there have been any changes in your medication regimen. • You will have an electrocardiogram (ECG) to measure the electrical activity of your heart. • You will be asked to confirm you have had no food or drink other than water in the **10 hours** before having blood collected at this visit. • You will have a blood test to measure the level of triglycerides and cholesterol (types of fat) in your blood. • Urine pregnancy test (females of childbearing potential) You will be reminded to maintain a stable diet and stable medication regimen for the remainder of the Screening period. You will be contacted by the Study Doctor after he/she has received your laboratory results. If the results are acceptable, you will be asked to return for the 3rd Screening visit.

Screening Visit 3 (Day -21 to Day -1) Approximately 1 hour *(At least 10-hr fasted state)*	If your Study Doctor confirms you are eligible to continue screening, you will be asked to return to the clinic for the 3rd Screening visit. You must have had no food or drink, other than water for **at least 10 hours** prior to coming in for the study visit. At the 3rd Screening visit, the following will occur: • Questions about your diet, health, and medications; including whether you have maintained a stable diet and whether there have been any changes to your medication regimen since the last Screening visit • You will be asked to confirm you have had no food or drink other than water in the **10 hours** before having your blood collected at this visit. • You will have a blood test to measure the level of triglycerides (a type of fat) in your blood. • You may be asked to give a urine sample or have other blood tests repeated if any test results from the 2nd screening visit should be repeated. • Urine pregnancy test (females of childbearing potential) • You may be asked to give a urine sample or have other blood tests repeated if any test results from an earlier Screening visit need to be repeated You will be asked to maintain a stable diet and remain on a stable medication regimen for the remainder of the Screening period. You will be contacted by the Study Doctor after your laboratory results have been reviewed. If the results are acceptable for this study, you will be scheduled for your Day 1 study visit.
TREATMENT & FOLLOW-UP PERIOD	
Study Site Visits (Study Treatment) Day 1 & Week 12 or Week 24 (for those randomized to 24 week dosing) *Approx. 3-4 hours* *(at least 10-hr Fasted State)*	You must abstain from consumption of alcoholic beverages **48 hours** prior to each dosing visit and be in a fasted state for **at least 10 hours** prior to having your blood collected. • Questions about your diet, health, medical history (Day 1 only), and medications • Physical examination may be performed • Weight • Vital signs (blood pressure, heart rate, breathing rate, temperature)

	• An ECG (to measure the electrical activity of your heart) will be done once prior to study drug administration and twice after study drug administration
	• Blood and urine samples will be collected to test for the following (you will be asked to fast for **at least 10 hours** prior to the study visit):
	  ○ Tests to assess your general health, including assessing the level of different types of lipids (fats) in your blood
	  ○ Test to see whether your blood contains any antibodies to the study drug
	  ○ PK blood samples will be collected before and after the study drug has been administered to check the amount of study drug in your blood
	  ○ A portion of your blood will also be collected with your consent and saved for future research purposes
	  ○ Optional genetic testing to see if you have certain gene mutations that might be associated with dyslipidaemia. If you have had this testing previously and the results are available, you may be requested to provide them. This test is optional and will only be completed if you provide separate consent for genetic testing (Day 1 only).
	  ○ Urine sample to assess general health
	  ○ Urine pregnancy test (females of childbearing potential)
	• The dose of ARO-APOC3 or placebo will be given by subcutaneous injection.
	• On the day after you receive the study drug, the Study Doctor or a member of the research team will contact you to see how you are feeling.

Study Site Visits
Week 4, 8, 16, 20 & 28
Approx. 1 hour
(at least 10-hr fasted state)
	• Questions about your diet, health, and medications
	• Physical examination may be performed
	• Vital signs (blood pressure, heart rate, breathing rate, temperature)
	• Blood and urine samples will be collected for the following (you will be asked to fast for **at least 10 hours** prior to your study visit):
	  ○ Tests to assess your general health, including assessing the level of different types of lipids (fats) in your blood
	  ○ Test to see whether your blood contains any antibodies to the study drug (Week 4 and 16). Participants in the 24 week dosing group will have an additional test completed on Week 28.
	  ○ A portion of your blood will also be collected with your consent and saved for future research purposes (Week 4 only).
	  ○ Urine sample to assess general health
	  ○ Urine pregnancy test (females of child-bearing potential)

Study Site Visits
Week 24 & 36
Approx. 2-3 hours
(at least 10-hr fasted state)
	• Questions about your diet, health, and medications
	• Physical examination may be performed
	• Vital signs (blood pressure, heart rate, breathing rate, temperature)
	• Weight
	• An ECG to measure the electrical activity of your heart
	• Blood and urine samples will be collected for the following (you will be asked to fast for **at least 10 hours** prior to the study visit):
	  ○ Tests to assess your general health, including assessing the level of different types of lipids in your blood
	  ○ Test to see whether your blood contains any antibodies to the study drug. Participants in the 24 week dosing group will have this test completed on Week 36.
	  ○ Urine sample to assess general health
	  ○ Urine pregnancy test (females of child-bearing potential)
	
	For participants in the 50mg 24-week dosing group only:
	  ○ PK blood samples will be collected before and after the study drug has been administered to check the amount of study drug in your blood (at the Week 24 visit only).
	  ○ The dose of ARO-APOC3 or placebo will be given by subcutaneous injection only for those randomized to receive the 50mg dose every 24 weeks.
	
	If you are in the dosing groups that are dosed at Day 1 and Week 12, you will also be asked to return to the study site in a **fasted state**

	(at least 10 hours) after approximately 48 hours (for a blood draw only) to assess the level of different types of lipids in your blood (Week 24 only). If you are in the dosing group that is dosed at Day 1 and Week 24; you will also be asked to return to the study site in a fasted state (at least 10 hours) approximately 48 hours before the week 24 visit (for blood draw only).

Study Site Visits
Week 48 or Early Termination
Approx. 1-2 hours
(at least 10-hr fasted state)
	• Questions about your diet, health, and medications
	• Physical examination may be performed
	• Vital signs (blood pressure, heart rate, breathing rate, temperature)
	• Weight
	• An ECG to measure the electrical activity of your heart
	• Blood and urine samples will be collected for the following (you will be asked to fast for **at least 10 hours** prior to the study visit):
	  ○ Tests to assess your general health, including assessing the level of different types of lipids in your blood
	  ○ Test to see whether your blood contains any antibodies to the study drug
	  ○ Urine sample to assess general health
	  ○ Urine pregnancy test (females of child-bearing potential)
	  ○ Test to see whether your blood contains any antibodies to the study drug
	You will also be asked to return to the study site in a **fasted state (at least 10 hours)** after approximately 48 hours (for a blood draw only) to assess the level of different types of lipids in your blood.

After all the Post-Study Treatment visits and procedures are completed, you are done with this study.

If you decide to participate in this research project, the study doctor will inform your local doctor.

Blood Sampling

The maximum amount of blood collected from each participant during the study will be up to 609.5 mL (approximately 30 tablespoons). If you consent to the participate in the additional blood sampling required to determine the level of study drug in your blood at Day 1, Day 2, Week 12 (or Week 24), and 24 hours post-dose from Week 12 (or Week 24), the maximum amount of blood collected from you will be up to 641.5 mL (approximately 32 tablespoons). These samples will be labelled with your anonymized study participant number.

This study includes 3 optional sub-studies which are described below. You do not need to participate in any of the sub-studies in order to participate in the main study. If you decide to participate in any of the sub-studies, you will be asked to sign a separate consent form for each after you have consented to participate in the main study.

Genetic testing (Sub-study)

As an optional part of this study, you may also be asked to undergo additional blood sampling on Day 1 that will be used for genetic research. To learn more about this optional sub study, please refer to the separate Optional Pharmacogenomic Participant Information Sheet and Consent Form. If you do not wish to take part in this optional testing, you can still take part in the main study.study.

Additional Blood Sample for Future Research (Sub-study)

As an optional part of this main research project, you will be asked to undergo additional blood sampling to determine the amount of study drug in your blood on Day 1, Week 4 and Week 12.
A separate Future Research ICF has more detail regarding this. If you do not wish to take part in this optional testing, you can still take part in the main study.

Pharmacokinetic (PK) testing (Sub-study)

In this type of testing, called pharmacokinetics (PK), researchers measure the amount of the study drugs in your blood and determine how the body absorbs, distributes, metabolises (processes), and eliminates (removes) it. For this test to be accurate, it is important you take your study drugs as directed by your study doctor. All participants in the main study will have a PK sample collected before and after each dose of study drug on Day 1 and Week 12. **If you do not allow this particular testing to be done, you may not be able to participate in this research project.**

In addition to this standard PK sampling, you may be asked to participate in additional blood sampling on these days. The total amount of blood drawn at each PK sub-study blood collection visit on Day 1 and Week 12 will be approximately 4 millilitres (less than 1 teaspoon). If you agree to undergo the additional blood sampling, you will be asked to sign a separate Participant Information Sheet and Consent Form . You are not required to participate in the optional PK sub-study in order to be eligible to participate in this study.

4 What do I have to do?

If you decide to be in this research project, there are certain requirements you must follow before, during, and after the research project. Some are listed below, but there could be others that your study doctor will discuss with you:

- You must be able to provide written consent to be in this research project.
- You must tell your study doctor all of the medications that you have been taking for at least 30 days before you take part in the research project. This includes vitamins, minerals, and medications that do not require a doctor's prescription. Some medications are not allowed. Your study doctor will discuss these with you in detail.
- If you are currently taking prescription medication(s) other than to lower your lipid levels, you may need to stop taking them. Your Study Doctor will inform you if any medication should be stopped.
- A stable diet is an important element of this study. The Study Doctor will review and discuss your diet and lifestyle with you during screening and at each study visit.

- You must remain on the specified diet as recommended by the Study Doctor in accordance with local standard of care, throughout the study.
- You must maintain a constant dosing regimen for any lipid lowering and diabetes mellitus therapies and other medications as discussed with the Study Doctor (unless otherwise specified by the Study Doctor for adequate supportive care).
- You must abstain from consumption of alcoholic beverages 48 hours prior to each dosing visit (Day 1 and either Week 12 or Week 24, as applicable).
- You must not drink more than 21 units of alcoholic drinks per week if you are male (not more than 3 units per day) and 14 units per week, if you are female (not more than 2 units per day) until your participation in the study has ended. (1 unit of alcohol = 1 glass of wine (150 mL) = 1 measure of spirits (45 mL) = approx. 360 mL of beer).
- You must abstain from recreational drug use before the screening visit and during the study.
- You must ask your study doctor before you take any new medications during the research project.
- If you decide to take part in this research project, it is very important that you attend all visits as scheduled, including the follow-up visit.

- You must follow all instructions given to you while you are participating in this research project. If you do not, you may be removed from the research project. If you are unsure about what you are supposed to do, ask the study doctor.
- You must not take part in any other studies while you are taking part in this research project.
- You need to inform your Study Doctor about any health problems, accidents or interventions that happen while you are in the study, even if you think it is not important.
- You need to 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 (such as a pain killer for headache).
- You need to advise your Study Doctor before any planned surgery.
- You need to inform the Study Doctor if you decide not to continue in the study. You do not have to give a reason for your decision.
- You must not be pregnant or become pregnant or get someone pregnant during this research project or for 24 weeks after the last time you take the study drug.
- You must use two highly effective forms of contraception (both male and female partners) for the duration of the study.
- You will be given a **Participant Identification Card** if you participate in this study, stating the name of the study and the Study Doctor's contact information. **This card should be carried with you at all times** so that you can contact the Study Doctor at any time and so you can show it to any other doctor, dentist, or pharmacist that you might visit while in this study.

5 Other relevant information about the research project

If you agree to take part in this research project, you will be one of about 320 participants at about 31 study sites globally. This research project is open to male and female participants, aged 18 years old or over, who meet all of the requirements.

Costs

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You will be reimbursed a flat rate of $100 per visit for your time and expenses associated with the research project visit.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with USC Clinical Trials.

7 What are the alternatives to participation?

Your alternatives include not participating in this study and continuing with your current therapy, dietary management and/or other lipid lowering treatments, or participating in a different research project. Your Study Doctor will discuss the risks and benefits of these other options with you. You can also discuss these options with your local doctor.

8 What are the possible benefits of taking part?

You are not expected to receive any direct medical benefits from your participation in the study. The information developed in this study may be used to further develop ARO-APOC3, which may help people with mixed dyslipidaemia in the future.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate, or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

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 treatment. Your study doctor will discuss the best way of managing any side effects with you.

While ARO-APOC3 has already been tested in healthy volunteers and patients with dyslipidaemia, the side effect profile is still being established and reactions that have not been

previously reported may occur. Results from studies so far show no serious side effects in 36 healthy volunteers exposed to the same dose levels being tested in this study. One serious event of pancreatitis (inflammation of the pancreas) was reported in one participant with severe hypertriglyceridemia receiving the 50mg dose of ARO-APOC3, which was determined not to be related to the study drug. The most common (equal or more than 10%) side effects that were reported in study participants include:

- Injection site reactions, including bruising and redness
- Upper respiratory tract infection
- Sore throat
- Headache
- Elevated liver enzymes
- Diarrhoea

There is always a risk of some unexpected serious, life-threatening side effects occurring following the administration of a new experimental drug. It is unknown whether some unexpected serious or life-threatening side effect could occur with ARO-APOC3. You will be monitored closely and treated if they occur.

In addition, an allergic reaction to an experimental drug is possible. If not treated promptly, 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 study includes regular laboratory measurements and assessments in an attempt to identify any possible risks that might develop during the study. The Study Doctor and the sponsor will closely monitor participants for signs or symptoms related to these possible risks during this study, and all ongoing and future clinical studies.

Having a drug injected or blood (or tissue sample) taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated. Please tell the study staff if you have ever fainted during a blood test.

Since the study drug is investigational, there is a risk that other side effects or drug interactions may occur that are unknown. You are requested to inform your Study Doctor about any side effects that you may experience. Even after your participation in the study ends, you are asked to report any serious side effects that you may experience to your Study Doctor.

Allergic Reactions

Occasionally, people have allergic reactions (including life-threatening reactions) when taking any medication. Symptoms of any allergic reaction can include: rash, hives, itching and/or trouble breathing, closing of the throat, swelling of the lips, tongue or face, and rarely death. Immediately get emergency medical care if you have any of these symptoms. Stop taking the study drug and let your study doctor know.

In general, allergic reactions to medicines are more likely to occur in people who already have allergies. If you are allergic to other drugs, foods or things in the environment, such as dust or grass, you should let your study doctor know. Also, if you have asthma, let your study doctor know.

If you have concerns that you are experiencing an allergic reaction, please call 000 or go to your nearest hospital emergency department.

Pregnancy and Breast-feeding

The effects of ARO-APOC3 on unborn children and on newborn babies are not known. Because of this, it is very important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding.

If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least 24 weeks after the last dose of study medication.

Both male and female participants are required to use effective contraception during the course of the research and for a period of 24 weeks after completion of the research project. You should discuss methods of effective contraception with your study doctor.

Sexual abstinence for the duration of the study and for 24 weeks following the last administration of study drug is acceptable only if it is in line with your usual lifestyle. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not considered “true” abstinence and are not acceptable methods of contraception.

Reproductive Risks for Females of Child-Bearing Potential

If you are a sexually active female of child-bearing potential it is very important that you do not become pregnant during this study.

A female 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 may be post-menopausal will have a blood hormone test to confirm menopausal status.

It is not known whether the study drug may cause birth defects and/or foetal deaths and so **females of child-bearing potential and their male partner(s) must use two highly effective forms of birth control** (contraception and male condom) or surgical sterilization during the study and for 24 weeks following the last dose of study drug.

Methods of contraception to be used in combination with a male condom:

- Intra-uterine device (IUD)
- Contraceptive Implant (for example, Nexplanon)
- Vaginal contraceptive ring (for example, NuvaRing)
- Injectable contraceptive
- Oral Contraceptive Pill
- Birth control patch

Methods of contraception that can be used without a male condom:

- Female surgical sterilization (for example tubal ligation, hysterectomy, bilateral oophorectomy)
- Male surgical sterilization (for example, vasectomy)

If you or your male partner are confirmed to be surgically sterile by your Study Doctor, there is no need to consider a further barrier method of birth control.

If you do become pregnant during the study, you must tell the Study Doctor as soon as possible. If you become pregnant during screening and prior to dosing on Day 1, your Study Doctor will withdraw you from the research project and advise on further medical attention. If you become pregnant between Day 1 and the second dose of study drug, you will not receive the second dose of study drug, but you may otherwise continue in the study. Your Study Doctor will refer you for further medical care and you will receive an additional consent form to allow us to monitor your pregnancy until completion and for up to 1 year after you give birth. Please, note that this pregnancy follow up does not constitute medical care, therefore you should continue to follow up your pregnancy with your local doctor.

You must also agree that you will not donate eggs during the study and for 24 weeks following the last dose of study drug.

Reproductive risks for sexually active men

If you are a sexually active man and have any partner who is of child-bearing potential (meaning a female who may become pregnant) **it is very important that you and your partner(s) use two highly effective forms of birth control** (contraception and male condom) or surgical sterilization for the during the study and for 24 weeks following the last dose of study drug.

Methods of contraception to be used in combination with a male condom:

- Intra-uterine device (IUD)
- Contraceptive Implant
- Vaginal contraceptive ring
- Injectable contraceptive
- Oral Contraceptive Pill
- Birth control patch

Methods of contraception that can be used without a male condom:

- Female surgical sterilization (for example tubal ligation, hysterectomy, bilateral oophorectomy)
- Male surgical sterilization (for example, vasectomy)

If you are confirmed to be surgically sterile by your Study Doctor, there is no need to consider a further barrier method of birth control.

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

If a pregnancy occurs, you must report this to the Study Doctor as soon as possible. Your partner will be asked to give consent for her information and her infant's information to be collected for monitoring purposes for up to 1 year after the birth.

You must also agree that you will not donate sperm during the study and for 24 weeks following the last dose of study drug.

Blood Samples

Taking blood from a vein (usually in your arm), may cause local pain, bruising, occasional light-headedness, fainting, and very rarely, infection at the site of the blood draw. A small hollow plastic catheter may be placed in your vein on days when for blood sample collection on days when frequent pharmacokinetic sampling is required.

Hepatitis Testing

The proposed blood tests include a screening test for hepatitis B, and hepatitis C. This is because the study doctors need to know if you have been infected with hepatitis. You will receive information and counselling before the test. If a test shows you have Hepatitis, you will have follow-up counselling and medical advice. If your test results are positive, the study doctors are required by law to notify government health authorities. Signing the consent form means that you agree to have this testing; it will not be done without your consent.

Electrocardiogram (ECG)

For the ECG, you will lie down and have adhesive patches (similar to Band-Aids®) placed on your chest, arms and legs. In some areas, it may be necessary to shave a small spot of body hair so the adhesive patches can be properly placed on your body. Wires from the machine are then attached to the adhesive patches. These wires record your heart's electrical activity. After you have an ECG, you may have mild irritation, slight redness, and itching at the places on your skin where the recording patches are placed.

Loss of Confidentiality:

Because we collect information about you in this trial, there is the possibility that a loss of confidentiality could occur. This means that other people might find out about your participation in this study or about your health and the treatments you are receiving.

Unknown or Unexpected Risks and Discomforts

In addition to the risks listed above, there are risks that are not known or do not happen often when participants take any study drugs, including severe or life-threatening allergic reactions or interactions with another medication. You will be informed in a timely manner, both verbally and in writing of any new information, findings or changes to the way the research will be done that might influence your willingness to continue to take part in this research project.

10 What will happen to my test samples?

The blood samples that you donate will be used to do this research project. You will not get copies of the results. If you decide to stop taking part in this study, your personal information and samples that we have already collected will still be used in the ways that you agreed to when you started in the study. If you do not want this to happen, you should discuss this with your Study Doctor. We will try to destroy samples, but if the samples are no longer linked to you, this might not be possible.

With your consent, a portion of blood collected at the visits specified above, may be used for future research to learn more about the disease, how ARO-APOC3 works and/or the body's response to it. Please see the Optional Future Research Participant Information Sheet/Consent Form for more information.

All samples will be destroyed by internationally accepted means (e.g. incineration) after all study related tests are completed by laboratories experienced in handling and testing samples from research studies.

By taking part in this research project you agree that your samples (or data generated from analysis of these materials) may be provided to Arrowhead Pharmaceuticals, Inc. including vendors contracted with Arrowhead Pharmaceuticals, Inc. to conduct research.

In the event of logistical disruptions (e.g., COVID-related) where a participant does not have direct access to the site, laboratory samples may be collected at an alternative location (e.g., home health, local laboratory) using the central laboratory kit and shipped to central laboratory for analysis.

All blood and urine collected from you will be sent to a Central Laboratory called named Medpace Reference Laboratories (MRL) located in Singapore for analysis, however some blood samples may be sent on to University of Western Ontario Robarts Research Institute in Canada for Genotype testing, Charles River Laboratories in Canada for ADA testing and Keystone Bioanalytical in USA for PK (full and intensive) testing.

Such urine samples and most blood samples will then be destroyed soon after analysis in at Medpace Reference Laboratories (MRL) located in Singapore. These samples and the information collected about you during the study may be used by the Sponsor or its research partners for purposes of this study only. At the conclusion of this study, these samples may be retained in storage by Arrowhead Pharmaceuticals, Inc. for a period up to 10 years. Arrowhead Pharmaceuticals, Inc. is responsible for the destruction of the samples. Any laboratory data will be kept confidential by your study doctor; however, if the tests reveal any unusual findings your study doctor will discuss these with you and your family doctor, if appropriate.

If you withdraw your consent to participate in this research project you are entitled to request that all previously retained identifiable biological samples are destroyed, to prevent further analysis according to national provisions. Samples of your blood and urine obtained for the purpose of this research project will be transferred to Arrowhead Pharmaceuticals, Inc.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the project team about any treatments or medications you may be taking, including non-prescription medications, vitamins or herbal remedies, acupuncture

or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

It may also be necessary for you to take medication during or after the research project to address side effects or symptoms that you may have. You may need to pay for these medications and so it is important that you ask your study doctor about this possibility.

13 What if I withdraw from this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the study at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and date, and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you, or your relationship with the study site.

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant project team members will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the Sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

If you decide to leave the research project, you are advised to:

- Tell your study doctor
- Return to the study doctor for one more visit

14 Could this research project be stopped unexpectedly?

- The Study Doctor may end your participation in this study without your consent for any of the following reasons:The study drug is shown not to be effective
- The results of your screening tests show that you cannot continue in the study
- You become pregnant or begin breast-feeding,
- It is in your best interest
- You do not follow the study instructions given to you by your Study Doctor or study team
- If during the study some of your laboratory results change and your Study Doctor decides that you should no longer be part of the study.
- Decisions made in the commercial interests of the Sponsor or by local regulatory/health authorities

- Unacceptable side effects
- You need additional medication
- You do not consent to continue in the research project after being told of changes in the research that may affect you, or for any other reason.

If your Study Doctor stops you from being in the study or if you decide not to continue, you will be asked to complete a set of tests and procedures that are planned for the end of the study visit.

15 What happens when the research project ends?

A decision will be made in consultation between you and your study doctor about the most appropriate treatment and follow-up arrangements for you when this research project ends.

16 Will the study drug continue to be available after the study is finished?

After completing 48 weeks of treatment in this study and completing the end of study visit, you will be invited to continue in a separate study where the study drug will be provided to you. You will be asked to sign a separate consent for the extension study.

Part 2 How is the research project being conducted?

17 What will happen to information about me?

The study will gather certain personal information about you. This information will be held by Arrowhead Pharmaceuticals, Inc. and its authorised representatives and will be re-identifiable.

Your data will be stored by the Sponsor for a minimum period of 15 years and will be accessed by the Sponsor and its authorised representatives. At the end of this storage period your data will be destroyed.

Your treating doctor/s will be notified of your participation in this study and the exchange of clinically relevant information noted by the trial doctor in the conduct of the trial will occur.

Unless required by law, only your doctor, the study team, the Sponsor and its authorised representatives, the Therapeutic Goods Administration (TGA), health authorities from other countries where the study drug may be considered for approval (or already approved) and the Bellberry Human Research Ethics Committee will have access to data which identifies you by name or from which your identity is otherwise apparent or can be reasonably ascertained.

Your medical files may be reviewed at the hospital (or study doctor's office) or remotely (outside of the study centre) in order to check the information and verify the clinical study procedures, without breaking your confidentiality. If your medical files are reviewed remotely, the records will include your participant code but will not include your name or other directly identifiable information, unless these records will be reviewed directly through the study centre's secure electronic medical records portal.

All personal information will be used only for the purpose of administering your participation in this study and in accordance with the laws governing the protection and privacy of personal information under Australian privacy legislation.

Participants should note that, some data derived from your participation in this study will be sent overseas; the regulatory regimes governing data access and use in other countries may not be the same as those that are in place in Australia. If you have any questions about this, direct them to the Principal Investigator.

By signing the attached consent form, you authorise the release of/or access to this confidential information to the relevant study personnel and regulatory authorities as noted above.

In most cases, you have the right to access personal information collected from you in connection with the study and request corrections of any such personal information that is incorrect.

18 Complaints and compensation

If you are injured as a result of your participation in this trial, you may be entitled to compensation. There are two avenues that may be available to you to seek compensation.

1) Sponsors of clinical trials in Australia have agreed that the guidelines developed by their industry body, Medicines Australia, will govern the way in which compensation claims from injured participants are managed by sponsors.

   However, as guidelines, they do NOT in any way dictate the pathway you should follow to seek compensation. The sponsor is obliged to follow these guidelines.

   These guidelines are available for your inspection on the Medicines Australia Website (www.medicinesaustralia.com.au) under Policy – Clinical Trials – Indemnity and Compensation Guidelines. Alternatively, your study doctor can provide you with a hard-copy of the guidelines.

2) You may be able to seek compensation through the courts.

It is the recommendation of the independent ethics committee responsible for the review of this trial that you seek independent legal advice before taking any steps towards compensation for injury.

19 Who is organising and funding the research?

This research project is being conducted and sponsored by Arrowhead Pharmaceuticals, Inc. IQVIA RDS Pty. Limited, on behalf of the Sponsor, will be conducting the research project in Australia.

The Sponsor may benefit financially from this research project if, for example, the project assists the Sponsor to obtain approval for a new drug.

By taking part in this research project you agree that samples of your blood and urine (or data generated from analysis of these materials) may be provided to the Sponsor.

The Sponsor may directly or indirectly benefit financially from your samples or from knowledge acquired through analysis of your samples.

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to the Sponsor.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to the Sponsor, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

USC Clinical Trials will receive a payment from the Sponsor for undertaking this research project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

20 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC).

The Bellberry Human Research Ethics Committee has reviewed and approved this study in accordance with the National Statement on Ethical Conduct in Human Research (2018) incorporating all updates.

This Statement has been developed to protect the interests of people who agree to participate in human research studies. Should you wish to discuss the study or view a copy of the Complaint procedure with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you may contact the Operations Manager, Bellberry Limited on 08 8361 3222.

21 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 or study coordinators at USC on 07 5456 3965*, or any of the following people:*

After-hours contact: Dr Nischal Sahai - 0492 983 402

In case of an emergency, please seek immediate medical treatment by dialling 000 or attending an emergency department. Please be sure to inform your study doctor at your earliest convenience should you receive treatment by a health care provider outside of the study.

Clinical contact person

Name:	Sharon Rankine
Position:	Clinical Operations Manager
Telephone:	07 5456 3989 / 0401 226 709
Email:	ctcHHM@usc.edu.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name:	Office of the Chief Operating Officer
Address:	University of the Sunshine Coast, Sippy Downs QLD 4556
Telephone:	(07) 5459 4759

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Bellberry Limited
HREC Executive Officer	Operations Manager
Telephone	(08) 8361 3222
Email	bellberry@bellberry.com.au

Main Consent Form

Title	Arrowhead Pharmaceuticals, Inc. / A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Mixed Dyslipidemia
Protocol Number	AROAPOC3-2002
Global Sponsor	Arrowhead Pharmaceuticals, Inc.
Local Sponsor	Arrowhead Australia Pty Ltd
Principal Investigator	Dr Nischal Sahai
Location	USC Clinical Trials L1, 19-31 Dickson Rd, Morayfield, QLD, 4506

Declaration by Participant

I am 18 years of age or older.

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I have been given sufficient time to consider whether or not to participate in this study.

I have had the opportunity to use a legal representative, family support or a friend to help me ask questions and understand the study.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my local doctors, other health professionals, hospitals or laboratories outside this hospital to release information to USC Clinical Trials concerning my personal information (including day/month/year of birth, race and ethnicity), disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I understand that my medical files may be reviewed remotely, and will include my study participant number, unless these records will be reviewed directly through the study centre's secure electronic medical records portal.

I understand the compensation provisions in case of injury during the study.

I understand that there may be risks associated with the treatment in the event of myself or my partner becoming pregnant. I undertake to inform my partner of the risks and to take responsibility for the prevention of pregnancy.

I agree to my urine and blood samples being sent overseas and I am aware that these samples will be disposed of using established guidelines for discarding biohazard waste.

I agree that if I decide to withdraw and leave the research project, the information and data collected about me up to the point when I withdraw may continue to be used.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the research project without affecting my future health care.

I agree to an approved auditor appointed by the Independent Ethics Committee, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.

I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.

I understand my responsibilities as a study participant.

I understand that I will be given a signed copy of this document to keep.

I will receive a summary of the results from the study upon request.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

I consent to my doctor or current healthcare provider being informed about my participation in the study and of any significant abnormal results obtained during the study.

Participant Signature of Consent:

Name of Participant (please print)	_____
Signature	_____ _____
Date	_____ Time _____

[The below witness section will be required for any Participant who is unable to read]

Under certain circumstances *(see Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 at 4.8.9)* a witness* to the informed consent process may be required. If a participant is unable to read, an impartial witness should be present during the entire informed consent discussion.

By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by the participant, and that informed consent was freely given by the participant.

☐ Not Applicable

Name of Witness* to the Informed Consent process (please print) _____

Signature _____ _____

Date _____ Time _____

*Witness is not to be the investigator, a member of the project team or their delegate.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ _____

Date _____ Time _____

†A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation

Title	Arrowhead Pharmaceuticals, Inc. / A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Mixed Dyslipidemia
Protocol Number	AROAPOC3-2002
Global Sponsor	Arrowhead Pharmaceuticals, Inc.
Local Sponsor	Arrowhead Australia Pty Ltd
Principal Investigator	Dr Nischal Sahai
Location	USC Clinical Trials L1, 19-31 Dickson Rd, Morayfield, QLD, 4506

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with USC Clinical Trials.

Name of Participant (please print) _____

Signature _____ _____

Date _____ Time _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

[The below witness section will be required for any Participant who is unable to read]
Under certain circumstances *(see Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 at 4.8.9)* a witness* to the withdrawal of participation discussion may be required. If a participant

is unable to read, an impartial witness should be present during the entire withdrawal of participation discussion.

By signing the withdrawal of participation form, the witness attests that the information was accurately explained, and apparently understood by the participant, and that withdrawal of participation was freely given by the participant.

☐ Not Applicable

Name of Witness* to the Withdrawal of Participation Discussion (please print) _____

Signature _____ _____

Date _____ Time _____

* Witness is not to be the investigator, a member of the project team or their delegate.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ _____

Date _____ Time _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the declarations or witness section must date their own signature.