Informed Consent Cover Page

Study Title:	GENETIC-AF – A **Gen**otype-Directed Comparative **E**ffectiveness **Tri**al of Bu**c**indolol and Toprol-XL for Prevention of Symptomatic **A**trial **F**ibrillation/Atrial Flutter in Patients with Heart Failure
Sponsor:	ARCA biopharma, Inc. 10170 Church Ranch Way, Suite 100 Westminster, Colorado 80021 Phone: 720.940.2100
Study Drug:	Bucindolol hydrochloride (bucindolol)
Comparator:	Metoprolol succinate (Toprol-XL, metoprolol)
IND No.:	118,935
Indication:	Atrial Fibrillation
NCT Number	01970501
Date:	20 April 2022

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title of Study: GENETIC-AF – A **Gen**otype-Directed Comparative **E**ffectiveness **Tri**al of Bu**c**indolol and Toprol-XL for Prevention of Symptomatic **A**trial **F**ibrillation/Atrial Flutter in Patients with Heart Failure

Investigator: *[name of site PI, contact information for PI and study team]*

WHAT ARE SOME GENERAL THINGS TO KNOW ABOUT RESEARCH STUDIES?
This form is called an informed consent document or consent form. It contains a full explanation about the study in which you are being asked to participate. Your participation is voluntary. If you agree to participate after reading this document and asking questions about this study, you will be asked to sign your approval for consent. This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

You are being asked to take part in this research study because you have heart failure (HF), which is when the pumping power of the heart is weaker than normal. You are also currently experiencing atrial fibrillation (AF), which is an abnormal, rapid heart rhythm, or have experienced AF in the last 4 months.

WHO WILL PROVIDE FUNDING?
ARCA biopharma, Inc. is paying *[PI]* and the doctor's research staff to do this study.

WHO WILL BE MY STUDY DOCTOR?
If you decide to take part in the study, *[PI]* will be your study doctor. The study doctor may contact your regular doctor while you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?
This study is being done to compare the effects of bucindolol hydrochloride (bucindolol) to metoprolol succinate (Toprol-XL) on the recurrence of symptomatic AF in people who have HF and a specific genotype (called the $\beta_1$389Arg/Arg AR variant). Your genotype consists of the inherited genes you received from your biological parents; differences between people's genes can affect many things, from how they look to how they respond to medication.

Both bucindolol and Toprol-XL belong to the class of drugs called beta blockers. Beta blockers reduce heart rate and lower blood pressure by blocking norepinephrine and epinephrine (stress hormones) from binding to certain receptors on heart cells known as beta adrenergic receptors.

Bucindolol is an investigational drug, which means it is still being tested in research studies and has not been approved by the US FDA. A previous clinical study in HF patients found that patients who had the $\beta_1$389Arg/Arg AR variant and received bucindolol were less likely to develop AF compared to patients who received placebo (a sugar pill). This effect was not seen in patients who did not have the $\beta_1$389Arg/Arg AR variant. About 50% of people with HF have the $\beta_1$389Arg/Arg AR gene variant.

Toprol-XL is approved in the US by the FDA to treat patients with HF and has been shown to decrease the rate of death and hospitalization in this patient population. Studies have also shown that Toprol-XL decreases the recurrence of AF when given to HF patients who have previously experienced AF. In the US, Toprol-XL is often prescribed for this purpose; however, the FDA has not approved it for this use.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
This study is being conducted in two phases, Phase 2B and Phase 3. In Phase 2B, approximately 200 patients will be enrolled at about 60 institutions in the United States and Canada. Phase 3 will begin after review of the Phase 2B data, unless the study is stopped early for any reason. Approximately 620 patients will be enrolled in Phase 3 at up to 200 institutions in the United States, Canada and other countries around the world. Patients who participate in Phase 2B of the study will continue to receive study drug during Phase 3.

Approximately *[number]* patients will be enrolled at this institution.

HOW LONG WILL I BE IN THIS STUDY?
Patients will receive study drug for a minimum of 27 weeks and possibly as long as 4 years. All patients will continue in the study until the end of Phase 3. It is currently estimated it will take approximately 4 years from the time of study initiation to complete the study.

You can choose to stop taking study drug or stop attending study visits at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in any part of the study, we encourage you to talk with your study doctor first.

WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study, you will be asked to sign this consent form before any study procedures are done. You will visit the study doctor at least 9 times in the first 6 months of the study, then once every 3 months until you stop the study. You may require additional visits to manage your study drug dose, or if you experience an illness during the study. The study visits are described below:

Screening
The Screening Visit will take about 1-2 hours. During this visit, tests and procedures will be completed to see if you qualify for this research study. The study staff will review the results of these tests and procedures with you. If you do not qualify, you will be told why.

At this visit the following procedures will be done:

- Collection of demographic information including date of birth, gender, ethnicity and race
- Collection of medical history (past and present illnesses/diseases, surgeries, smoking history and alcohol use)
- You will be asked about the medications you have taken and are currently taking
    - Some medications should not be taken with either bucindolol or Toprol-XL and some medications are not allowed on the study. You will be asked to discontinue these medications to participate in the study. Your study doctor will tell you which medications need to be stopped, as well as how and when to stop them.
- Records from tests that you have done in the past will be reviewed
    - If the test to measure your left ventricular ejection fraction (LVEF) was not done in the last 12 months, you will undergo additional testing to determine your

LVEF. The LVEF is a measurement of the percentage of blood leaving your heart each time it contracts and is a general measure of a person's heart function.

- Vital signs (sitting blood pressure, heart rate and respiratory rate), weight and height will be collected
- An electrocardiogram (ECG), which shows a tracing of the heart's electrical activity, will be done
- Approximately 2 teaspoons (9 ml) of blood will be collected for lab safety tests and to check for the presence of the $\beta_1$389Arg/Arg AR variant
- If you are female and able to have children, ½ teaspoon (3 ml) of blood will be collected to test for pregnancy; you cannot participate in this study if you are pregnant

If you qualify for the study after completing all of the above, you will be scheduled to return to the clinic for the Randomization Visit within 28 days.

Medtronic Device Substudy
You will be asked to participate in a Medtronic Device Substudy to continuously monitor your heart rhythm using an implanted device.

If you already have an eligible device, that device can be used for the substudy. Eligible Medtronic devices include pacemakers, implantable cardioverter-defibrillators (ICD), cardiac resynchronization therapy (CRT) devices or insertable cardiac monitors (ICM). Only Medtronic devices can be used for the substudy.

If you do not already have an eligible Medtronic device, your study doctor may choose to insert one as part of your regular medical care, or you can choose to have a Medtronic ICM inserted as part of this study after it is confirmed that you qualify for the study. The Medtronic ICM is approved by the US FDA for use in patients with AF. Discuss the best option for you with your study doctor.

If you do choose to have an ICM inserted for this study, the insertion will occur after confirmation that you qualify for the study and up to 7 days after the Randomization Visit. The ICM insertion procedure takes between 5-20 minutes depending on the device model and can be done under local anesthetic. The doctor will make a small incision, creating a pocket the same size and shape of the ICM and place the device just under the skin of your chest to the left of your breastbone.

You do not have to agree to participate in the Medtronic Device Substudy to participate in the study, but there will be a limited number of patients allowed to enroll without a device during Phase 2B of the study.

DNA Bank Substudy
If you agree, a portion of the blood sample collected at Randomization will be kept for future genetic tests; this is called DNA Banking. The DNA Bank may be used in future studies to look at genetic markers for AF or HF, and/or to determine if any specific genetic markers may predict how patients with AF or HF respond to treatment. The results of these tests will not be available to you or your study doctor. Your identity will never be stored with these results; your DNA sample will be identified only by a unique identification number, and every effort will be made to maintain your confidentiality. The sample may be kept for up to 15 years, but you can choose to have the sample destroyed early if you change your mind. You do not have to agree to provide a blood sample for the DNA Bank to participate in this study.

Randomization
The Randomization Visit will take about 1 ½ hours and will take place within 28 days of the Screening Visit.

At this visit the following procedures will be done:

- You will be asked about any changes to your health and medications since your last visit, including questions about your HF and AF symptoms
- You will be asked about the medications you are taking
- A physical exam including your weight and vital signs will be done
- You will complete a short questionnaire about your overall health
- Approximately 2 teaspoons (9 ml) of blood will be collected to measure heart function and to assess two additional genes that may influence the effects of the study drug
    - If you agree, part of this blood sample will be kept in a DNA Bank as described above
- If you are female and able to have children, a urine pregnancy test will be done; you cannot participate in this study if you are pregnant
- An ECG will be done
- If you are participating in the Medtronic Device Substudy, data will be downloaded from your device.

Study Drug Randomization and Dosing
After all of these procedures are complete and if you continue to qualify for the study, you will be randomized to receive either bucindolol or Toprol-XL. Randomized means that the study treatment you receive will be assigned by chance, like flipping a coin. Neither you nor your study doctor will ever know if you are taking bucindolol or Toprol-XL. However, your study doctor can find out what you are receiving in a medical emergency if necessary.

- Bucindolol will be provided in dosage strengths (amounts) of 6.25, 12.5, 25, 50 and 100 mg. Toprol-XL will be provided in dosage strengths of 25, 50, 100 and 200 mg. You will take two capsules a day. If you are assigned to bucindolol, both capsules will contain study drug; if you are assigned to Toprol-XL, one capsule will contain study drug and one will contain placebo (inactive drug). Since you will not know which study drug you have been assigned, it is important that you take both capsules every day as instructed by your study doctor.
- You will begin on a lower dose of study drug and your dose will be increased slowly over several weeks.
- At the Randomization Visit you will receive 1-2 cards of study drug. Each card contains enough study drug for one week. You will take one capsule in the morning and one in the evening, with or without food. If you miss a dose, you may take it up to 6 hours after breakfast or dinner, but do not take two doses at the same time.
- Do not remove a capsule from the card until you are ready to take a dose; do not fill pill containers with the study drug. It is important that you leave all of the unused capsules in the card so your study doctor or nurse can count the number of capsules that you took.

Dose Increases and Decreases
After the Randomization Visit you will return to the clinic 2 or 3 more times over the next 4 to 5 weeks to evaluate your response to the study drug and have your study drug dose increased or decreased as appropriate.

- You will return all study drug cards, including all unused capsules, at these visits and receive enough new study drug cards to last until your next visit.

- You may be counseled on dosing instructions if you do not take the study drug as prescribed.

Week 0 Study Visit / Start of Follow-up Period
The Week 0/Start of Follow-up Visit will take place approximately 3 weeks after randomization. This visit can occur as early as 1 week, or as late as 5 weeks, after you begin the study drug, depending on your medical condition. This visit will take approximately 4 hours.

At this visit the following procedures will be done:

- You will be asked about any changes to your health and medications since your last visit, including questions about your HF and AF symptoms
- Vital signs and weight will be collected
- An ECG will be done on all patients, regardless of whether you entered the study with a regular heart rhythm or AF
    - If you entered the study with AF and this ECG shows that you now have a regular heart rhythm, you will return to the clinic in 24 hours and approximately 1 teaspoon (6 ml) of blood will be collected to measure how much study drug is in your blood. You should not take your study drug on the morning of the blood draw; the study doctor or nurse will remind you not to take your study drug dose on the morning of the blood draw visit. You will be asked to report the approximate times at which you took study drug for the previous 2 days or if you have missed any doses during this time period.
    - If this ECG shows that you have AF, you will undergo a procedure called electrical cardioversion (ECV) to restore your heart's regular rhythm. ECV is a standard treatment for AF during which an electric current is used to reset the heart's rhythm back to its regular pattern using metal paddles or patches applied to the chest. You may need to have the ECV procedure repeated at a later date if the first procedure is not successful.
- You will return all study drug cards, including all unused capsules, and receive enough new study drug cards to last until your next visit. You may be counseled on dosing instructions if you do not take the study drug as instructed.
- If you have a regular heart rhythm at the end of this visit (with or without having undergone ECV) you will be provided with a Transtelephonic Monitoring (TTM) device and instructed on its use as described below.
- Your heart rhythm will be assessed again on the day after this visit either in the clinic with an ECG or at home using the TTM device.

Transtelephonic Monitoring (TTM)
If you have a regular heart rhythm at the end of the Week 0/Start of Follow-up Visit (with or without having undergone ECV), you will be given a TTM device and instructed on its use (if you have AF at Week 0 and the ECV does not result in regular heart rhythm you will not participate in TTM monitoring). The TTM device is used to record your heart rhythm and to send that information via telephone to the study's Receiving Center for review by a study Cardiologist and entry into the study database.

On the day after the Week 0 visit, you will use the TTM device to collect a single recording of your heart rhythm at least 24 hours after your Week 0 ECV, if applicable.

You will use the TTM device to collect <u>TWO</u> recordings of your heart rhythm, at least 10 minutes apart at the following time points:

- At 4-week intervals during the 24-week Follow-up Period of the study, beginning at Week 2. The TTM recording and transmission schedule is as follows:
    - Week 2, Week 6, Week 10, Week 14, Week 18, Week 22
- Any time you experience symptoms of AF or Atrial Flutter; within 2 hours of onset (up to Week 24)

To perform a recording you will hold the TTM device (about the size of a deck of cards) against your bare chest and press the RECORD button for two seconds until an audible tone is heard, then release. Then you will hold as still as possible for approximately 60 seconds. The recording is complete when a 'phone ringing sound' is heard from the TTM device. You will then wait at least 10 minutes, and perform a second recording without deleting the first from the TTM device (except on Day 1 where only a single TTM recording is required). When the second recording is complete, you will call the Receiving Center using a toll-free contact number to transmit the data. The phone technician will ask you some questions about the symptoms you have been experiencing, and then will ask you to transmit the TTM data. The technician may not be able to tell you about your recordings, but will contact your study doctor if it is suspected that you have an abnormal heart rhythm.

24-Week Follow-up Period: Weeks 4, 8, 12, 16, 20 and 24
During the 24-Week Follow-up Period of the study, you will be asked to return to the clinic every 4 weeks. These visits will take approximately 1 hour.

At these visits, the following procedures will be done:

- You will be asked about any changes to your health and medications since your last visit, including questions about your HF and AF symptoms
- Vital signs and weight will be collected
- You will complete a short questionnaire about your overall health (Weeks 12 and 24 only)
- Blood sample collection:
    - Approximately 2½ teaspoons (11.5 ml) of blood will be drawn for lab safety tests and to measure heart function (Weeks 4, 12 and 24 only)
    - Before your morning dose of study drug, approximately 1 teaspoon (6 ml) of blood will be drawn to measure the amount of study drug in your blood. You will be asked to report the approximate times you took your study drug dose for the previous 2 days or if you have missed any doses during this time period. The study doctor or nurse will remind you not to take your study drug dose prior to the visit. (Weeks 4 and 12 only)
- If you are participating in the Medtronic Device Substudy, data will be downloaded from your device (Weeks 12 and 24 only)
- An ECG will be done.
- You will return all study drug cards, including all unused capsules, and receive enough new study drug cards to last until your next visit. You may be counseled on dosing instructions if you do not take the study drug as instructed.
- You will return the TTM device, if applicable (Week 24 only)

Treatment Extension Period
After the Week 24 Visit, you will enter the Treatment Extension Period of the study and return to the clinic every 12 weeks. These visits will take approximately 1 hour. You will remain in the Treatment Extension Period and continue to receive study drug for up to 4 years.

At the Treatment Extension Visits, the following procedures will be done:

- You will be asked about any changes to your health and medications since your last visit, including questions about your HF and AF symptoms
- Vital signs and weight will be collected
- Approximately 1 ½ teaspoons (6.5 ml) of blood will be collected for lab safety tests
- If you are participating in the Medtronic Device Substudy, data will be downloaded from your device
- An ECG will be done
- You will return all study drug cards, including all unused capsules, and receive enough new study drug cards to last until your next visit. You may be counseled on dosing instructions if you do not take the study drug as instructed.
- You will be asked to contact your study doctor or nurse if you notice any new or worsening AF symptoms during the treatment extension period. You may also be asked to provide a blood sample to measure your heart function.

End of Study Visit
When the study ends, you will be asked to return to the clinic for a final study visit that will take approximately 1 hour.

At the End of Study Visit, the following procedures will be done:

- You will be asked about any changes to your health and medications since your last visit, including questions about your HF and AF symptoms
- Vital signs and weight will be collected
- Approximately 1 ½ teaspoons (6.5 ml) of blood will be collected for lab safety tests
- If you are participating in the Medtronic Device Substudy, data will be downloaded from your device
- An ECG will be done.
- You will return all study drug cards, including all unused capsules.
- Your study doctor may prescribe a different medication for you.
- You will be contacted approximately 3 days after this visit to check on your health status and medications
- You will be contacted yearly to check on your health status

Early Discontinuation
If you stop taking the study drug, you will be asked to return to the clinic and complete an End of Treatment Visit. All of the procedures described above for the End of Study Visit will be completed.

After you have stopped the study drug, will be asked to remain in the study and complete all of the regularly scheduled visits described above. If you do not wish to continue in the study after stopping study drug, you will return to the clinic for an End of Study Visit as described above and then will be contacted yearly to check on your health status.

WHAT ARE THE RISKS OF THE STUDY?
The possible risks and/or discomforts associated with treatments and procedures described in this consent form are detailed below. There may be side effects that are not known at this time.

<u>Bucindolol and Toprol-XL</u>
Bucindolol is an investigational drug and is not approved by the US FDA for the treatment of HF or AF. Toprol-XL is FDA-approved for the treatment of HF but not for AF. Hospitalization,

mortality and other HF outcomes will be monitored carefully by an independent safety board to assess potential risk.

Bucindolol and Toprol-XL are both in the beta blocker class of drugs. Beta blockers should not be given to patients with pre-existing second or third degree heart block; sick sinus syndrome arrhythmias; very slow heart rate (severe bradycardia), unless controlled by a permanent pacemaker; or cardiogenic shock or decompensated HF requiring the use of IV inotropic medication (medication that changes the strength of heartbeats).

Remember to talk to your doctor before stopping your study drug. Stopping beta blockers quickly can result in worsening angina (chest pain), heart attack or irregular heartbeat.

Toprol-XL may cause some, all, or none of the side effects listed below.

- tiredness
- dizziness
- depression
- shortness of breath
- slow heart rate (bradycardia)
- low blood pressure (hypotension)
- diarrhea
- itchy skin (pruritus)
- rash
- worsening angina
- heart attack (myocardial infarction)
- worsening HF
- worsening of the heart's ability to send electrical impulses (AV block)
- accident and/or injury

Bucindolol may cause some, all, or none of the side effects listed below.

- fatigue
- dizziness
- weight gain
- diarrhea
- joint pain (arthralgia)
- high blood sugar (hyperglycemia)
- stiff muscles (hypertonia)
- low blood cells (anemia)
- back pain
- slow heart rate (bradycardia)
- lazy eye (amblyopia)
- sinus infection (sinusitis)
- high uric acid level in blood (hyperuricemia)

Prior to starting bucindolol, patients should not be fluid overloaded (too much fluid in the tissues), as this is a symptom of worsening HF. Patients with a history of bronchial asthma or related bronchospastic conditions, especially those taking bronchodilators, should not take bucindolol. Patients with a history of severe anaphylactic reactions (severe allergic reactions that start quickly and may result in death) should not take bucindolol. There is little information about the use of bucindolol in patients with moderate to severe hepatic (liver) or severe renal (kidney) problems. Therefore, the use of bucindolol in these patients is not recommended.

<u>Cancer History</u>
In a previous bucindolol HF study, there was a higher number of patients in the bucindolol group who had a history of pre-cancerous tumors and/or cancer at the time they were enrolled (prior to receiving drug) compared to patients in the placebo group. At the end of the study, there were still more bucindolol patients with pre-cancerous tumors and/or cancer than placebo patients. You will be asked about your cancer history before you enter this study, and your health will be monitored thorough out the study. If you have a history of cancer that was treated recently or has not been treated, you may not be eligible for this study.

Implanted ICM Device and Device Data Download
Risks associated with the ICM and implant procedure include swelling, redness or irritation at the implant site; infection at the implant site, or movement of the device.

Participating patients will have their device data downloaded periodically during the study. The download is painless and is done by placing a small box (about the size of a pager) over the device and waiting while the information is transmitted. There is no risk since this procedure only transmits data, device settings will not be changed by the transmission process.

Electrical Cardioversion (ECV)
ECV is a standard treatment for AF to reset the heart's rhythm back to its regular pattern. During this procedure, an electric current is directed to the heart using metal paddles or patches applied to the chest wall. ECV is a non-invasive therapy which takes a few minutes to complete. You will typically receive medication to control pain and cause relaxation. In some cases, the procedure may be repeated if the heart rhythm remains abnormal. Risks include slight reddening or irritation of the skin where the electrical energy was applied, a reaction to medications given for the procedure, worsening of your irregular heartbeat, or in rare cases, a blood clot.

The cardioversion may or may not require the performance of a transesophageal echocardiogram (TEE), which involves passing a long, thin, flexible instrument down the throat to briefly look at the heart and how it is functioning. Possible risks associated with a TEE include, but are not limited to, breathing problems and damage to the esophagus.

Standard ECG
An electrocardiogram (ECG) shows the electrical tracings of your heart. You will be asked to lie down and remain still for a short period. Electrode patches will be attached to your arms, legs and chest. The ECG is painless. There is no risk of shock since this procedure only records electrical activity and does not send out electricity. Some patients may have itching, bruising, rash, or irritation at the spots where the patches were placed.

Transtelephonic Monitoring (TTM)
The TTM device records your heart rhythm; you will need to hold the device up to your bare chest for about 60 seconds. Recording your heart rhythm with the TTM device is painless. There is no risk of shock since this procedure only records electrical activity and does not send out electricity.

Blood Samples
Possible side effects from drawing blood include faintness, inflammation of the vein, mild pain, bruising, irritation, redness, or bleeding at the site of the puncture. In rare cases, you may get an infection.

Genetic Testing
Genetic testing will be done to test for the $\beta_1$389Arg/Arg AR variant as well as for two other genes that could influence the effects of the study drug. In addition, if you agree to participate in the DNA Banking Substudy, a portion of the blood sample drawn at the Randomization Visit will be kept and potentially used in future genetic tests.

Since these are genetic tests, there is a potential risk for loss of confidentiality. Every effort will be made to protect your confidential information, but this cannot be guaranteed. Information from which you may be personally identified will be maintained in a confidential, secure location, accessible only by authorized members of the study team, and will not be disclosed to third

parties except as described in this consent form, with your permission, or as may be required by law.

In the US, The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:

- Health insurance companies and group plans may not request genetic information from this research;
- Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premiums;
- Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Reproductive Risks for Females

You may not take part in this study if you are female and pregnant, think you are pregnant or trying to get pregnant. If you are pregnant, there may be risks to you and the fetus that are not known at this time. If you are a woman who is able to get pregnant, pregnancy tests will be done.

If you are sexually active, you must agree to use appropriate contraception for as long as you are taking the study drug. Medically acceptable contraceptives include:

- Surgical sterilization (such as a tubal ligation or hysterectomy)
- Approved hormonal contraceptives (such as birth control pills, patches, implants or injections)
- Barrier methods (such as a condom or diaphragm) used with a spermicide
- Intrauterine device (IUD), or
- Exclusive sex partner who has been surgically sterilized or a same sex partner.

Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you become pregnant during this study or if you have unprotected sex, you must inform your study doctor immediately. If you become pregnant you should stop taking study drug; your study doctor will discuss the risks to you and your fetus.

In addition, there may be uncommon or previously unknown problems that might occur. You should report any problems you have to the study team.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. The information that is learned from this study may benefit other people with the same condition as yours and may advance medical understanding of abnormal heart rhythms. You may benefit from being evaluated at regular intervals, as required by the study visit schedule.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?

You do not have to participate in this study. You can get treatment or care for your illness even if you are not in a research study. Your alternative choices are to continue your current treatment as is with no change. Other alternatives may include drug therapy to treat AF, catheter ablation procedure, an ablation of the AV node (cluster of cells between the atria and ventricles that slows the electrical current as it passes to the ventricles) followed by implantation of a permanent

pacemaker, or an open heart operation. Your abnormal heart rhythm may also be treated with a pacemaker or other device that can activate when your abnormal heart rhythm occurs. Each of these treatments are available outside of the study and each has its own risks and benefits. You should think about all of your choices and talk with your doctor about them before you decide if you will take part in this study.

WHAT PERSONAL HEALTH INFORMATION ARE YOU ASKING PERMISSION TO GET FROM MY MEDICAL RECORD?
By signing this form, you authorize access to your medical record for study purposes.

What information may be used and given to others?
The study team will look at your personal and medical information. For example:

- Past and present medical records
- Research records including phone calls made as part of this research
- Records about your study visits
- Information gathered for this research about:
    - Physical exams
    - Laboratory, x-ray, and other test results
    - Records about procedures and implantable devices you have or receive

Who may use and give out information about you?
The study doctor and staff.

Who will get this information?
The Sponsor of this research, ARCA biopharma, Inc. "Sponsor" means any persons or companies that are working for, or with, the Sponsor, or are owned by the Sponsor.

Your information may be given to:

- The US Food and Drug Administration (FDA), Department of Health and Human Services agencies, Health Canada and other governmental agencies
- The Review Board for this institution who reviewed and approved this study

Why will this information be used and/or given to others?

- to do the research
- to study the results
- to see if the research was done correctly

If the results of this study are made public, information that identifies you will not be used.

If you want to participate in this study, you have to sign this authorization to allow access to your medical records. If you choose to not sign it, you are still able to receive medical treatment not related to the study. If you do sign it, you can change your mind later by writing a letter that states you are taking back your permission. Mail the letter to *[Address]* or you can send us an email at *[email address]*. Stopping your authorization will prevent sharing of information in the future, but will not affect any information that has already been shared.

Research information collected about you might be put in your medical record. It is possible that you may not be able to see some of the research study information that has become part of your medical record until the entire research study is over.

The permission you give us to access your medical record will last until the end of the study. You will be given a copy of this authorization.

If the results of this study are made public, information that identifies you will not be used.

HOW WILL MY PRIVACY BE PROTECTED?
We will not use your name or your identity for publication or publicity purposes. Wherever possible, study records that identify you will be kept confidential and you will not be identified by name, address, telephone number, or any other direct personal identifier in study records disclosed outside of [*INSTITUTION/HEALTHCARE PROVIDER]*.

Your entire medical record will be reviewed by the Sponsor and may be reviewed by the US FDA, Health Canada, Health Authorities, Government agencies, or any other applicable agency for the purpose of confirming the accuracy of the research data.

A copy of this consent form will go into your medical record. This will allow the doctors caring for you to know what study medications or tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study.

A description of this clinical study will be available on http:www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE THE COSTS TO ME IF I PARTICIPATE IN THIS STUDY?
ARCA biopharma, Inc. will provide the study drug free of charge for your use in this study as well as pay for any tests and procedures that are required for this study but are not considered to be part of your routine medical care or medically indicated for your condition.

(Select the best option regarding device reimbursement for the substudy, based on your site contract:)
Sponsor pay option:
ARCA biopharma, Inc will also pay for the cost of the ICM, implant procedure and removal procedure, for patients participating in the Medtronic Device Substudy.

Insurance pay option:
For those patients participating in the Medtronic Device Substudy: new ICMs are approved for people with AF but are not always considered necessary, so these cost may be denied by your insurance provider. If the claim is denied, Medtronic (the device manufacturer) will provide your doctor with guidance on how best to file the claim. If the claim is rejected twice, then Medtronic has agreed to pay for the ILR. New therapeutic devices (e.g., pacemakers) are considered standard of care and will not be reimbursed by Medtronic.

You may wish to contact your insurance representative to discuss costs further before making your decision about participating in the study.

You and/or your insurance provider will be responsible for all costs related to your routine medical care, which is care you would have received whether or not you were part of this study.

WHAT ABOUT COMPENSATION?
You will not be paid for participation in this study *[OR]* You will be reimbursed up to $_____ for your expenses related to your participation to cover your parking, gas, and time.

WHAT IF I AM INJURED?
Immediate necessary medical care is available at *[medical center]* in the event that you are injured as a result of your participation in this research study.

If you are injured as a direct result of any properly performed procedure (carried out according to the protocol), the Sponsor will pay for reasonable costs related to your treatment that is not covered by your health insurance. Treatment must be authorized by the study doctor except in the event of an emergency (in which case the study doctor should be notified as soon as possible). Payment for lost wages, disability, discomfort, etc. due to injury is not available. Further information regarding medical treatment, reimbursement, or a research related injury can be obtained from [*insert name here*]. By signing this form you do not give up any of your legal rights.

If you have questions about this study, or have a research related injury or illness claim, you should contact the study doctor at the phone number listed on page 1 of this form. If you have any questions regarding your rights as a research patient, you may contact the Ethics Committee/Institutional Research Office at: [*name and contact information of Ethics Committee/Institutional Research Office*]

For questions about the study or research-related injury, contact Dr. *[PI]* at [*phone number here with area code*] during regular business hours or at [*PI's 24-hour number with area code*] after hours and on weekends and holidays.

WHAT IF I WANT TO STOP BEFORE MY PART IN THE STUDY IS COMPLETE?
You can stop taking study medication or withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped. If you withdraw your participation, no new information will be collected but we will use data that has already been collected.

If you need to stop study drug for any reason during the study, or if you decide to stop the study, you will be asked to complete an End of Treatment/Study Visit as described above. Remember to tell your study doctor before you stop the study drug because stopping the drug suddenly may harm you. You must return all study drug cards (used and unused) and the TTM device when you stop the study.

NEW FINDINGS
If important new findings come up that might change your decision to be in this study, you will be given information about those findings as soon as possible. If you choose to stay in the study, you may be asked to sign a new version of the consent form.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have complaints, concerns or suggestions about the research, contact Dr. *[PI]* at *[PI's number with area code]* during regular business hours and at *[PI's 24-hour number with area code]* after hours or on a weekend or holiday.

For questions about your rights as a research participant, contact *[the REB name and contact number]*

STATEMENT OF CONSENT

The purpose of this study, the procedures to be followed and the study's risks and benefits have been explained to me. I have been allowed to ask questions and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to talk about problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form (or it has been read to me) and I agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a copy of this consent form and that a copy of this form will become part of my medical record.

I authorize the use and disclosure of health information from my medical record to the people or groups identified in this consent form for the purposes described in this document.
I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

OPTIONAL Medtronic Device Substudy:

I wish to participate in the Medtronic Device Substudy as described in this consent form.

☐ **YES** ☐ **NO**

OPTIONAL DNA Bank Substudy:

I wish to participate in the collection of a blood sample for the DNA Bank Substudy. I understand that I can change my mind at any time, and that withdrawing this sample will not affect my participation in the study.

☐ **YES** ☐ **NO**

_____ _____
Signature of Research Patient Date

_____
Printed Name of Research Patient

_____ _____
Signature of Research Team Member Who Obtained Consent Date

_____
Printed Name of Research Team Member Who Obtained Consent

This section should only be completed when a patient requests or has a need to prematurely and permanently discontinue study participation.

Premature Discontinuation of Study Participation & Agreed Method of Contact after Discontinuation

Please note agreed method of contact if patient wishes to discontinue study participation.

***To be filled in by the investigator or delegate and signed by the patient*:**

Protocol: BUC-CLIN-303 Patient Initials: _____

Site Number: _____ Patient ID: _____

Date of discontinuation of study drug: ……

Agreed method of contact:

- ☐ I do not want to continue treatment or attend further follow-up visits. I agree that you may continue to contact me and have access to my medical records to assess the status of my health.
- ☐ I do not want to continue treatment, study visits or follow up. I withdraw my consent to further participation in the study.

_____ _____
Signature of Patient Date of Signature

_____
Printed name of Patient (BLOCK CAPITALS)

_____ _____
Signature of witness Date of Signature

_____
Printed name of witness (BLOCK CAPITALS)