

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

**Title:** A Randomized, Multicountry, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Atrasentan on Renal Outcomes in Subjects with Type 2 Diabetes and Nephropathy SONAR: Study Of Diabetic Nephropathy with Atrasentan

**Protocol No.:** M11-352

WIRB® Protocol #20131336

00091442

**Sponsor:** AbbVie Inc.

**Investigator:** Karen L Hall, MD

Family Medicine at Main

1707 North Main Street

Gainesville, Florida 32609

United States

**Site(s):** Family Medicine at Main

1707 North Main Street

Gainesville, Florida 32609

United States

**STUDY-RELATED**

**PHONE NUMBER(S):** Karen L Hall, MD

352-265-7001 (24 Hours)

**Name of person seeking your consent:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Place of employment & position:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Participant (“Study Subject”) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

## Why is this research study being done?

You have been asked to voluntarily participate in a research study of an investigational study drug called atrasentan in subjects with type 2 diabetes and nephropathy (kidney disease). AbbVie is sponsoring this study. AbbVie is paying the study doctor to perform this study. An investigational study drug is one that has not been approved by the regulatory authorities in your country, such as the U.S. Food and Drug Administration (FDA).

Being in this study does not replace your regular medical care.

The purpose of this study is to evaluate whether or not atrasentan is effective in delaying the worsening of kidney disease by comparing the time to serum creatinine doubling or the onset of end stage renal disease in subjects with type 2 diabetes and kidney disease. Another purpose of this study is to test the safety of atrasentan.

In addition, this study will compare atrasentan with a placebo to see if taking atrasentan is better than taking a placebo. The placebo is a tablet that looks like a drug but has no drug or other active ingredient in it.

Be aware that this form refers to atrasentan and placebo as "study drug."

**What will be done as part of your normal clinical care (even if you did not participate in this research study)?**

You will continue to take your regular renin-angiotensin system (RAS) inhibitor and diuretic medications during the study. The study doctor may adjust the doses of your regular medications before you take the study drug, or while you take the study drug if your symptoms change. Ask the study doctor or study staff if you have questions about this.

**What will be done only because you are in this research study?**

Study Information

This study was designed to enroll approximately 4,148 subjects for scientific, regulatory and ethical reasons; therefore, if the target number of subjects has been enrolled, and you are in screening, there is a possibility that you will not be enrolled.

After Screening, this study has three main periods: a Run-In Period where you will take your regular medications, an Enrichment Period where you will take atrasentan, and a Double-Blind Dosing Period where you will be randomly assigned by chance (like the flip of a coin) to receive atrasentan or placebo (inactive substance that looks identical to atrasentan) once per day.

Procedures

If you agree to be in this study, you will undergo some activities, tests and evaluations to determine if you are eligible for this study.

Tests done only for research purposes will not be evaluated or used to diagnose or treat any of your medical problems. This/these test(s) may need to be repeated if required for your medical care in the future.

At every Study Visit, you will be asked about:

* all prescription and over the counter medications you are taking will be recorded along with any changes in the medications you are taking
* any problems you are having
* any side effects you are experiencing, which may or may not be related to the study
* whether you have made any visits to other doctors or hospitals

Please note that you may be asked to repeat a procedure or test if your study doctor feels it is needed to evaluate your condition.

Screening Period

Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. If you consent and are suitable to participate in the study, the tests and procedures noted in the table in Appendix A will be performed.

If, based on the Screening tests and procedures, you qualify to participate in this study, the study doctor will contact you to let you know and will schedule the first Run-In Visit.

Run-In Period

If you pass Screening, you will be in the Run-In Period for at least 2 weeks and up to 12 weeks. The length of time you are in the Run-In Period will depend on the time necessary to adjust your current ACEi or ARB (RAS inhibitor) and diuretic schedule if needed.

The tests and procedures noted in the table in Appendix A will be performed during this Period.

Enrichment Period

The Enrichment Period will last for 6 weeks. During the Enrichment Period, you will receive 0.75 mg of Atrasentan and will be instructed to take 1 tablet of study drug per day for 6 weeks. This period of the study is an open-label period where you, your study doctor and the sponsor all know that you will be receiving atrasentan.

Tests and procedures noted in Appendix A will be performed.

Double-Blind Dosing Period

Based on the results of the tests and procedures performed during the Enrichment Period, you may or may not continue to qualify to participate in this study. If it is determined that you do not qualify to continue, you will be asked to complete the Premature Discontinuation visit and the Follow-Up (F1) visit.

If it is determined that you continue to qualify, you will enter into the Double-Blind Dosing Period with will last up to 48 months. Tests and procedures to be performed are noted in the table in Appendix A.

At the randomization visit, you will be randomly assigned by chance (like the flip of a coin) to receive either atrasentan or placebo (inactive substance). You will have a 1 out of 2 chance of receiving 0.75 mg of atrasentan once per day and a 1 out of 2 chance of receiving placebo once per day. This period of the study is double-blinded, which means neither you, your study doctor or AbbVie will know to which study group you were assigned. In case of an emergency, your study doctor can find out this information.

You will receive enough supplies of study drug to take at home and be instructed to take 1 tablet of study drug per day, at approximately the same time each day, preferably in the morning.

During the first 2 weeks after randomization, you will receive a telephone call from the study staff.

During this dosing period and between visits, you will have to measure and record your weight weekly at home. At the first visit of the Double-Blind Dosing Period (Randomization), you will receive instructions for measuring your weekly weight.

Premature Discontinuation Visit (PD)

If you permanently stop study drug early, this visit will occur within approximately 9 days after your last dose of study drug. The tests and procedures noted in the table in Appendix A will be performed during this study visit.

**Follow-Up (F1) Visit**

If you have received at least one dose of study drug, this visit will occur 45 days following your last dose of study drug. The tests and procedures noted in the table in Appendix A will be performed during this study visit.

**Post-Discontinuation Visits/Calls**

If you have permanently discontinued study drug during the Double-Blind Dosing Period, you will be asked to continue to attend study visits and have tests and procedures performed as per the study activities table above.

If unable or unwilling to continue attending study visits, you may be asked to be contacted by telephone every 3 months to collect information about current treatment, occurrence of renal (kidney) or cardiovascular (heart) events, and recent lab values.

If unwilling to either come to the study center or receive telephone calls, you will be asked to sign an authorization form to release information from your either medical records or through contacts with your treating physician.

If your study doctor or study staff is unable to contact you or your care-giver for 3 consecutive times, you will be considered as lost to follow-up. For this reason, and where available and permitted by law, your study doctor or study staff designee may obtain information regarding your health status from additional sources, including from national patient registries (e.g., National Death Registries, Cancer Registries, Vital Registries), or any other publicly available sources.

At the end of this form you will be able to indicate if you do not want to allow such follow-up activities.

**You do not have to give your permission for the study doctor or staff to search information about your post-withdrawal status if you don't want to. You can still be in the main study even if you don't want to provide this permission.**

If you agree and later change your mind to not allow any of the follow-up activities to be conducted as described above, you should inform your study doctor in writing and clearly state that you do not wish study staff to engage in these follow-up activities. Please note that any information that has already been collected at the time you withdraw your permission will be kept and, where the law allows, will continue to be used in order to complete the research that has already started.

Subject Responsibilities

In order for this study to provide good information about how atrasentan works in subjects with type 2 diabetes and kidney disease, you will be expected to do the following:

* Follow the instructions of your study doctor including requirements to use an appropriate birth control method for males.
* Come to all your scheduled study visits and procedures.
* Take and store your study drug as instructed and return the unused study drug and/or empty containers to the study doctor's office at each visit.

Do not share your study drug with anyone.

* Keep the study drug and study supplies out of the reach of children and persons of limited ability to read or understand.
* Fill out your dosing cards, FMV collection cards and weight diary completely and honestly, and bring them to the study doctor's office at the appropriate site visit (check the study activities table).
* Do not change any of your type 2 diabetes medications or blood pressure medications or start any new type 2 diabetes medications or blood pressure medications without checking with your study doctor.
* Tell the study staff about any health problems you are having even if you don't think they are important.
* Tell the study staff if you wish to stop being in the study.
* Do not participate in any other research studies during your participation in this study.
* All study supplies provided to you during the study must be returned at the final study visit

In the event of an emergency, dial your local emergency phone number immediately.

If you require emergency care, be sure to tell the emergency care provider about your participation in this study. Contact the study doctor or study staff as soon as possible.

If you have questions about your participation in this study or if you think you have had a study-related injury or reaction to the study drug, or if you have any concerns or complaints about your participation in this study, contact the study doctor at the phone numbers listed on page 1 of this Informed Consent Form.

If you have questions concerning your rights as a research subject, if you are not able to resolve your concerns with the study doctor or study staff, if you have a complaint, or if you have general questions about what it means to be in a research study, you may contact:

Western Institutional Review Board® (WIRB®)

1019 39th Avenue SE Suite 120

Puyallup, Washington 98374-2115

Telephone: 1-800-562-4789 or 360-252-2500

E-mail: Help@wirb.com

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Optional Research Sub-Studies

There are two optional research sub-studies that are in addition to the activities and procedures to which you are being asked to consent for participation in the research portion of the main study.

**Optional 24-Hour Urine Collection Sub-Study**

If you agree to participate in this sub-study, you will be provided with urine collection containers prior to each visit where 24-hour urine is required (visits E1, E5, Yearly and F1 visits). You will be given specific instructions for collection and storage of your 24‑hour urine. You will bring your urine collection to your study visits.

Researchers want to look at your 24-hour urine collection results to learn if your body responds to atrasentan. The specific purposes of this sub-study are:

* To learn about reasons why certain people respond differently to atrasentan
* Finding out more information about how atrasentan and similar drugs work

The optional 24-hour urine collection sub-study will be limited to only 800 subjects; therefore, while you may provide consent to participate, your participation may not be necessary.

**Optional Genetic Sub-Study**

You are also being asked to provide a blood sample to look at your genes, which are often called "DNA." Genes are in your DNA, and they contribute to making you different from anyone else. Some genes influence things like the color of your hair or eyes. Other genes influence the chance that you will get certain diseases.

Researchers may want to look at your DNA to learn if your genes affect their response to the study drug you will be taking, atrasentan. This is called a "pharmacogenetic research sub-study." The specific purposes of this sub-study are:

* To learn about genetic reasons why certain people respond differently to atrasentan
* Finding out more information about how atrasentan and similar drugs work
* Generating information needed for research, development, and regulatory approval of tests to predict response to atrasentan and similar drugs

The study doctor or study staff will take a blood sample of about 1 teaspoon (4 mL) at the Randomization visit for pharmacogenetic research. People who work for AbbVie will purify DNA from your blood sample, and store your DNA in a secure storage space. They will store your DNA sample for up to 20 years after the end of the study, and then AbbVie will destroy your DNA sample.

AbbVie will not use your samples or data generated from those samples for any purpose other than what is described in this form. Your samples and the accompanying data will only be used by researchers at AbbVie or people or companies AbbVie works with. Your samples will not be sold to other people or companies.

If you decide to participate in the genetic sub-study, you can request to have your samples withdrawn at any time by writing to Danielle Poulton at the “site” address on the first page of this form. If you do this, there will be no penalties or loss of benefits, but you will be withdrawn from the genetic sub-study. Once AbbVie is notified, no new research will be started, and your samples will be destroyed unless the FDA requires the sponsor to keep the samples.

However, if the sponsor did any testing before being informed that you changed your mind, the sponsor will not destroy the data generated from your samples and will still use those results.

Are There Any Risks to Participating in the Optional Genetic Sub-Study?

The blood sample will be done at the same time that the blood is taken for the main study. Pain, bruising, bleeding or other discomfort at the blood drawing site have been seen. Fainting or infection at blood drawing site may occur (very unlikely).

There is also a risk that information about you is released without your permission. If information from your records relating to testing of your DNA sample is released, there is a risk that this information could be used in a discriminatory way against you. However, the researchers will take all reasonable steps to protect your records and assure that your name will be kept private, and the chance that this information will be given to someone else who would use it to discriminate against you is very small, and there are laws that protect against misuse of such information. You can find out more about the protection of your information in the section entitled "**Confidentiality**."

Will Being in The Sub-Studies Help Me or Others?

Participating in the sub-studies will not help you. Information from the sub-studies may help researchers come up with new tests or medicines to help others in the future.

Will It Cost Anything to Be in The Sub-Studies?

There will be no cost to you if you agree to participate in either or both of the sub-studies.

Will You Be Paid for Participating in the Sub-Studies?

You will not be paid for your participation in the sub-studies. The sponsor and people or companies working with the sponsor on the sub-studies may use your samples when developing new tests, procedures and commercial products. If this happens, the sponsor does not plan to share any profits with you.

**You do not have to be in the pharmacogenetic sub-study or the 24-Hour Urine Collection research sub-study if you don't want to. You can still be in the main study even if you don't want to be in either or both of the sub-studies.**

**You will be asked to indicate your choice about the sub-studies at the end of this form.**

## How long will you be in this research study?

Your participation in this study will last approximately 4.5 years and may include approximately 32 study visits to the research center.

## How many people are expected to take part in this research study?

This study is being conducted at approximately 800-900 research centers worldwide. Approximately 4,148 subjects with type 2 diabetes and kidney disease will participate in this study.

**What are the possible discomforts and risks?**

Study Drug Risks

Your study doctor will be monitoring you for side effects from atrasentan. It is important that you report any side effects you have had to your study doctor right away. Your study doctor may give you other drugs to help with side effects. If you or your study doctor think that you cannot tolerate the side effects, the study drug may be stopped altogether and you will be withdrawn from the study.

Ask the study doctor for the risks of ACEi or ARB (RAS inhibitors) and diuretics you are taking concomitantly.

Ask the study doctor if you have questions about the signs or symptoms of any side effect you read about in this consent form.

Please tell the study doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think these are related to the study drug.

**Female Reproduction:**

In long-term animal studies abnormal microscopic changes were seen in the female organs (uterus, mammary gland, and ovaries) of rats and dogs. The importance of this for women is not known.

Women should not breastfeed while taking atrasentan. If you are pregnant or nursing a child while receiving atrasentan, there may be risks to your unborn baby or nursing child. Nobody knows what these risks are right now. Some drugs cause premature (early) birth or birth defects.

Birth Defects (Teratogenicity):

Atrasentan is likely to cause birth defects if used by a pregnant female. This information comes from animal studies of atrasentan and other similar medicines. All women must be postmenopausal before entering the study, defined as having no menstrual period in the previous two years. If a woman is less than 50 years old, a blood test will be conducted to check hormone levels to confirm she is not premenopausal. During the study, if any woman somehow becomes pregnant or suspects she is pregnant, she must stop the study treatment and contact her doctor immediately.

Male Fertility:

There may be a risk of developing sterility (the permanent inability to father children) with extended use of atrasentan or other similar drugs. Injury to testicular cells and/or impaired fertility has been linked with the long-term administration of drugs similar to atrasentan in animals. In a study of male rats that were given atrasentan for a 4-month period (at higher doses than you will take) abnormal changes in the tissues of the testes and infertility developed. These changes did not reverse following atrasentan discontinuation in the animals. In a 6-month study of bosentan (a medicine like atrasentan) a decrease in sperm count was seen in 25% of men during treatment. The effect of prolonged administration of atrasentan on development and production of sperm and fertility in humans is not known.

If you are a man who is sexually active with women you should notify any female partner of your participation in this study and should not use this study drug if you or your partner are planning to have a baby. You must agree to use two methods of effective contraception while participating in this study and at least 90 days following completion of your participation or ninety days after your last dose of study drug. All female partners who are not sterilized or post-menopausal must use two methods of contraception. Contraception methods may include: intrauterine device (IUD), hormonal contraceptives (oral, vaginal, parenteral or transdermal) or the following two barrier methods: a male condom and a diaphragm with spermicidal jelly or cream.

You are responsible for informing your partner(s) of the risk and for reporting any pregnancy to your study doctor. If your partner becomes pregnant, an authorization form will be provided to the pregnant partner about known effects of atrasentan on the unborn child and a Consent Form for Pregnant Partners will also be provided to request information about your partner’s pregnancy and the health of the baby at birth. If your partner becomes pregnant during the study you must notify your study doctor immediately.

Sperm donations should not be performed while taking atrasentan and at least 90 days after stopping the study drug.

Because of the possibility of irreversible infertility due to therapy with atrasentan, subjects may desire to seek advice on cryoconservation (freezing) of sperm prior to treatment.

Other Risks:

While in the study, you are at risk for the following additional side effects. These side effects have been identified through past studies in over 2,000 patients with prostate cancer, using doses of atrasentan over 12 times higher than you will be exposed to daily. These side effects will vary from person to person.

Fluid Retention

* Swelling of the legs (most common), arms or face has been seen with the use of atrasentan and other medicines in this family. These findings are important because they can be the first signs of fluid retention and can progress to fluid accumulation in the lungs (heart failure).
* Heart failure has been seen with atrasentan and is potentially a serious condition. Heart failure symptoms may include shortness of breath with daily activities, chest pain and/or swelling (especially of the legs), coughing, feeling tired, and quick/excessive weight gain, (greater than 2 kg [4.4 lbs.] in 2 weeks). It is important for you to report symptoms like these to your study doctor immediately.

Decreases in Blood Pressure

Atrasentan use has been associated with decreases in blood pressure in subjects with diabetes and proteinuria (protein in your urine). Clinically symptomatic decreases in blood pressure have occurred in 2.5% of patients taking atrasentan. You should suspect that your blood pressure is decreased if you feel tiredness at rest or lightheaded especially when getting up quickly from a sitting or lying position. If you experience these symptoms you should report them to your study doctor immediately.

Decrease Blood Cell Count

Red blood cell count decreases have been seen in studies of atrasentan and medicines like it. Low red blood cell count (anemia) has been seen in patients taking atrasentan. Decreases in red blood cell count are usually mild and occur in the first few weeks after starting the medication. Symptoms include feeling tired, loss of energy, dizziness, and pale skin. Alert your study doctor if you experience these symptoms. Your study doctor will be checking your blood cell count as part of the study.

Other Reported Side Effects from Clinical Studies with Atrasentan Have Been:

* dizziness (5.4%)
* infection (4.1%)
* runny/stuffy nose (sinus congestion) (2.1%)
* headache (18.8%)
* rash (3%)
* ocular hyperaemia (irritation and redness of the thin membrane covering the eye) (1.1%)

Allergic Reactions:

Sometimes people have allergic reactions to drugs. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic reaction (anaphylaxis) are:

* a rash
* having a hard time breathing
* wheezing
* a sudden drop in blood pressure (making you feel dizzy or lightheaded)
* swelling around the mouth, throat, or eyes
* a fast pulse
* sweating

Inform the study doctor if you have had any allergic reaction to drugs in the past or if you know that you have an allergy or are sensitive to any other drugs like atrasentan.

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during this study.

Side Effects from Blood Drawing:

Pain, bruising, bleeding or other discomfort at the blood drawing site have been seen. Fainting or infection at blood drawing site may occur (very unlikely).

Risks Associated with Placebo

Some people in the study will get placebo instead of atrasentan. Receiving placebo is the same as not receiving any active treatment. Please ask the study doctor or study staff if you have any questions about placebo.

Unknown Risks

You might have side effects or discomforts that are not listed in this form, which may include your type 2 diabetes and kidney disease getting worse. There may also be risks and side effects to you that are currently unknown. Tell the study doctor or study staff right away if you experience any side effects or discomforts.

**What are the possible benefits to you?**

You may or may not receive any direct medical benefit from being in this study. Your condition may get better, it may get worse, or it may stay the same.

## How could others possibly benefit from this research study?

The information that is obtained during this study may be useful scientifically and thus be helpful to others with the same condition in the future.

## How could the researchers benefit from this research study?

The sponsor is paying the University of Florida for conducting this research study. In general, presenting research results helps the career of a scientist. Therefore, the study doctor may benefit if the results of this study are presented at scientific meetings or in scientific journals.

**If you choose to take part in this study, will it cost you anything?**

The study drug, Atrasentan and the Placebo will be provided at no cost to you while you are participating in this study.

The Sponsor will pay for all medical services required as part of your participation in this study.

There will be no cost to you. If you receive a bill related to this study, please contact Karen Hall MD at 352-265-7001 or Danielle Poulton at 352-265-9552.

All other medical services provided to you that are not directly related to the study will be billed to you or your insurance company. You will be responsible for paying any deductible, co-insurance, and/or co-payments for these services, and any non-covered or out-of-network services.

Some insurance companies may not cover costs associated with studies. Please contact your

insurance company for additional information.

**Will you be paid for taking part in this research study?**

You will not be paid for your participation in this study. You will receive reimbursement only for the visits you have completed up to a maximum of **$38** per visit, totaling a maximum of $1216. Reimbursement will be paid **after each study visit**. If you have any questions regarding your reimbursement for participation, please contact the study doctor at the telephone number listed on page 1 of this consent document.

**What if you are injured because of the research study?**

If you are injured as a direct result of your participation in this study, the Sponsor will pay for all reasonable and necessary medical expenses required to treat your injury, as long as:

1. The injury occurs during your participation in the study.
2. The injury results directly from the Study Product or Study-required procedures.
3. The injury is not the result of the natural course of your disease or some other underlying condition.
4. The study doctor and/or study staff has followed the study procedures.

The Sponsor and the Principal Investigator will determine whether your injury is related to your participation in this study.

No additional compensation is offered. The Principal Investigator and others involved in this study may be University of Florida employees. As employees of the University, they are protected under state law, which limits financial recovery for negligence.

Please contact Karen Hall MD at 352-265-7001 if you experience an injury or have questions about any discomforts that you experience while participating in this study.

**What other choices do you have if you do not want to be in this research study?**

You do not have to participate in this study to get help for your condition. Alternatives to this study for the treatment of your diabetes and kidney disease may include drugs already approved or being used for the treatment of this disease such as diuretics or RAS inhibitors. Your study doctor can discuss the risks and advantages of these alternative treatment methods with you. In addition, you may discuss your options with your regular healthcare provider.

New Information

You will be informed in writing in a timely manner and will be asked to sign a new (revised) informed consent if new information that could affect your willingness to continue participation in this study becomes available.

**Do you have to be in this study?**

Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

If you leave this study for any reason, please contact Karen Hall, MD at 352-265-7001 or Danielle Poulton at 352-265-9552. They will tell you how to stop your participation safely.

## Can you be withdrawn from this research study?

Your study doctor may end your participation in the study at any time without your consent if:

* she believes that it is in your best interest, or
* if you are unable to follow the requirements of the study.

In addition, AbbVie may end your participation in the study at any time without your consent.

When you withdraw from the study for any reason, all study drug(s) and study drug bottles, including those unused and empty must be returned to the study site to complete the Premature Discontinuation visit and the Follow-Up (F1) visit.

If you do not sign this form you cannot be in the study.

**AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES**

The Privacy Rule of the federal Health Insurance Portability & Accountability Act (HIPAA) is a law that protects the confidentiality of your personal health information. This Authorization describes your rights and explains how your health information will be used and disclosed.

If you agree to participate in this study, the study doctor will create, collect, and use private information about you and your health. This information is called protected health information or PHI. In order to do this, the study doctor needs your authorization. The following section describes what PHI will be collected, used and shared, how it will be collected, used, and shared, who will collect, use or share it, who will have access to it, how it will be secured, and what your rights are to revoke this authorization.

* Your protected health information may be collected, used, and shared with others to determine if you can participate in the study, and then as part of your participation in the study. This information can be gathered from you or your past, current or future health records, from procedures such as physical examinations, x-rays, blood or urine tests or from other procedures or tests. This information will be created by receiving study treatments or participating in study procedures, or from your study visits and telephone calls. More specifically, the following information may be collected, used, and shared with others:

When you are a subject, we will collect health information about you that also includes your name, address, telephone number, or other data that could identify the health information as yours. Under HIPAA, this health information is protected and can't be used without your permission, unless otherwise permitted by law. If you sign this authorization, you are giving permission for AbbVie to use and disclose your personal health information as described below

* Your personal health information could include
  + results of tests and procedures such as physical examinations and results of blood and tissue testing
  + your biological samples
  + information about your medical conditions and history
  + The collected information may contain your name, address, telephone number, social security number, health plan number, date of birth, medical record numbers, dates relating to various medical procedures, and/or other identifying information.

This information will be stored in locked filing cabinets or in computers with security passwords.

Some of the information collected could be included in a "limited data set" to be used for other research purposes. If so, the limited data set will include only information that does not directly identify you. For example, the limited data set cannot include your name, address, telephone number, social security number, or any other photographs, numbers, codes, or so forth that link you to the information in the limited data set. If limited data sets are created and used, agreements between the parties creating and receiving the limited data set are required in order to protect your identity, confidentiality, and privacy.

Your PHI may be collected, used, and shared with others to make sure you can participate in the research, throughout your participation in the research, and to evaluate the results of the research study. More specifically, your PHI may be collected, used, and shared with others for the following study-related purpose(s):

* To evaluate whether or not atrasentan is effective in delaying the time to serum creatinine doubling or the onset of end stage renal disease in subjects with type 2 diabetes and kidney disease and to test the safety of atrasentan.

Once this information is collected, it becomes part of the research record for this study.

Only certain people have the legal right to collect, use and share your research records, and they will protect the privacy and security of these records to the extent the law allows. These people include:

* the study doctor, and research staff associated with this project.
* other professionals at the University of Florida or Shands Hospital that provide study-related treatment or procedures
* The University of Florida Institutional Review Board

Your PHI may be shared with:

* the study sponsor *AbbVie*
* United States and foreign governmental agencies who are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections
* Government agencies who are responsible for overseeing public health concerns such as the Centers for Disease Control and federal, state and local health departments
* Western Institutional Review Board®
* Your insurance company for purposes of obtaining payment

We will keep your personal health information as confidential as possible. We will only share it as described above or if required or permitted by law. It is not likely your information will be given to others without your permission. However, once your information leaves **the University of Florida**, we can't control how it is used, and it will no longer be covered by the HIPAA Privacy Rule.

Otherwise, your research records will not be released without your permission unless required by law or a court order. It is possible that once this information is shared with authorized persons, it could be shared by the persons or agencies who receive it and it would no longer be protected by the federal medical privacy law.

Your PHI will be used and shared with others for 50 years unless you revoke (cancel or withdraw) authorization sooner, since information collected for research purposes continues to be analyzed for many years. If the results of the study are published your identity will remain confidential.

You are not required to sign this consent and authorization or allow researchers to collect, use and share your PHI. Your refusal to sign will not affect your treatment, payment, enrollment, or eligibility for any benefits outside this research study. However, you cannot participate in this research unless you allow the collection, use and sharing of your protected health information by signing this consent and authorization.

You have the right to review and copy your protected health information. However, we can make this available only after the study is finished.

You may have the right to access, correct and make a copy of your medical and/or clinical study records as allowed by applicable privacy laws. You may ask to see your records by requesting such records from the study doctor or the facility(ies) where the study is being conducted. However, to ensure the valid results of the study, you agree that you may not be able to review or make a copy of some of your records related to the study until after the study has been completed.

If you agree to participate in the optional sub-studies, your test results will be for research only and will not help your doctor or the investigator treat your disease. For this reason, you will not be given your test results and they will not be put in your medical records.

You can revoke your authorization at any time before, during, or after your participation in this study. If you revoke it, no new information will be collected about you. However, information that was already collected may still be used and shared with others if the researchers have relied on it to complete the research. You can revoke your authorization by giving a written request with your signature on it to the study doctor.

If you revoke your authorization, you will no longer be allowed to be in this study.

How will you keep my health information confidential?

Your study records and research samples will be assigned a code that will replace your identity and contact details. The list that links the code to your name will be kept separate from your personal health information. The sponsor will not be able to link the assigned code number with your identity. The people and groups listed in the table above, as well as people and companies hired by the sponsor to work on the study, will have access to your coded study data and samples.

Why is access to my health information being requested?

To help answer the research questions, the investigator and research team will use and store personal health information about you. We are asking your permission to use and share it with others, as explained below. If you don't give this permission, you won't be able to take part in the research study.

**Involvement of Your Primary Care Physician/Family Doctor**

If you wish to take part in the study, you must agree that the study doctor inform your primary care physician of your participation in the study. This is done to make sure all doctors involved in your medical care are aware of the medicines or treatments you are taking.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

**Who would you call if you have any questions?**

Contact Dr. Karen Hall at 352-265-7001 (24 hours) for any of the following reasons:

* if you have any questions about your participation in this study,
* if at any time you feel you have had a research-related injury or a reaction to the study drug, or
* if you have questions, concerns, or complaints about the research

If you have questions about your rights as a research subject or if you have questions, concerns, input, or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)

1019 39th Avenue SE Suite 120

Puyallup, Washington 98374-2115

Telephone: 1-800-562-4789 or 360-252-2500

E-mail: Help@wirb.com

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

### or

The University of Florida liaison in Gainesville at (352) 273-9600.

**Consent to participate in this research study.**

I have been informed about this study’s purpose, procedures, possible benefits and risks. I have also been told alternatives to being in the study and how my protected health information will be collected, used, and shared with others. I have been given the opportunity to ask questions. My questions have all been answered satisfactorily. I agree to be in this research study. I have received a copy of this form.

By signing this consent form, I am not giving up any of my legal rights.

By signing this informed consent form, I am authorizing access, use and transfer of my personal data as described in this informed consent.

|  |  |  |  |
| --- | --- | --- | --- |
|  | I agree to allow the study doctor to inform my primary care physician of my participation in this study. | | |
| (Initials) |  | | |
| Name of Subject (Printed) | |  |  |
| Subject Signature and Authorization | |  | Date |
|  | |  |  |

Consent to Optional Pharmacogenetic Research Sub-Study

Please initial one of the following:

\_\_\_\_\_\_\_\_ I agree to participate in the pharmacogenetic sub-study.

(Initials)

\_\_\_\_\_\_\_\_ I do NOT agree to participate in the pharmacogenetic sub-study.

(Initials)

Consent to Optional 24-Hour Urine Research Sub-Study

Please initial one of the following:

\_\_\_\_\_\_\_\_ I agree to participate in the 24-Hour Urine sub-study.

(Initials)

\_\_\_\_\_\_\_\_ I do NOT agree to participate in the 24-Hour Urine sub-study.

(Initials)

**Optional Post-Withdrawal Search of Health Status Information**

\_\_\_\_\_\_\_\_ **Yes – I do agree** to allow the study doctor or study staff designee to search

(Initials) information regarding my health status from additional sources, including from national patient registries (e.g., National Death Registries, Cancer Registries, Vital Registries), or any other publicly available sources if I am considered lost to follow-up during the Double-Blind Dosing Period (the study doctor or study staff is unable to contact me or my care-giver for 3 consecutive times).

\_\_\_\_\_\_\_\_ **No – I do not agree** to allow the study doctor or study staff designee to search

(Initials) information regarding my health status from additional sources, including from national patient registries (e.g., National Death Registries, Cancer Registries, Vital Registries), or any other publicly available sources if I am considered lost to follow-up during the Double-Blind Dosing Period (the study doctor or study staff is unable to contact me or my care-giver for 3 consecutive times).

The study staff can contact my caregiver, spouse or friend if they are not able to get in touch with me at the scheduled times. I will provide the name of the contact person directly to the study doctor and this information will be recorded in my medical files.

**Yes**, I do give my permission for the study staff to contact my caregiver, spouse or friend to confirm my current health status should I not be available.

**No**, I do not give permission to the study staff to contact my caregiver, spouse or friend for additional information on my health status.

As an investigator or the investigator’s representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study, the alternative to being in the study; and how the subject’s protected health information will be collected, used, and shared with others:

|  |  |  |
| --- | --- | --- |
|  |  |  |
| Name of Person Conducting Informed Consent Discussion (Printed) |  |  |
|  |  |  |
| Signature of Person Conducting Informed Consent Discussion |  | Date |

**Appendix A – Study Activities**

| **Visit Duration in Weeks Until Randomization** | **Screening (2 Weeks)** | | **Run-In Period (Up to 12 Weeks)a** | | | **Enrichment Period**  **(6 Weeks)** | | | | | **Dosing Period** | | | | | | | **F/U Period** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Wk**  **–14** | **Wk –13** | **Wk**  **–12** | **Wk**  **–10, –8, –6, –4** | **Wk –2** | **Day**  **1** | **Wk 1** | **Wk 2** | **Wk 4** | **Wk 6** | **Wk**  **7** |  |  |  |  |  |  |  |
| **Activities** | **S1** | **S2** | **R1** | **R2, R3, R4, R5** | **R6** | **E1** | **E2** | **E3** | **E4** | **E5** | **Random-ization** | **Wk 1 Call** | **Wk 2 Call** | **T 1** | **Every 3 Mths** | **Yearly Visits** | **Final Treatment Visit (PD)b** | **F1c** |
| Medical History – including questions regarding tobacco and alcohol use | X | Xl | Xl | Xl | Xl | Xl |  |  |  |  |  |  |  |  |  |  |  |  |
| Complete Physical Exam |  |  |  |  |  | X |  |  |  |  |  |  |  |  |  |  | X |  |
| Vital Signs (blood pressure, heart rate, weight and temperature)d | X | X | X | X | X | X | X | X | X | X | X |  |  | X | X | X | X | X |
| Assess Limb Swellinge | X | X | X | X | X | X | X | X | X | X | X |  |  | X | X | X | X | X |
| Blood Drawsf | X |  | X | X | X | X |  | X | X | X | X |  |  | X | X | X | X | X |
| First Morning Void Urine Collectionsg |  | X |  |  | X | X |  |  | X | X |  |  |  | X |  | X | X (if discontinued during dosing period only) | X |
| Optional Genetic Sample |  |  |  |  |  |  |  |  |  |  | X |  |  |  |  |  |  |  |
| Urine Testsh | X |  |  |  |  | X |  |  |  | X | X |  |  |  | X (T3 only) | X | X | X |
| Blood Pressure Medication Dose Adjustments | X | X | X | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Receive Study Drug |  |  |  |  |  | X |  |  | X |  | X |  |  | X | X |  |  |  |
| Return Study Drugi |  |  |  |  |  |  | X | X | X | X | X |  |  | X | X | X | X |  |
| ECG (a painless test which records the electrical activity of your heart) |  |  |  |  |  | X |  |  |  |  |  |  |  |  |  | X | X |  |
| Telephone Contactsj |  | X |  |  | X | X |  |  | X | X | X | X | X | X | X | X | X | X |
| Questionnaires (questions about your health and how you are feeling) |  |  |  |  | X |  |  |  |  |  | X |  |  |  | T3, T6 and T9 only | X | X |  |
| Measure Weekly Weightk |  |  |  |  |  |  |  |  |  |  | X |  |  | X | X | X | X (if discontinued during dosing period only) |  |

a. The length of time and number of visits you have to attend during the Run-In Period will depend on the time necessary to adjust your current dose of your blood pressure medications (ACEi or ARB (RAS inhibitor)) and diuretic schedule. If no adjustments to your current dose are required you may proceed directly to the last Run-In visit (R6). If adjustments are required, you may be in this period for a minimum of 4 weeks and a maximum of 12 weeks.

b. If you permanently discontinue study drug at any stage of the study you will have to complete a premature discontinuation (PD) visit within 9 days after your last dose.

c. Follow-Up Visit (F1) will be completed at least 45 days after last dose of study drug.

d. Vital signs including BP, weight and pulse rate, will be collected at every visit. Height will be collected at initial Screening visit only. Temperature will be collected at Randomization visit only. Weight gain will be assessed at each visit.

e. Checking for any swelling of the extremities (arms, legs, feet and hands).

f. Approximately 6.5 mL (1 teaspoon) of blood will be collected at the S1 visit. Approximately 2.5 mL (half a teaspoon) of blood will be collected at the R1 visit. Approximately 2.5 mL (half a teaspoon) of blood will be collected at the R2, R3, R4 and R5 visits. Approximately 4.5 mL (1 teaspoon) of blood will be collected at the R6 visit. Approximately 15 mL (3 teaspoons) of blood will be collected at the E1 visit. Approximately 4.5 mL (1 teaspoon) of blood will be collected at the E3 visit. Approximately 8.5 mL (2 teaspoons) of blood will be collected at the E4 visit. Approximately 19.0 (4 teaspoons) of blood will be collected at the E5 visit. Approximately 18.5 mL (4 teaspoons) of blood will be collected at the Randomization visit. If you consent to the optional pharmacogenetic sample, an additional 4 mL (approximately 1 teaspoon) of blood will be collected at the Randomization visit. Approximately 20.5 (4 teaspoons) of blood will be collected at the T1 visit. Approximately 17.0 mL (3.5 teaspoons) of blood will be collected at T3 visit. Approximately 8.5 mL (2 teaspoons) of blood will be collected at the T6, T9, T18, T30 and T42 visits. Approximately 29.0 mL (6 teaspoons) of blood will be collected at the yearly visits (T12, T24 and T36). Approximately 4.5 mL (1 teaspoon) of blood will be collected at the T15, T21, T27, T33, T39 and T45 visits. Approximately 29.0 mL (6 teaspoons) of blood will be collected at the T48/PD visit. Approximately 25 mL (5 teaspoons) of blood will be collected at the F1 Visit. At the following visits, you will have laboratory testing collected under fasting conditions (you should have nothing to eat or drink except water 8 hours prior to the visit): E1, T1, yearly visits (T12, T24 and T36) and the F1 visit. If you are a female of < 50 years old, a blood test for hormone levels (FSH) will be conducted to check your pre-menopausal status at S1.

g. For Screening, the first morning void (FMV) urine collection will consist of two consecutive first morning void (FMV) samples collected within 2 days of the S2 visit. Each of these urine samples should be collected after 5 AM on each day and should be your FMV (bladder emptying). For Run-In and Enrichment, the first FMV urine collection will consist of three consecutive FMV samples collected within 3 days prior to the Run-In R6 Visit, E1 visit, E4 visit and the E5 visit. For visits during the Double-Blind Dosing Period and the F1 visit, the FMV urine collection will consist of one FMV sample collected within 1 day of the next Double-Blind Dosing Period visit (with the exception of 3 FMVs to be collected at the T24 visit). For the PD visit, the FMV urine collection will consist of one FMV sample collected within 1 day of the PD visit. You do not need to provide a FMV urine sample if you have prematurely discontinued during the Enrichment Period.

h. Urine analysis to be collected at the S1, Randomization, T12, T24, T36 and T48/PD visits. Urine Biomarkers to be collected at the E1, E5, T3, T48/PD and the F1 visits.

i. You will return your unused atrasentan (including the empty bottles) to your study doctor to check that you've taken the tablets as instructed. If you have missed any doses or if your last dose was delayed, it is important that you tell your study doctor.

j. You will receive a telephone call from the study staff 2 to 4 days, before your next study visit to remind you to collect your FMV urine samples, bring your weight diary to the visit, and fast if necessary. In addition, you will be contacted once per week for the first 2 weeks after being randomized to ask you about any signs and symptoms of hypotension(when your blood pressure gets too low)

k. You will receive a weight diary beginning at the Randomization visit to record your weekly weight during the Double-Blind Dosing Period.

l. Updates.