UF | Institutional Review Board
UNIVERSITY of FLORIDA

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
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1707 North Main Street
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United States

SITE(S): Family Medicine at Main
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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 participate in a research study of an investigational study drug called atrasentan in subjects with type 2 diabetes and nephropathy. 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).

The researchers at this study center study the nature of kidney disease and attempt to develop and improve methods of treatment for proteinuria, (presence of an excess of serum protein in the urine), which is a sign of renal (kidney) damage. Diabetics, like you, usually suffer from damaged kidneys and develop proteinuria.

This study drug was previously tested in humans in a research study which included 348 male and female subjects from the United States, Canada, Puerto Rico, Taiwan and Japan that had type 2 diabetes with kidney diseases. The previous research studies have observed the effects of the study drug atrasentan at the following doses (0.25 mg/day, 0.75 mg/day, 1.25 mg/day and 1.75 mg/day) and have determined from these studies that the optimal dose is 0.75 mg per day. This research study will be observing the effects of atrasentan at a dose of 0.75 mg per day.

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 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)?
All subjects will continue to take their 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 0.75 mg once per

day of atrasentan, and a dosing period where you will be randomly assigned by chance (like the flip of a coin) to receive 0.75 mg per day of atrasentan or placebo (inactive substance that looks identical to atrasentan) once per day.

Neither you nor your study doctor will be able to pick which study drug you receive during the dosing period. You will have a 50% chance (1 in 2) of receiving atrasentan and a 50% chance (1 in 2) of receiving placebo. The dosing period is double-blinded, which means neither you, your study doctor or the sponsor will know to which study group you were assigned. In case of an emergency, your study doctor can find out this information.

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. Such tests and evaluations are completed during a screening period that takes place before participation in the main part of the study. A signed informed consent form must be given to your study doctor before any procedures are done on the screening day. If you are eligible to participate in this study, you will undergo the procedures listed in the table below.

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.

Study Activities

	Screening (2 Weeks)		Run-In Period (1 to 12 Weeks)			Enrichment Period (6 Weeks)[a]					Double-Blind Dosing Period					F/U Period
Visit Duration in Weeks Until Randomization	**Wk –14**	**Wk –13**	**W –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**	**Randomization**	**T1**	**Every 3 Mths**	**T 12, T 24, T 36[b]**	**T 48/ PD**	**F1[c]**
Medical History – including questions regarding tobacco and alcohol use	X	X	X	X	X	X										
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
Assess limb swelling[e]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Blood tests[f]	X		X	X	X	X		X	X	X	X	X	X	X	X	X
First Morning Void Urine Collections[g]		X			X	X			X	X		X	X		X	X

Study Activities (Continued)

	Screening (2 Weeks)		Run-In Period (1 to 12 Weeks)			Enrichment Period (6 Weeks)[a]					Double-Blind Dosing Period					F/U Period
Visit Duration in Weeks until Randomization	**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**	**Randomization**	**T1**	**Every 3 Mths**	**T 12, T 24, T 36[b]**	**T 48/ PD**	**F1[c]**
Optional Genetic Sample[f]											X					
Urine Analysis Tests[h]	X					X				X	X		X	X	X	X
Blood Pressure Medication Dose Adjustments			X	X												
Receive Study Drug						X			X		X	X	X			
Return Study Drug[i]							X	X	X	X	X	X	X		X	
ECG (a painless test which records the electrical activity of your heart)						X								X	X	
Reminder telephone calls[j]		X			X	X			X	X	X	X	X	X	X	X

Study Activities (Continued)

Questionnaires (questions about your health and how you are feeling)					X								T3, T6 and T9 only	X	X	
Measure Weekly Weight[k]											X	X	X		X	

a. The E1 visit will take place approximately 2 weeks after the R6 visit. The E2 visit will take place approximately 1 week after the E1 visit. The E3 visit will take place approximately 1 week after the E2 visit. The E4 visit will take place approximately 2 weeks after the E3 visit. The E5 visit will take place approximately 2 weeks after the E4 visit.
b. The procedures listed for yearly are in addition to the every 3-month procedures.
c. Completed at least 45 days after last dose of study drug.
d. Vital signs include 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 mL (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 mL (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 teaspoon) of blood will be collected at the T48/PD visit. Approximately 25.0 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 starting from midnight before the visit): Randomization, T1, yearly visits (T12, T24 and T36), T48/Premature Discontinuation 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 samples collected prior to the second Screening 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 Treatment and the 45-Day Follow-up visit, the FMV urine collection will consist of one FMV sample collected within 1 day of the next Treatment Period Visit (with the exception of 3 FMVs to be collected at the T24 visit).
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, T12, T24, T48/PD and the F1 visit.
i. You will return your unused atrasentan (including the empty bottles) to your study doctor to check that you take the tablets as instructed.
j. You will receive a telephone call from the study staff about 2 to 4 days, depending on the visit, before your next study visit to remind you to collect your morning void urine samples, bring your weight diary to the visit, and fast if necessary.
k. You will receive a weight diary beginning at the Randomization visit to record your weekly weight during the dosing period.

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.

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

Screening Period

Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. You will have up to 2 Screening Visits to determine if you qualify to take part in this study.

Screening Visit 1

The tests and procedures noted in the table above will be performed.

You will be asked to give personal information, such as your gender, age, race, etc.

If, based on the Screening Visit 1 tests and procedures, you qualify to participate in this study, the study doctor will contact you to let you know and will schedule the second Screening Visit at that time.

Screening Visit 2

The tests and procedures noted in the table above will be performed.

If, based on the Screening Visit 1 and Screening Visit 2 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. If, based on the screening tests and procedures, you do not qualify to participate in this study, you will not continue to the Run-In Period; however, you will be allowed to re-screen twice.

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.

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

If, based on the results of the tests and procedures performed during the Run-In Period, you continue to qualify to participate in this study, the study doctor will contact you to let you know and to schedule your Enrichment E1 visit.

Enrichment Period

If you pass the screening and Run-In Periods, you will be enrolled into the Enrichment Period. During the Enrichment Period, you will receive atrasentan at 0.75 mg 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. The Enrichment Period will last for 6 weeks. You will return to the study site one week apart for the first 3 Enrichment Period visits and then 2 weeks apart from the E3 to the E4 visit and the E4 to the E5 visit.

Enrichment E1 Visit

The tests and procedures noted in the table above will be performed.

You will receive your first dose of atrasentan at the study site during this visit. You will receive a 4-week supply of study drug. You will be instructed to take 1 tablet of study drug per day.

Enrichment E2 – E6 Visits

The tests and procedures noted in the table above will be performed.

Dosing Period

The Dosing Period will last up to 48 months. You will return to the study site one month apart for the first 2 Dosing Period visits, return in 2 months from the T1 to the T3 visit, and then every 3 months thereafter.

During this period and between visits, you will have to measure your weight weekly. At the first visit of the dosing period (Randomization), you will receive instructions for measuring your weekly weight under the same circumstances (i.e., same scale, same day each week, same time, removing shoes and coat), and a weight diary for recording your weight at home. You should bring your diary with you to each study visit for site staff to review. If you notice a weight change greater than 2 kgs (or approximately 4.4 lbs) within 2 weeks you should notify your study doctor.

Randomization Visit

The tests and procedures noted in the table above will be performed.

If, based on the results of the tests that were taken during the previous Enrichment visits and procedures from the Randomization visit, you continue to qualify to participate in this study, 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 Dosing Period is a double-blind portion of the study, which means neither you nor the study doctor will know which of these study drugs you are assigned. In case of an emergency, however, the study doctor can get this information.

You will receive your first dose of blinded study drug at the study site. You will receive a 3 month supply of study drug. You will be instructed to take 1 tablet of study drug per day.

Dosing Visit T1 and Every 3 Months (T3 – T45) Visits

The tests and procedures noted in the table above will be performed.

Yearly Visits (Visits T12, T24 and T36)

The tests and procedures noted in the table above will be performed during the yearly study visits in addition to the procedures that will take place at the Every 3 Month visits.

Dosing T48/Premature Discontinuation

The tests and procedures noted in the table above will be performed during this study visit. This visit will occur at the end of your 48th month of study drug during double-blind dosing or within 5 days after your last dose of study drug if you stop participating early.

45-Day Follow-Up Period

The tests and procedures noted in the table above will be performed during this study visit. This study visit will occur 45 days following your last dose of study drug.

Subject Responsibilities

In order for this study to provide good information about how atrasentan works in subjects with type 2 diabetes and nephropathy, 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.
- You may be required to stop certain medications and supplements you are currently taking. Certain medications you are taking or have taken in the past may keep you from being in this study. Please review all of your medications with your study doctor.
- Some procedures/conditions you may have had in the past may keep you from being in this study.
- 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. You are the only person allowed to take the study drug.
- 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 start any new type 2 diabetes 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.

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 Blood Sample For DNA (Genotyping) Analysis Sub-Study on Randomization Day Visit

In addition to the other activities and procedures to which you have been asked to consent, 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

AbbVie will not use your DNA for any other tests without your permission. In particular, AbbVie will not use your DNA for any tests to learn your risk of developing any disease. No one other than AbbVie (or people or companies AbbVie works with) will test your DNA. AbbVie (or people or companies AbbVie works with) will not give or sell your DNA to other people or companies.

You do not have to be in this pharmacogenetic 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 this pharmacogenetic research portion of the main study.

How Will Your DNA Be Collected?

The study doctor or study staff will take a blood sample of about 1 teaspoon (4 mL) at the Randomization Day 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, and then the sponsor will destroy your DNA sample.

Are There Any Risks to Providing a DNA Sample?

Your test results are confidential. However, if your test results got into the wrong hands, the confidentiality of your health information may be lost. The sponsor, AbbVie, will make every effort to make sure no one gets your test results except those people or companies you read about in this form.

In addition, your test results may reveal information about members of your biological family (blood relatives).

A federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law will generally protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information from this research.

- If health insurance companies and group health plans do somehow receive your genetic information from this research, they may not use it to make decisions about your eligibility or premiums.

- Employers with 15 or more employees may not use your genetic information from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

How Will the Sponsor Protect Your Identity?

Your blood sample will not have your name on it. Your blood will be collected in a tube with a code on it. The code will link your blood sample to information about the test results and other medical information. Only the study doctor and study staff will be able to link the code to identifying information such as your name. The sponsor will not have this link.

Will Being in This Pharmacogenetic Sub-Study Help Me or Others?

Being in this sub-study will not help you. Information from this study may help researchers understand proteinuria and come up with new tests or medicines to help others in the future.

Will It Cost Anything to Be in This Pharmacogenetic Sub-Study?

You will not have to pay for any of the tests that are part of this genetics portion of the main study.

Will You Be Paid for Being Part of the Pharmacogenetic Sub-Study?

No. Your blood, along with blood from other participants in this sub-study, might help the sponsor come up with new tests or medications in the future. If the sponsor makes new tests or medications, you will not get any money for these tests or medications. The sponsor will own the results of this sub-study and any new tests or medications the sponsor makes because of this sub-study.

Will You Get the Results of Your Pharmacogenetic Test?

Your test results are for research only. The test results are not for personal use, like making decisions about your medical care and whether or not to have children. For this reason you will not be given your test results. Your test results will not be put in your medical records. The sponsor will not give your test results to any insurance company, your employer, your family, the study doctor, any other doctor, or anyone else, except as described in this form.

You will be asked to indicate your choice about pharmacogenetic testing at the end of this form.

Optional 24-Hour Urine Collection Sub-Study

In addition to the other activities and procedures to which you have been asked to consent, you are also being asked to participate in a 24-hour urine collection sub-study. The 24-hour urine collection will be collected six times (at visits E1, E5, T12, T24, T36 and T48/PD) for each subject during the study that agrees to participate in this sub-study. If you provide consent, you will be provided with urine collection containers prior to each visit where 24-hour urine is required. You will be given specific instructions for collection and storage of your 24-hour urine. You will start your 24-hour collection within 1 day prior to the visit where it is required, after the third FMV is collected during Enrichment and the T24 visit during the dosing period and after the one FMV (with the exception of the T24 visit) is collected during dosing period. The 24-hour urine collection will end on the morning of your scheduled study visit. 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

You will be asked to indicate your choice about the 24-hour urine collection sub-study at the end of this form.

You do not have to be in this 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 this 24-Hour Urine Collection research portion of the main study.

How long will you be in this research study?
Your participation in this study will last up to 4.5 years and may include up to 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 research centers worldwide. Approximately 4,148 subjects with type 2 diabetes and nephropathy 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.

Pregnancy and Breastfeeding:

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.

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 breast feed while taking atrasentan.

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 effective contraception while participating in this study and at least 1 month 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 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 1 month 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 will vary from person to person.

<u>Fluid Retention</u>

- 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). 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

Low red blood cell count (anemia) has been seen is studies of atrasentan and medicines like it. The 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 (4.5%)
- infection (4.3%)
- runny/stuffy nose (nasal congestion) (1.3%)
- headache (0.9%)
- rash (0.3%)
- paresthesia (an abnormal sensation like pins and needles or burning) (0.2%)
- dry mouth (0.1%)
- conjunctivitis (irritation and redness of the thin membrane covering the eye) (< 0.1%)

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).

There may also be risks and side effects to you that are currently unknown.

Risks Associated with Placebo

Some people in the study will get placebo instead of atrasentan. Receiving placebo is the same as not receiving anything for your type 2 diabetes and nephropathy. 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 nephropathy getting worse. Some side effects may not be known yet. 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 only be reimbursed for actual expenses incurred for each visit up to a maximum of **$1216**. If you do not complete the study, you will receive reimbursement only for the visits you have completed up to a maximum of **$38** per visit. 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. You will also be asked to return to the study site within 5 days so that the study doctor may perform a final evaluation, which may include a physical examination and/or laboratory tests.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

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:

- Your personal health information from your original medical records
- All data resulting from your participation in this research will be collected during the course of this study.

- Your personal health information could include
    - Physical examination details, as well as
    - The results of any blood testing, ECGs, or other medical procedures including personal health information collected about you.

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
- The only people with access to your personal health information in identifiable form will be the study doctor, personnel helping the study doctor conduct the study at the facility, sponsor representatives who are checking that the study is conducted properly, WIRB and regulatory authorities where required by law.
- In order to complete the research, AbbVie, the study doctor and personnel at the facility, WIRB and domestic and foreign regulatory authorities responsible for overseeing research studies (including the US Food and Drug Administration [FDA], US Department of Health and Human Services, and/or equivalent government agencies in other countries) will have access to your coded health information.

Additionally, your personal health information may no longer be protected by HIPAA (Health Insurance Portability and Accountability Act) once it is disclosed to AbbVie and others as described in this form by the study doctor. However, AbbVie will take reasonable measures to keep your personal health information confidential. However, absolute confidentiality cannot be guaranteed.

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 may not participate in this study unless you give your permission to use and disclose your personal health information. By signing this document you are allowing the study doctor and personnel at the facility to permit AbbVie and others described in this form to have access to your personal health information for the purpose of collecting data, verifying the data is correct, and checking that the study is conducted properly.

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.

When you sign this document, you agree to the access, collection, processing and transfer of your personal health information as described in this informed consent document. If you do not sign this form, you cannot be in the study.

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 Your Data Will Appear:

Your identity and contact details will not be disclosed except as described in this form, unless required by law. Rather, your identity and contact details will be replaced by a code, such as a number.

Why We Collect this Data:

Your personal health information will be used for clinical research and may also be used for seeking approval from regulatory authorities to market the studied atrasentan. It may also be used in study reports or for scientific presentations, but in a way that will not identify you by

name. Your personal health information will be kept confidential and, unless required by law, will not be made publicly available. After this study has been completed, it is possible that your coded health information will be used for future research.

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
Puyallup, Washington 98374
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)

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.

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