Consent to Participate in a Research Study

Study Title: Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) Study

Study #: M16-100

Sponsor: Testosterone Replacement Therapy (TRT) Manufacturer Consortium acting through AbbVie Inc.

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You are being asked to voluntarily participate in a research study of a drug called AndroGel 1.62%. AndroGel 1.62% is a testosterone replacement therapy (TRT) approved by the U.S. Food and Drug Administration (FDA) to treat certain conditions associated with a deficiency or absence of natural testosterone (a male hormone) production.

You are being asked to join this study because you may have hypogonadism (a condition where low blood testosterone levels are associated with clinical symptoms). While you may not have the specific causes of low testosterone that AndroGel 1.62% is currently approved for, this study is designed to answer further questions about the effect of TRT, which could not be answered in earlier studies prior to the drug's approval.

The major question this study is trying to answer is how safe and effective is TRT in people with low testosterone (hypogonadism) and either cardiovascular (CV) disease or risk factors for CV disease.

What is a research study?

A research study is an experiment whose purpose is to answer specific questions, such as:

- Does this drug work?
- Is it safe?
- What kind of drug is better?

To answer these questions, doctors and scientists need volunteers to participate in research studies. These volunteers are called "subjects" or "participants." The doctor in charge of the study at the study site is called the "study doctor" or "investigator." The study doctor and scientists who run the research study are called "researchers", and other people who help them run the study are called the "research team" or "study staff."

Quorum Review has reviewed this study. Quorum Review is a group of people who review research studies to see if they meet federal laws and ethical standards. Only you can decide if being in this study is the right decision for you. Feel free to talk about this study with your family, friends, and personal doctor before you decide. We will answer any questions you may have so that you can make an informed decision.

The Sponsor for this study is the Testosterone Replacement Therapy (TRT) Manufacturer Consortium, whose members include AbbVie, Acerus Pharmaceuticals Corporation/Aytu Biosciences, Inc., Allergan Sales, LLC., Endo Pharmaceuticals, and Upsher-Smith Laboratories, LLC. The Sponsor pays the study site for the study doctor and study staff to run the study and for other expenses incurred by the study.

Purpose of the Study:

The primary purpose of this study is to compare the effect of testosterone replacement therapy (TRT) and matching placebo (a gel that is made to look like the TRT but does not have any testosterone drug in it) on major CV events such as heart attack and stroke in men who do not produce enough testosterone (hypogonadal men) and have symptoms from not enough testosterone.

The study will also determine if the use of TRT affects 1) the chance of having prostate cancer and how serious it may be, and 2) the chance of having broken bones (fractures).

Other potential effects of TRT being studied include potential improvement of sexual function, mood, anemia, and reducing the tendency to develop diabetes. These effects will be examined in subjects who qualify. Thus, the goal of this study will be to learn more about the safety and overall effects of TRT.

Study Information:

AndroGel 1.62% is currently approved for doses ranging from 20.25 mg up to 81 mg. However, the highest possible dose level (101.25 mg) that may be used in this study is investigational because this dose is not approved for the treatment of low testosterone levels.

This is a phase 4, randomized, double-blind, placebo-controlled, multicenter study of topical (rubbed onto the skin) TRT in men with low testosterone (hypogonadal) who are at increased risk for CV disease. “Phase 4” means that AndroGel 1.62% has already been approved by the FDA to treat certain causes of low testosterone, and this is a study to answer further questions about the effect of TRT, which could not be answered in earlier studies before the drug was formally approved.

“Randomized” means that whether or not you receive AndroGel 1.62% or the placebo will be determined by chance, such as in the flip of a coin. Neither you nor the study doctor or study staff will be able to pick which study group you are in. A placebo is not a drug. It is designed to look and feel just like the drug being studied but it is not designed to treat any disease or illness. This is done so study scientists can best judge if the drug being studied has effects that are greater than the effects that are expected by chance. In this study, half of the subjects will randomly receive placebo and the other half will receive AndroGel 1.62%.

"Double-blind" means that neither you nor the study doctor or study staff will know if you are receiving AndroGel 1.62% or placebo. This "blinding" is done so that you and your study doctor's knowledge of what drug you are on won't affect the overall management of your symptoms, and the only effect will be that of the AndroGel 1.62%. Your study doctor can find out what you have been assigned to if there is an emergency or if it is needed to know for your health. It is important for you to understand that you will not know whether you are receiving AndroGel 1.62% or placebo until the study has been completed, so we may truly evaluate the effects of the AndroGel 1.62%.

If you qualify to participate in this study, you will be randomized on Day 1 to receive either placebo or AndroGel 1.62%.

Be aware that this form refers to AndroGel 1.62% and placebo as "study drug."

The study doctor/study staff will help show you where and how the study drug will be applied to your skin. All participants will be started at 40.5 mg of study drug. The amount and dose of study drug you will apply may change throughout the study, and the study doctor/study staff will discuss any changes with you. No one will be assigned a dose below 20.25 mg or above 101.25 mg during the course of the study.

We expect that there will be approximately 400 research sites in North America including Puerto Rico participating in this study, which will include approximately six thousand (6,000) men between the ages of 45 and 80 years.

If you qualify for the study, your participation may last up to approximately 5 years depending on when you begin the study and when the study ends. There are up to 27 required study-related contacts (approximately 17 office visits and 10 phone calls). For the phone calls, a study staff member will call you and collect the study information over the phone. The study staff will tell you when to come in to the office for your study visits. You should ask the study staff how long each visit will last.

This study includes:

- A Screening Period of up to 60 days consisting of 2 to 3 visits to determine if you are eligible to participate.
- A 60-month (5 years) period during which you will apply study drug once a day. During this period, the dose of study drug you receive may be adjusted based on your testosterone levels.
- If you need to interrupt taking the study drug, you may be able to start taking it again at a later time.
- Thirty (30) days after your last dose of study drug, if you complete the study entirely or if you discontinue from the study completely (withdraw consent) prior to the last study visit, you will be called on the phone and asked about any ongoing or new medical events since your last visit. All medical events will be followed until they resolve or, if they are ongoing at the end of the study, the status of the medical event will be recorded.
- Labs will be collected to monitor your health throughout the study. The additional testing for anemia and diabetes will be done based on these routine study blood draws.
- Questions will be asked about your symptoms, quality of life, and health at every visit. You will also be asked if you have had any broken bones since your last study visit.

- **Optional Sub-studies (Sexual Function and Persistent Depressive Disorder):** If you qualify for one or both sub-studies, based on responses to questions you had given prior to receiving your first dose of study drug and if you agree to participate in the sub-studies, you will complete additional questionnaires during your regularly scheduled in-person visits. You will indicate your choice(s) about the sub-studies at the end of this form.

Study Screening Procedures:

In order to determine if you are eligible to participate in the study, you will complete the following screening procedures (activities, tests and evaluations) described below.

- **Informed Consent:** This form will explain the purpose, possible benefits, and potential risks of this study.
- **Medical/Surgical History/Cancer & CV Family History:** Questions will be asked about your current and past medical conditions and surgeries. These questions will include your CV risk, cancer history, tobacco, alcohol and drug use. You will also be asked about any CV family history
- **Physical Exam:** Similar to what your regular doctor would do at your annual physical.
- **Vital Signs:** You will have: a) your blood pressure checked by putting a band (sphygmomanometer) around your arm (this will squeeze your arm for about a minute), b) your pulse taken (number of heart beats per minute), c) your respiration (number of breaths per minute), and d) your temperature taken.
- **Weight and Height:** How much you weigh and how tall you are.
- **Electrocardiogram (ECG):** A common heart test, which measures the electrical activity of your heart. Pads are placed on your chest and arms and a machine records the activity.
- **Blood Tests (to monitor your health as well as testosterone levels):** Samples collected during the study will be used for research purposes, will be tested by a central laboratory, and may be transferred to third parties for testing.
- **Urinalysis:** A test to look at the appearance, concentration and content of your urine.
- **Review of any Medications:** Such as over-the-counter medicines, prescription medicines, vitamins, and herbal remedies you are taking or have taken in the past.
- **Electronic Questionnaires:** An electronic device (tablet) will be used to collect your answers to questions regarding your health, prostate symptoms, sexual function, hypogonadal symptoms, lower urinary tract symptoms, and mood. This device meets all regulations for use in clinical studies, including those related to your privacy. Your answers to these questions will be transferred to a storage facility via a secure internet connection and will be viewed by your study site, the Sponsor, and their representatives.
- **Digital Rectal Exam (DRE):** An exam during which a gloved finger is inserted into the rectum to check for growth, enlargement, or abnormalities of the prostate gland. The results from a DRE performed within 6 months of the first Screening Visit can be used as long as written documentation of the DRE result is provided.

Study Procedures:

If you are eligible to participate in this study, you will undergo one or more of the study procedures described in this form at each study visit. It is important that you consider whether your schedule will allow for these visits.

- **Clinical Laboratory Blood Testing:** Some blood will be drawn to look at your health such as hematology, clinical chemistry, prostate specific antigen (PSA), serum creatinine, HbA1c, and sex steroids (testosterone, free testosterone, dihydrotestosterone [DHT], and estradiol). The amount of blood that will be taken at the in-person study visits will vary (see activities table at the end of this consent form). The maximum blood drawn at a scheduled study visit is approximately 4 teaspoons. Certain lab test results will not be available until the end of the study.
    - During the study you may need to have a lab test or tests repeated. If you need to have a lab test or tests repeated, you will be asked to come to the study site to have a blood draw done after your dose has been changed. If the further lab test(s) need to be repeated, you will be asked to return to the study site. You may be asked to stop study drug based on the results of the blood tests.
- **Unscheduled Clinical Labs:** May be obtained at any time during the study if your study doctor feels it is necessary as directed by the study plan; these lab sample(s) will be sent to the central lab.
- **Digital Rectal Exam (DRE):** As described above in the Screening section.
- **Urinalysis:** As described above in the Screening section.
- **Electrocardiogram (ECG):** As described above in the Screening section.
- **Electronic Questionnaires:** As described above in the Screening section.
- **Health and Medication Questions:** You will be asked questions during your study visits about your health, medical history, and the medications you take. Please answer these questions to the best of your ability.
- **Weight:** As described above in the Screening section.
- **Vital Signs:** As described above in the Screening section.
- **Physical Exam:** The study doctor may perform an exam if you have any changes in your health or medications.
- **Study Drug:** You will be given a supply of study drug and told how to apply it. You are to bring back all used and unused bottles of study drug to each visit. The first dose of study drug will be administered at the study site on Day 1 after all procedures are completed.

The site will NOT store your samples; the samples will be sent to the central lab, tested and destroyed.

Please see the Study Activities Table at the end of this Informed Consent Form for more detailed information on study procedures.

Subject Responsibilities:

If you choose to participate, you will have certain responsibilities. In order for this study to provide good information about how the study drug works in subjects with your condition, you will be expected to do the following:

- Attend all study visits.
- You will be asked at every visit (both in person and phone contacts) whether you have had certain health problems, such as a heart attack or stroke.
- Tell the study doctor if you are feeling bad or worse than before.
- You should not have direct skin-to-skin contact with a pregnant or nursing woman after applying the gel.
- Follow the below steps after applying the gel to minimize the risk of testosterone transfer to another person:
    - **Apply the study drug only to your shoulders and upper arms that will be covered by a short-sleeve T-shirt.**
    - **Wash your hands right away with soap and water after applying study drug.**
    - **After the gel has dried, cover the application area with clothing. Keep the area covered until you have washed the application area well or have showered.**
    - **If you expect to have skin-to-skin contact with another person, first wash the application area well with soap and water.**
- You should not apply study drug prior to any of the in-person visits.
- For study visits when you have blood drawn, you should be fasting (no food or drinks except water) for a minimum of 8 hours.
    - No fasting is required until after you have signed the consent form.
- Tell the study doctor if you have any changes in medications during the study.
- Always tell your study doctor about use of erectile dysfunction medications (tadalafil, sildenafil citrate, or vardenafil hydrochloride) and/or if you are taking any form of organic nitrate/organic nitrite.
- Follow the directions of the study doctor and study staff.
- Refrain from participation in other research studies while you are in this study.
- Fill out your questionnaires completely and honestly.
- Report any health problems, including hospitalizations and emergency room and physician visits, to the study doctor immediately. If you become sick during the study and cannot report a medical event yourself, ask a family member to report the event to the study doctor.
- While in the study, do not take any other testosterone medications, including those available without a prescription.
- Contact the study site if you stop your study drug for any reason.
- Due to the expected length of this research study, you are expected to continue with your routine medical care from your regular doctor.

Risks:

AndroGel 1.62% Risks:

AndroGel 1.62% is a testosterone hormone replacement prescription medicine and it should only be used while you are under the care of a doctor.

Because testosterone may affect your health, you should tell the study doctor if you have a history of any of the following:

- Breast or prostate cancer
- Problems urinating due to an enlarged prostate
- Heart problems
- Swelling or fluid retention due to heart, liver, or kidney problems (edema)
- Problems breathing while you sleep (sleep apnea)
- Have any other medical conditions

The most common side effects (Adverse Events) reported in men during clinical trials with AndroGel 1.62% that may be caused by testosterone include:

- A rise in PSA levels (a blood test) used to screen for and monitor men with prostate cancer
- Mood swings such as anger, aggression, or depression
- Rise in red blood cell count
- Rise in blood pressure

In one instance, a blood clot in a vein was reported during clinical trials of AndroGel 1%. This event was not reported during clinical trials of AndroGel 1.62%.

Side effects (Adverse Events) reported by men prescribed and using AndroGel 1.62% include:

- Abnormal blood tests including sugar, cholesterol, other lipids, and tests checking function of kidney and liver
- Acne
- Blood clot (deep vein thrombosis and pulmonary embolism)
- Breast enlargement or breast tenderness
- Decrease in sperm count
- Difficulty emptying the bladder
- Dizziness, nausea, and headache
- Fluid retention or edema
- Heart attack (myocardial infarction) and stroke
- Increase in body hair
- Prolonged erection
- Elevated PSA and prostate cancer

Skin reactions have been reported by some men at the site where AndroGel 1.62% was applied. All of these reactions were mild and did not lead to stopping AndroGel 1.62% in the clinical studies.

Application of Study Drug to Minimize Risk of Transfer:

Study drug is supplied as a gel that is applied on the skin. ***It is possible that the study drug could be transferred to another adult or child through skin-to-skin-contact.*** You should follow the important instructions on how to avoid transferring study drug to others through skin-to-skin contact as described in the "Subject Responsibilities" section above.

Transfer of study drug could lead to unwanted health effects in women and children who come in contact with the gel. You should avoid direct skin-to-skin contact with women and children after applying study drug.

The following precautions are meant to be strictly followed by others in your household to minimize the risk of study drug transfer to them:

- Children and women should avoid contact with unwashed shirts or exposed skin at the application site(s) of men using study drug.
- If a child or woman's skin comes in contact with study drug, either directly or by touching your skin where the study drug was applied, he/she should wash the areas that have been exposed to the study drug thoroughly with soap and water, to remove the study drug as soon as possible.

You are responsible for letting others (adults and children) know that you may be using AndroGel 1.62%, of the risks mentioned above regarding transfer of study drug to another adult or child, and what to do if they accidentally come into contact with study drug either directly or by touching your skin.

Below are some of the signs and symptoms of secondary exposure to testosterone in children and women. If any of the below are seen in a child or woman in your household, you should stop using study drug and should contact the study doctor right away:

- In children: unexpected sexual development including inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior.
- In women: changes in hair distribution, increase in acne, or other signs of testosterone effects such as abnormal hair growth on the face or deepening of the voice.

Risk to Pregnancy:

The effects of AndroGel 1.62% on an unborn or nursing baby are unknown. There is a possibility that AndroGel 1.62% may be transferred from a man to a pregnant or nursing mother through direct skin-to-skin contact. There may be harm to the baby, such as virilization (development of male characteristics) if a pregnant or nursing woman comes into contact with AndroGel 1.62%. Further, it is not known how much testosterone from a nursing mother exposed to AndroGel 1.62% would get into breast milk, which in turn may cause side effects in nursing infants.

You should not enroll in this study if your wife, partner, or significant other is pregnant, plans to become pregnant, or is nursing.

Please follow the directions in the above section titled "Subject Responsibilities" to minimize the transfer of testosterone to the pregnant woman.

If your partner becomes pregnant while you are in this study, you must inform the study doctor. If she agrees, she may be asked questions about the outcome of the pregnancy and the health of the baby.

You are responsible for letting your partner(s) know that you may be using AndroGel 1.62% and of the risks mentioned above regarding pregnancy. If your partner(s) become pregnant, a Consent Form will be provided to her, to request information about her pregnancy and the health of the baby at birth, and this information may be shared with the Sponsor.

Allergic Reactions:

As with any medication, allergic reactions may occur. 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:

- Fast heart rate
- Having a hard time breathing
- Wheezing when you breathe
- Hives
- Rash
- Sudden drop in blood pressure (making you feel dizzy or lightheaded)
- Sweating
- Swelling around the face, mouth, lips, tongue, throat, or eyes
- A feeling of dread
- Inability to breathe without assistance

If you feel that you have any of the above allergic reaction symptoms, get medical help immediately and/or go to the hospital emergency room, then call the study doctor.

Other Risks:

Ask the study doctor if you have questions about the signs or symptoms of any side effects that 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 problems are related to the study drug.

It is possible that not all of the risks and side effects associated with the use of AndroGel 1.62% are known at this time. If you experience any of the symptoms mentioned above or are having any unusual symptoms, call your study doctor immediately and/or go to the hospital emergency room.

It is possible that using AndroGel 1.62% may change how your regular medications, vaccines, or supplements work. It is very important that you tell the study doctor about any medications, supplements, or vaccines before you take them during the study.

Prostate cancer: About half of the men over age 65 have areas of cancer in their prostate glands that appear not to hurt them. It is unknown if testosterone in this study could change these prostate cancers into harmful ones or increase the frequency of identifying the cancers that appear not to hurt men due to increased monitoring. When testosterone was given in previous studies to men over the age of 65, there was no increase in prostate cancer, but not enough men participated in those studies to know for sure if using testosterone will affect the chance of prostate cancer. Also, some men who have prostate cancer have an improvement in the cancer if their blood testosterone is lowered.

Men who have had prostate cancer will not be allowed to take part in the study. Also, men who have a prostate lump or hardness on the rectal examination will not be permitted to join the study, unless a previous biopsy shows that the lump is not cancer. If a prostate lump or hardness is detected during the screening period, these abnormalities will be evaluated further in order to determine if you qualify for the study.

If the blood PSA (a protein released by the prostate) level increases by a certain amount, and if the same result is found when we measure it again, we will recommend that you see a urologist (a doctor who specializes in the urinary system) to discuss whether you should have a prostate biopsy (a procedure to take small samples of tissue and study them under a microscope). Before going to see the urologist, you may view a short informational video about prostate cancer during a study visit. At that time and prior to receiving a prostate biopsy, the urologist will discuss with you the chances that you actually have prostate cancer, the risks to your overall health that result from prostate cancer, and the risks and potential benefits of treating prostate cancer if it is found. If a prostate biopsy is done, we will request these medical records and slides (these contain the tissue samples from your prostate biopsy) from the healthcare provider.

Enlarged prostate (Benign prostatic hyperplasia/BPH): Testosterone dosing of older men might also increase the size of the prostate and cause a decrease in urine flow. Other studies of testosterone have not shown worsening of urination problems, but the number of men studied so far is too small to know for sure. To reduce the chance of urination problems in this study, only men who do not have a lot of difficulty urinating will be eligible. This will be known by the score on the questionnaire that assesses your urinary habits (the IPSS).

High red blood cell count: Testosterone may increase the number of red blood cells, which is why men may have higher red blood cell counts than women. If a man had a high red blood cell count when his testosterone was low, increasing the blood testosterone level with a TRT may increase his red blood cell count to higher than normal. This might increase the chance of a blood clot. For this reason, only men with red blood cell counts below a certain value will be allowed to be in the study, and blood cell counts will be looked at periodically during your participation in the study.

Venous Thromboembolism (blood clots): There have been reports of blood clots in the legs and lungs in men prescribed testosterone products such as AndroGel 1.62%.

Cardiovascular (CV): Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, studies have been unable to determine whether or not TRT increases the risk of CV events, such as heart attack and/or stroke.

Sleep apnea: Testosterone may increase the risk of sleep apnea, a condition in which not enough oxygen gets into the blood during sleep, resulting in excessive sleepiness during the day. Although it is not certain that testosterone has this effect, men who have been diagnosed with sleep apnea will be eligible only if they are being treated for it.

Risks to Subjects on Placebo: Some people in the study will get placebo instead of AndroGel 1.62%. Placebo is a gel that looks like a drug but has no drug in it. If you use placebo during the study, it is possible that your symptoms may get worse; please ask the study doctor or study staff if you have any questions about placebo. In addition, there may still be risks associated with study procedures.

Risks related to Study Procedures:

- **Clinical Laboratory Blood Testing:** Taking a blood sample may cause pain, bleeding, and/or bruising at the site. You may feel dizzy or faint, and/or in rare instances develop an infection with redness and irritation at the site where blood is drawn. The amount of blood that will be taken at the in-person study visits will vary (see activities table at the end of this consent form). The maximum blood drawn at a scheduled study visit is approximately 4 teaspoons. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.
- **Electrocardiogram (ECG):** For the ECG, you will have pads placed on different parts of your body. There is no pain or discomfort during an ECG; however, the gel from the pads or removing the pads may cause some irritation to your skin.
- **Questions, Questionnaires:** Completing the questionnaires could lead you to feel uncomfortable or upset. Please tell the study doctor or study staff if you feel that way while completing a questionnaire. You have the right to refuse to answer any question.
- **Physical Exam:** There are no special risks with an exam.
- **Digital Rectal Exam (DRE):** This procedure may cause mild discomfort, and a small amount of bleeding from the rectum may occur after an examination. You may feel lightheaded and faint.
- **Loss of Confidentiality:** There is a risk of loss of confidentiality of your information. You will read more about the protection of your information later in this form. Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study.

Possible Benefits:

You may or may not benefit from being in this study, but your participation in this research study may benefit other people in the future. Your condition may get better, it may get worse, or it may stay the same.

Alternatives to Participation:

You have the option not to participate in this study and to receive the standard of care treatment from your regular doctor who can discuss the potential benefits and risks for these treatments with you.

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.

Withdrawal/Voluntary Participation:

Participation in this study is voluntary. You can stop participating in the study at any time. If you decide not to participate in the study or to withdraw from the study, the quality of your medical care or any benefits to which you are otherwise entitled will not be affected and there will be no penalty to you.

Your study doctor may end your participation in the study, without your consent, if he/she believes that it is in your best interest or if you are unable to follow the requirements of the study. In addition, the Sponsor may end your participation in the study at any time without your consent.

If you withdraw from the study for any reason, all 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 if you discontinue from the study completely, so that the study doctor can perform a final evaluation, which may include a physical examination and/or laboratory tests.

If you leave the study, the study doctor and study staff will still be able to use and disclose your information that they have already collected.

<u>What if I work for the study center or Sponsor? What if I am a family member of someone who works for the study center or Sponsor?</u>

Study center/Sponsor employees and their family members do not have to be in this study. No one should influence or pressure you to be in this study. An employee's or his/her family member's decision to be in the study, or to leave the study early, will not affect the employee's job or job benefits.

Continued Contact with the Study Site:

If you participate in this study, you will be asked to maintain continued contact with the study site so they can monitor your health and provide any study updates as they occur. To help the study site accomplish this, they will ask you to provide a contact list (names and phone numbers) that can be used if the study site is unable to reach you.

To evaluate the effect of the study drug, it is important for all study subjects to continue to take the study drug as instructed by the study doctor until the study has finished. However, if after discussing with the study doctor that you should stop taking the study drug for any reason before the study ends, the study doctor would like to keep in contact with you regularly for as long as you permit. The study site will ask you to continue to come to your regularly scheduled study visits, because the information that we will collect is still important to the study results. If

you don't want to continue your regularly scheduled visits, you will be asked if you can be followed up by phone, email, or text at the time of your regularly scheduled visits throughout the study. If that is not possible, you will be asked if the study doctor can follow up on your health through review of your medical records and/or contact with your primary care doctor or other health professional managing your ongoing care. You may be asked to sign an additional network medical release form to allow for use of records in other health care facilities where you may have received care. This form is optional.

Please note that the decision not to come back for study visits or to be followed by phone calls may affect the value of this study. If you choose to completely withdraw from the study, move, or otherwise lose contact with the study doctor and study staff, and we are unable to reach you by telephone to complete a scheduled visit, we will contact the emergency contact person you have identified to try to obtain new contact information on you. We will also check local resources and hospital records and conduct compliant internet searches to try to obtain new contact information. If these efforts do not help to re-establish contact with you, we will submit your information, i.e., your name, gender, date of birth, last known address and telephone number, via Acurian , Inc. to OmniTrace Corp., a US-based clinical trial support company who will attempt to obtain updated contact information via legally permissible means including when available and permitted, search publicly available information resources, database research, genealogical research and onsite visits to local municipal resources. When authorized, OmniTrace, Corp. or its contractors may contact you directly in order to determine your vital status.

As it is described in this ICF, you will have to come to the study clinic for appointments and you will have other responsibilities as part of your participation in the study. To help you remember these appointments and responsibilities, an automated messaging system is available to you. This will allow you to receive reminder messages via text message, email, or phone. The messages will offer tips, resources, and information on hypogonadism and clinical trials, along with reminders about the study. Acurian, Inc. ("Acruian") is the US-based company that manages this messaging service.

This is an optional service. It is entirely your choice whether you would like to receive these messages. You may opt out at any time. Opting out of these messages has no impact on your participation in the study.

If you would like to receive these messages, your study coordinator will ask you for your cell phone number and/or email address. You can decide if you want to receive study information via text messages, emails, or phone calls. In addition, you will also be offered the option of downloading a mobile application ("App") to your smartphone, at no charge. If you download the App and opt into receiving messages, the messages will also be stored within the message center of the App. The study coordinator will provide your study-specific subject ID to Acurian along with your name, phone number, email address and the date you started on this study. If you choose to download the App then you need to provide both your phone number and email address. This information will not be released to anyone other than Acurian. Acurian will not share this information with anyone else except with Twilio Inc, a US-based third-party service provider, unless required by law.

These messages will not result in any additional charges beyond your standard SMS messaging rates. The App is available to download at no charge.

If at any time the phone number or email address provided in this document changes, please alert the study personnel so that your information can be updated.

Request to Receive Optional Messages

☐ Yes I would like to receive these messages. I have read and understood the information above. I confirm that the contact information I am providing is accurate.

I prefer to be contacted by:

☐ **Text Message:** _____

☐ **Email:** _____

☐ **Telephone Call:** _____

Bone Fracture, Anemia, and Diabetes:

Bone Fracture: During the study, you will be asked whether or not you experienced a fracture since your last visit at every study contact. If you experience fractures during the study, you will be asked to provide all documentation, including medical records of the fractures. No additional procedures will be performed.

Anemia: During this study, you will have blood drawn (hematology) at certain visits as indicated in the study activities table at the end of this consent. Your blood count will be looked at to determine if you have anemia. No additional procedures will be performed.

Diabetes: Pre-diabetes is a condition of elevated blood sugar that can increase the chance of developing diabetes. You will have blood drawn (Fasting Glucose and HbA1c) at certain visits as indicated in the study activities table at the end of this consent. Your blood sugar levels will be looked at to determine 1)if you had pre-diabetes prior to starting study drug and 2) if at any time in the study your sugar levels improved or got worse or stayed the same.

OPTIONAL Sub-Studies:

If you meet the additional inclusion and none of the additional exclusion criteria, you may volunteer to participate in one or both of the below sub-studies; this research is separate from the main study. You do not have to participate in either of the optional sub-studies if you don't want to. If you qualify for one or both of the sub-studies below and choose not to participate, your decision will not affect your participation in the main study.

Sexual Function Sub-Study (OPTIONAL): This sub-study will examine overall sexual activity, sexual desire, and erectile function through completion of additional questionnaires. If you choose to participate in this sub-study, you will be required to complete additional health questionnaires on the tablet during your in-person study visits. Also, you will complete the Psychosexual Daily Questionnaire (PDQ) by telephone or via a web-based system (online) prior to certain visits as shown in the table below. The additional questionnaires should take approximately 10 minutes to complete.

Schedule of Sexual Function Sub-Study Activities:

Activity (Questionnaires)	**Total number of questions**	**7 Consecutive days prior to Day 1**	**Day 1**	**Week 26**	**Week 52**	**Week 104**	**Final Visit/Week 260 OR if you stop the study early**
International Index of Erectile Function (IIEF-5)	5		X		X	X	
Psychosexual Daily Questionnaire (PDQ; Question 4) To be completed for 7 consecutive days prior to each visit	12	X		X	X	X	
Patient Global Impression of Improvement (PGI-I Libido)	1				X	X	X

Persistent Depressive Disorder (PDD) Sub-Study (OPTIONAL): This sub-study will examine depressive symptoms in men with low-grade, mid-life-onset PDD through completion of additional questionnaires. If you choose to participate in this sub-study, it will require you to complete additional health questionnaires during your in-person study visits. The additional questionnaires should take approximately 10-15 minutes to complete.

Schedule of PDD Sub-Study Activities:

Activity (Questionnaires)	Total number of questions	Day 1	Week 26	Week 52	Week 78	Week 104	Final Visit/Week 260 OR if you stop the study early
Patient Health Questionnaire-9 (PHQ-9)	10		X	X	X	X	
Additional Persistent Depressive Disorder (PDD) Questions	Up to 10	X	X	X		X	
Geriatric Depression Scale (GDS)	15	X	X	X		X	
Patient Global Impression of Improvement (PGI-I Mood)	1			X		X	X

Costs:

Neither you nor your insurance company will have to pay for the study drug (AndroGel 1.62% or placebo) or procedures that are done only for the study.

Reimbursement and Payments:

The IRB has also agreed that you may be paid $40.00 for each completed study visit, and $15.00 for each completed telephone visit. We may have to report this payment to the IRS if applicable.

The below Sponsor service is only intended for emergency use when a subject cannot provide his own travel to the study site:

A study travel organization can assist you with travel arrangements for emergency situations to and from your study appointments if you do not have any means of transportation after the Day 1 visit. This service is for emergency purposes only (i.e., your car broke down, your ride is not available, etc.) and not meant to be a permanent way of transportation to and from study visits. The cost of your participation in the Travel Assistance Program is covered by the study Sponsor and the service is provided by third-party companies, Acurian, Inc. (“Acurian”) and its partner Colpitts World Travel (“Transportation Company”). If you participate in this program, you will need to provide your contact information, such as full name, address, phone number and email address ; your date of birth; the date and time of your study visit; and the site’s name and address to the Transportation Provider. This service is only for ground transportation. Once the booking is complete, you or your study site, depending on your choice, will receive the travel itinerary via email.

The travel assistance request form can be completed online or over the phone. Your information is securely transmitted to the Transportation Provider.

Your information will only be collected for the purpose of organizing your travel arrangements to and from your study appointments. All personal information that you provide will be kept completely confidential and will not be disclosed to any other third party except if it is required by law or to transportation providers (e.g. car service providers) to the extent it is necessary for booking your travel arrangements. Your information will not be given or sold to anyone else, including the study Sponsor and you will not be contacted for any purpose outside of those detailed above.

You do not have to use this service for travel arrangements; your decision to use it is voluntary. If you decide to use this service, you can change your mind at any time and cancel it. If you decide not to use the service, or if you decide to cancel the service, you can still take part in the clinical study.

If you need to use this Travel Assistance Program, and your site is providing reimbursement for travel expenses, you may only use the Sponsor's Travel Assistance Program OR the reimbursement provided by the site.

Research Related Injuries:

Treatment for bodily injuries that result from the study drug or study procedures is available. Your study doctor will discuss with you the available medical treatment options. You may arrange to have treatment performed by the study doctor or a licensed doctor selected by you.

If you experience any injuries that result from the study drug or study procedures, the Sponsor will provide reimbursement for reasonable medical expenses that are necessary to treat such injuries.

The Sponsor makes no commitment to provide compensation except as described above. You will not lose any of your legal rights or release the Sponsor, the study doctor, the study staff, or study site from liability for mistakes or intentional misconduct by signing this consent document.

INFORMATION ABOUT CONFIDENTIALITY AND HIPAA AUTHORIZATION

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.

Why is access to my health information being requested?

To help answer the research questions, the investigator and research team will need to use and store personal health information about you. We are asking your permission to collect, use, and store your personal health information, as well as to share your personal health information with others, as explained below. If you don't give this permission, you won't be able to take part in the research study. You can still be in the main part of the study even if you do not give permission for the use and sharing of your information for the optional part(s) of the study. If you do not want to give permission for the use and sharing of your information for the optional part(s) of the study you should not agree to take part in them.

We will only share your personal health information as described below or if required or permitted by law.

What information will be collected and used?

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.

The following are examples of personal health information that may be collected:

- results of tests and procedures such as physical examinations and blood and tissue testing
- information about your biological samples
- information about your medical conditions and history

Who will see my protected health information?

The study doctor and the research team will use your personal health information to carry out this study. By signing this consent, you allow access to your personal health information (including direct access to your medical records at the study site or any other facility where the study is conducted) to the following:

Who may have access:	**Purpose:**
The Sponsor and its representatives	To oversee the study and the optional research and make sure the information is correct and to report to government agencies as required by law
The study doctor and the research team	To conduct the study and the optional research and make sure the information is correct
The FDA and government agencies that regulate research in the U.S. and other countries	To make sure applicable laws are being followed
Quorum Review	To protect the rights and welfare of study subjects
Centers for Medicare & Medicaid Services (the agency that runs Medicare)	To determine if Medicare should pay for services related to the study, including diagnosis and treatment for research-related injuries
Clinical trial recruitment and retention company (and the people and organizations they work with on this study)	To reach out to you for appointment reminders, study instructions, and other important study updates

If the Sponsor is going to pay for health care services that you receive in connection with the study, we may also need to disclose your personal health information to the Sponsor and its representatives in order for the Sponsor to comply with a Medicare reporting requirement.

Please note that the study doctor or study staff may also share personal information about you if required by law (for example, if the study doctor or study staff suspects that you are going to harm someone or yourself). If you have questions about this, please ask the study doctor.

After the study has been completed, it is possible that your coded data will be used for future research relating to the study drug, your disease or condition, or similar diseases and medical conditions.

Will you keep my health information confidential?

We will keep your personal health information as confidential as possible. If the results of the trial are published, your identity will remain confidential. It is not likely your personal information will be given to others without your permission. However, once your information leaves the study site, we can't control how it is used, and it will no longer be covered by the HIPAA Privacy Rule.

Your study records and biological samples will receive a unique code (subject number) in place of information that can be used to identify you (such as your name or address). The Sponsor and people and companies working with the Sponsor will have access to and use these coded records and samples and accompanying data to conduct the research described in this form. However, they will not be able to see the key that links the code to you.

How long will my personal health information be used?

Access to your personal health information begins as soon as you sign this form. This authorization expires fifty (50) years after the date that you sign this form, unless you revoke it sooner.

If you don't want us to use and disclose your personal health information any more, you must let the study doctor know in writing. If you revoke your permission, you will not be able to continue in the research study. We will stop collecting information from you, but we will still use, analyze, and disclose any information that we gathered before you revoked your permission. You can revoke your permission for the optional part(s) of the study and remain in the main study.

Can I see my study records?

You have the right to see and get a copy of your medical records. However, by signing this informed consent, you agree that you may not get to see your records relating to the study until after the study is over, including whether you are taking AndroGel 1.62% or placebo.

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.

Voluntary Participation and Withdrawal

You do not have to be in the main study or any of the optional research. You may still participate in the main study if you decide not to participate in the optional research. There is no penalty or loss of benefits if you don't want to participate or if you change your mind, and your decision won't affect your regular medical care.

You may withdraw from the main study and optional research, or just the optional research, and you may request that your samples be withdrawn, at any time, by notifying the study doctor in writing at the address on page 1 of this form. There will be no consequences or penalties if you do this.

If you leave the study, the study doctor and study staff will still be able to use and disclose your information that they have already collected.

The study may be stopped early by the Sponsor, the study doctor, Quorum Review, or the FDA. You could be withdrawn from the study without your consent, at any time and for any reason.

Who should I contact with questions, concerns, or complaints about this research study?

In the event of an emergency, dial 911 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.

You can ask questions about the study at any time. You can call the study doctor or study staff at any time if you have any concerns or complaints. You should call the study doctor or study staff at the phone number listed on page 1 of this form if you have questions about the study procedures, study costs (if any), study payment (if any), or if you get hurt or sick during the study.

Quorum Review reviewed this study. Quorum Review is a group of people who review research studies to protect the rights and welfare of research participants. Review by Quorum Review does not mean that the study is without risks. If you have questions about your rights as a research participant, 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 can call Quorum Review or visit the Quorum Review website at www.QuorumReview.com.

> Quorum Review is located in Seattle, Washington.
> Office hours are 8:00 AM to 5:00 PM Pacific Time, Monday through Friday.
> Ask to speak with a Research Participant Liaison at 888-776-9115 (toll free).

If you need medical attention, go to the nearest emergency room.

Study Activities Table

Activity	Screening Visit 1	Screening Visit 2	Screening Visit 3	Day 1	Week (W) 2	W 4	W 12	W 26	W 39 (phone)	W 52 (year 1)	W 65 (phone)	W 78	W 90 (phone)	W 104 (year 2)	W 116 (phone)	W 130	W 142 (phone)	W 156 (year 3)	W 168 (phone)	W 182	W 194 (phone)	W 208 (year 4)	W 220 (phone)	W 234	W 246 (phone)	W 260/Final Visit (year 5)	Leave study early	Unscheduled	30-Day Call after Study Completion
INTERVIEWS & QUESTIONNAIRES																													
Informed Consent	X																												
Review qualifications for study (inclusion/exclusion criteria)		X	X	X																									
CV Risk Assessment		X																											
Medical/Surgical History/Cancer History/CV Family History		X		X																									
Alcohol and Nicotine Use		X																											
Ask About Your Health	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications (List of all your medications)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Site Endpoint Questions (you will be asked about CV symptoms, prostate symptoms, and any fractures)					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone call									X		X		X		X		X		X		X		X		X				X
Modified Rankin Scale																												X	

(Questions asked of men who have had a stroke)																											

Study Activities Table (Continued)

Activity	Screening Visit 1	Screening Visit 2	Screening Visit 3	Day 1	Week (W) 2	W 4	W 12	W 26	W 39 (phone)	W 52 (year 1)	W 65 (phone)	W 78	W 90 (phone)	W 104 (year 2)	W 116 (phone)	W 130	W 142 (phone)	W 156 (year 3)	W 168 (phone)	W 182	W 194 (phone)	W 208 (year 4)	W 220 (phone)	W 234	W 246 (phone)	W 260/Final Visit (year 5)	Leave study early	Unscheduled	30-Day Call after Study Completion
Participant Reported Outcome Questionnaires																													
I-PSS (Prostate Questionnaire)		X		X			X			X								X								X	X		
DISF – SRII Section I (Sexual Function Questionnaire)		X																											
HIS-Q (Hypogonadism Questionnaire)				X				X		X				X												X	X		
PHQ-9 (Health Questionnaire)		X																											
PGI-I Hypogonadism (Health Questionnaire)								X						X												X	X		
EXAM																													
Height & BMI, Weight		X		X			X			X				X				X				X				X	X		
Physical Examination		X					X	X		X				X				X				X				X	X	X	
DRE (Digital Rectal Exam)		X								X								X								X	X	X	

Vital Signs (Blood Pressure, Respiratory Rate, Heart Rate [pulse], Temperature)		X		X	X	X	X	X		X				X				X				X				X	X	X	
Electrocardiogram		X																								X	X	X	

Study Activities Table (Continued)

Activity	Screening Visit 1	Screening Visit 2	Screening Visit 3	Day 1	Week (W) 2	W 4	W 12	W 26	W 39 (phone)	W 52 (year 1)	W 65 (phone)	W 78	W 90 (phone)	W 104 (year 2)	W 116 (phone)	W 130	W 142 (phone)	W 156 (year 3)	W 168 (phone)	W 182	W 194 (phone)	W 208 (year 4)	W 220 (phone)	W 234	W 246 (phone)	W 260/Final Visit (year 5)	Leave study early	Unscheduled	30-Day Call after Study Completion
CENTRAL LABS (Blood and Urine Tests)																													
Testosterone (Blood Test)	X	X	X		X	X	X	X		X		X		X				X				X				X	X	X	
Free Testosterone (Blood Test)		X	X							X																			
DHT, Estradiol (Blood Test)				X						X								X								X	X		
PSA (Blood Test)	X						X			X				X				X				X				X	X	X	
Hematology (Blood Test)		X		X				X		X		X		X				X				X				X	X	X	
HbA1c (Blood Test)		X								X				X				X				X				X	X	X	
Fasting Glucose (Blood Test)		X		X						X				X				X				X				X	X	X	
Chemistry (Blood Test)		X								X																X	X	X	
Urinalysis		X																								X	X	X	

hsCRP (Blood Test)		X																										
Serum Creatine (eGFR assessment) (CKP-EPI equation)		X																							X	X		
Approximate amount of blood drawn in teaspoons	1	2.5	1	1.5	0.5	0.5	1	1		4		1		2				2.5				2				3	3		
STUDY DRUG DOSING																													
Randomization (First dose)				X																								
Receive Study Drug				X	X	X	X	X		X		X		X		X		X		X		X		X				X	
Return Study Drug					X	X	X	X		X		X		X		X		X		X		X		X		X	X		
Study Drug Compliance Discussion					X	X	X	X		X		X		X		X		X		X		X		X		X	X		

CONSENT AND AUTHORIZATION

- I have read this form, and the research study has been explained to me. I have been given the chance to ask questions, and my questions have been answered.
- I will receive a copy of this consent form after it is signed.
- I do not give up any of my legal rights by signing this form.
- I authorize the use and disclosure of my personal health information as described in this form.
- I agree to participate in the main research study described above.

If you agree, your own doctor or specialist may be:

- Informed about you taking part in this study
- Asked to provide details of your medical history and any new information about your health during the study

I agree that my family doctor or specialist be informed about my participation in this study.

☐ Yes ☐ No ☐ I don't have a family doctor or specialist

Optional Sexual Function Sub-Study

☐ **Yes.** I volunteer to participate in the Sexual Function Sub-Study described in this form if I qualify.

☐ No, I **DO NOT** volunteer to participate in the Sexual Function Sub-Study described in this form. I can still be in the main study.

Optional Persistent Depressive Disorder (PDD) Sub-Study

☐ **Yes.** I volunteer to participate in the Persistent Depressive Disorder Sub-Study described in this form if I qualify.

☐ No, I **DO NOT** volunteer to participate in the Persistent Depressive Disorder Sub-Study described in this form. I can still be in the main study.

Optional Early Withdrawal Follow-up

If you choose to stop participating in this study or to withdraw from the study, may the study staff call you at the end of the study (when the entire study is over) to assess your health?

☐ **Yes.** The study staff may call me when the entire study is over.

☐ No, **I DO NOT** want the study staff to call me when the entire study is over.

Optional Travel Assistance Program

If you need to use the Travel Assistance Program, will you provide your contact information including your full name, address, phone number and email address to the study travel organization and authorize the use of your personal information for the purpose of organizing your travel arrangements to and from your study appointments?

☐ **Yes.** I agree to provide the described personal information and authorize the use of my personal information for the activities described above.

☐ No, **I DO NOT** agree to provide the described personal information or authorize the use of my personal information for the activities described above. I will not be able to use the Travel Assistance Program. I can still be in the main study.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

I attest that the individual providing consent had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participation in this study.

_____
Printed Name of Person Explaining Consent

_____ _____
Signature of Person Explaining Consent Date