CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Sponsor / Study Title:	**Kolon TissueGene, Inc. / "A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Phase 3 Study to Determine the Efficacy of TG-C in Subjects with Kellgren and Lawrence Grade 2 or 3 Osteoarthritis of the Knee"**
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Subject ID: _____

1. WHY HAVE I BEEN GIVEN THIS FORM?

You are being invited to take part in a clinical research study of an investigational new drug named TG-C to treat osteoarthritis (degenerative joint disease). "Investigational new drug" means that it is a drug that has not been approved for marketing by the United States (US) Food and Drug Administration (FDA), except for use in research studies. The FDA is allowing TG-C to be used in this research study. This clinical research study is being sponsored by Kolon TissueGene, Inc. (hereafter referred to as the Sponsor).

You are being asked to take part in this research study because you have knee osteoarthritis. If you meet the study criteria and agree to take part in this study, you will come to the study center for about 11 visits over about 2 years. What will happen during the study is described in Section 5. The possible direct benefits of taking part in this study are delayed progression of your knee osteoarthritis, longer preservation of your knee joint, and improved quality of life. However, you may not get any direct benefit from taking part in this study. The study treatment

may not help treat your specific osteoarthritis. What is learned from this study may provide benefits in the future for other people with knee osteoarthritis. Better scientific gain depends on the quality and completeness of data. Premature discontinuation (stopping) and missing scheduled study visits can have a negative effect on the analysis (examination) of the study data. The FDA wants complete data across visits for a proper evaluation of the treatment effect (results). The side effects most often reported with TG-C treatment include injection site pain, swelling, and mild inflammation (such as joint redness, swelling, warming sensation, pain, and stiffness). You do not have to be in this study to get treatment for your knee osteoarthritis. Your doctor can discuss other treatment options with you.

Before you decide if you want to take part in this study, it is important for you to understand why the research is being done, how your information will be used, what the study will involve, and the possible benefits, risks, and discomforts. Please take time to read the following information carefully. Some terms may be unfamiliar to you. If there is anything you do not understand or if you would like more information, please ask the study doctor or study staff. You may also discuss the study with family members, friends, and your own doctor if you wish.

If you decide that you want to take part in this study, you will be asked to sign the consent statement at the end of this form (you will be given a copy of this form to take home with you). No tests or procedures related to the study will be done until you have read and signed this form. You will be free to withdraw from the study at any time without having to give any reason. A decision not to take part in this study, or to withdraw at any time, will not affect your health care.

2. WHAT IS THE BACKGROUND AND PURPOSE OF THE STUDY?

Osteoarthritis is a joint disease that causes an inflammatory response (the body's response to disease or injury such as redness, swelling, warmth, and pain), which worsens over time. Osteoarthritis is a serious condition that can affect the different parts of the joint including cartilage, bone, synovium (membrane that covers the joint and releases fluid), ligaments (connects bones to each other), and meniscus (cartilage between joints). Cartilage is a thin covering on the surface of joints that acts as a cushion, which protects your bones and helps your joints to move smoothly.

When parts of the joint deteriorate or get worse, a condition known as degenerative joint disease, or osteoarthritis, occurs, with damage to and loss of cartilage. This joint deterioration often happens over a period of many years. This problem usually occurs in people after 50 years of age but may begin sooner if there is a history of joint injury. If you are aware of any significant injury to your knees, please let your study doctor know because cartilage damage can predispose you or increase your risk to develop osteoarthritis. Without healthy cartilage to protect joints, bones are left unprotected, and pain, swelling, and gradual loss of the ability of the joint to move smoothly can occur.

The Sponsor is evaluating whether TG-C may reduce damage caused by osteoarthritis. TG-C is composed of two different components: 1) cartilage cells from a single healthy living human donor; and 2) a gene transfer product made from GP2-293 cells. Retroviral gene transfer means that copies of a gene are put into the second component to make the product. In addition to donor cartilage cells, the second component of TG-C (GP2-293 cells) produces a growth factor called TGFβ1. TGFβ1 is a type of protein called a cytokine that is normally present in your body in low

levels. In animal studies, TGFβ1 has been shown to cause the growth of cartilage. In a laboratory, a retrovirus (a type of virus) is used to insert the gene needed to make TGFβ1. This gene is then placed into the GP2-293 cells. The retrovirus that is used to place the gene into the new cell is called a vector. TG-C is being studied in subjects who have osteoarthritis of the knee to see if it will cause new cartilage to grow in the diseased joint.

Before this study began, TG-C had already been given to subjects in 2 previous studies in the US. The TG-C used in these 2 studies was made using the same process used for this study.

In addition, TG-C made using a different process and at different doses has been given to patients in 4 studies in Korea.

In previous studies, TG-C showed preliminary results of reducing joint pain and improving function in subjects with knee osteoarthritis. This study will help us determine whether TG-C will provide benefit in relieving pain and improving function in knee osteoarthritis.

While the formulation (or ingredients) of TG-C for this study has not changed from the formulation used in the studies listed above, the process used to make the product for this study involves use of cells whose identity is different than originally thought. Specifically, a failure to filter during the cell line generation process led to GP2-293 cells becoming the recipient of the gene instead of cartilage cells as originally planned. Further testing confirmed that a TG-C component is made using irradiated (exposed to radiation) GP2-293 cells expressing TGFβ1, previously thought to be irradiated human cartilage cells expressing TGFβ1. The cells have not changed but what they were initially identified as was not correct. GP2-293 cells originate or come from human embryonic kidney cells (HEK-293) that are grown in tissue culture. HEK-293 cells have been used widely in genetic and biotechnology research and development for many years. During the process to make TG-C, the GP2-293 expressing TGFβ1 cells are irradiated with the goal of making them incapable of multiplying. There have been no occurrences (events or instances) of cancer linked to the use of TG-C; however, use of retrovirus to generate GP2-293 cells expressing TGFβ1 requires surveillance (or monitoring) for the occurrence of cancers, which will be assessed throughout the study. If any new safety information becomes available, you will be informed in a timely manner.

The purpose of this study is to find out more about your knee symptoms and joint structure and potential side effects associated (or connected) with TG-C treatment. The questionnaires will help determine if TG-C can help reduce knee pain and improve knee function, based on changes in activities of daily living. The X-rays and MRI (magnetic resonance imaging) will help to document (record) if there are structural changes in your knee that can be detected (identified) during therapy with TG-C.

3. WHAT IS THE STUDY ABOUT?

This is a study of the effects of TG-C treatment on osteoarthritis of the knee. This study will include men and women 40 years of age and older who have osteoarthritis of the knee that meet certain X-ray and medical standards. Eligible subjects who agree to be in this study will receive a single injection (using a needle) of either TG-C or placebo into the joint space of one of your knees called the "target" knee. The target knee will be selected by your study doctor based on the results of your knee X-rays (grade of disease) and evaluations (symptom [pain] scores). A

placebo looks similar to TG-C (the investigational study drug) but it does not contain any of the active ingredients of TG-C. A placebo should have no effect on your body and will not harm or help you. The placebo used in this study is sterile normal saline (water with a small amount of sodium chloride commonly known as salt).

To make comparing TG-C and a placebo as fair as possible, this study is "double-blinded." This means that neither you nor the study doctor evaluating your treatment will know which study treatment (TG-C or the placebo) you are receiving. The study treatment you will be given will be decided at random (by chance), like picking out of a hat, in a ratio of 2:1 for study drug vs. placebo. Therefore, about 67% of subjects will receive TG-C and about 33% will receive the placebo. Therefore, you should take part in this study only if you are willing to receive either TG-C or the placebo.

You will be one of about 510 subjects in this study at about 30 study centers in the US. You will come to the study center for about 11 visits over about 2 years with additional annual cancer safety follow up for a total of 15 years following receipt of study drug if you do not agree to participate in a separate 15-year long-term safety study. You will be contacted by phone approximately every month between clinic visits for the first 2 years to inquire about your health. You will be contacted starting each year until 15 years following the injection of study drug to complete the annual cancer questionnaire if you do not participate in the separate 15-year long-term safety study. If you cannot be reached during this long-term follow-up period, when possible, we will attempt to contact your primary care physician to ask about any cancer diagnosis.

4. DO I HAVE TO TAKE PART?

No, you don't. It is up to you to decide whether or not to take part in this study. You are free to refuse to take part in it. Even if you refuse to take part in this study, you will not be disadvantaged in any way, including medical treatment and care you are entitled to receive. If you decide to take part, you may change your mind and decide to withdraw from the study at any time and for any reason. You may be asked to provide written notification of your decision to withdraw from the study. You are not required to explain your reasons for withdrawing. If you withdraw, you will not suffer any penalty or loss of benefits regarding your future care.

The study doctor can withdraw you from the study at any time if he or she feels it is in your best interest or if you cannot follow the study directions.

In addition, your taking part in the study may be stopped by the Sponsor or by the regulatory authorities (for example, FDA) or by an independent ethics committee (for example, Institutional Review Board [IRB]/Institutional Biosafety Committee [IBC]; these committees review study safety and ethics to ensure that subjects' rights are not violated) at any time without your consent (agreement), after the reason(s) for doing so (for example, your own safety, study treatment safety, or Sponsor's decision) have been explained to you and after you have been given advice about continued care for your condition, if this is appropriate. Also, the Sponsor has the right to stop the study for medical or business reasons. If this happens, all subjects taking part in the study will be withdrawn.

If you choose to withdraw from the study, it is recommended that you speak with your study coordinator or study doctor before withdrawing. If you withdraw (or are withdrawn) from the study, you will be asked to have withdrawal procedures (described in Section 5.2 of this informed consent form) done, and information about you will be collected as described in Section 13.

5. WHAT WILL HAPPEN TO ME DURING THE STUDY?

5.1. Screening

Before you receive study treatment, you will take part in a Screening period of up to 45 days. During the Screening period, the study doctor will check your arthritis, ask you questions about your pain, and do blood tests to find out if you are eligible to take part in the study. All of the things that will be done during the Screening period are described below under Visit 1 (Screening).

5.2. Study Visits

The information below describes the tests and procedures that you will have at each study visit. There is a table at the end of this consent form that also shows you what will be done at each study visit.

You will be asked to fast (nothing to eat or drink except water) for at least 8 hours before some study visits when blood and/or urine samples are taken for certain laboratory tests (Visits 2, 6, 7, 8, 9, 10, and 11).

Visit 1 (Screening). This visit will take about 2-3 hours. After you give your consent (agreement) to participate in this study, some procedures will be performed to see if you qualify to participate in the study. To find out if you qualify to be in this study, the following tests and procedures will be done:

- Medical history will be reviewed.
- Physical examination, including height, weight, and Body Mass Index (BMI).
- Vital signs (blood pressure, heart rate, breathing rate, and body temperature).
- Examination of both knees.
- A review of medications you take (prescription and non-prescription commonly referred to as "over the counter" medicines) and therapies you receive (including physical therapy and acupuncture). If eligible to participate in the study, you will be asked to stop taking any prohibited medications (medications not allowed) 14 days before your dose of study medication.
- Questionnaires related to your condition will be completed.
- X-rays of both knees.
- MRI of the target knee (must be performed at least 7 days prior to Visit 2, Day 0). Additional time/travel may be required for visit, depending on where the MRI is done.
- Blood and urine samples will be collected for laboratory testing. More information about blood and urine samples is provided in Section 5.3.
- You will be instructed not to take analgesic (pain relieving) medications for 24 hours before in-clinic visits and you will be reminded prior to each visit.

If necessary, the study doctor may contact your primary care physician for information about your medical history.

Visit 2 (Day 0). Visit 2, which is the study treatment dosing visit, will take place within 45 days after Visit 1 (Screening). Visit 2 will take about 4 hours.

The following tests and procedures will be done before the injection of study treatment on Day 0:

- Questionnaires related to your condition and general health will be completed before other study procedures performed.
- Eligibility criteria will be confirmed.
- Examination of the target knee.
- Any changes in medications and therapies will be reviewed.
- Physical examination, including weight
- Vital signs (blood pressure, heart rate, breathing rate, and body temperature).
- Blood (fasting) and urine samples will be collected for laboratory testing. More information about blood and urine samples is provided below.

Study Treatment Injection

If you are still eligible to take part in the study after the tests and procedures in this visit are done, you will receive a single injection of study treatment (TG-C or a placebo) into your target knee. The injection will be given by a clinician injector who is a medically trained member of the study staff (for example, a licensed and qualified injector, such as a physician [MD or DO] or a physician extender [such as a physician assistant or nurse practitioner]) but is not the study doctor overseeing your study tests and procedures. Neither you nor your study doctor will know which study treatment you were given. If there is a medical need or reason to find out which study treatment you received, then the study doctor can find that out.

To give you the study treatment injection, you will lay down on your back and be asked to keep your target knee in the correct position (bent at an angle). Before the study treatment is injected, a topical (on your skin) anesthetic (pain reducer) may be used to numb (lessen the feeling of) the injection site in your target knee. The study treatment will then be injected into your target knee. To make sure the needle is in the right place when injecting the study treatment into your target knee, the clinician injector will use ultrasound, as described in Section 7.

After the study treatment is injected into your target knee, you will be monitored for 2 hours. Your vital signs (blood pressure, heart rate, breathing rate, and body temperature) will be measured about every 15 minutes for the first hour and about every 30 minutes for the second hour. You will be monitored for any side effects during this period, and your target knee will be re-checked at the end of the period. At the end of the period, if there are no problems seen with your target knee, you will be allowed to resume light activity such as walking, you will be given instructions on how to care for your target knee at home, and you will be allowed to go home. You will be told not to drive for 48 hours after the injection.

Visits 3 and 4 (Day 1 and Week 1, respectively). These visits will take about 1 hour. You will be asked to avoid medications to treat pain for the 24 hours before your appointment. At these visits, the following tests and procedures will be done:

- Questionnaires related to your condition will be completed before other study procedures.
- Physical examination, including weight.
- Vital signs (blood pressure, heart rate, breathing rate, and body temperature).
- Examination of the target knee.
- Any illness or injury since your last visit will be reviewed.
- Any changes in medications and therapies will be reviewed.
- Blood and urine samples will be collected for laboratory testing. More information about blood and urine samples is provided below.

Visit 5 (Month 1). You will be contacted by telephone by a member of the study staff who will ask you questions about your health and about any changes in your medications or other therapies. An office visit may be scheduled if the study doctor believes that it is needed.

Visits 6, 7, 8, 9, 10, and 11 (Months 3, 6, 9, 12, 18, and 24, respectively). These visits should take between 1 and several hours, depending on the tests and procedures needed at each visit. You will be asked to avoid medications to treat pain for the 24 hours before your appointment. At these visits, the following tests and procedures will be done:

- Questionnaires related to your condition and general health will be completed before other study procedures.
- Physical examination, including weight.
- Vital signs (blood pressure, heart rate, breathing rate, and body temperature).
- Examination of the target knee.
- Any illness or injury since your last visit will be reviewed.
- Any changes in medications and therapies will be reviewed.
- Blood (fasting) and urine samples will be collected for laboratory testing. More information about blood and urine samples is provided below.
- MRI of the target knee will be performed at Visits 7, 9, and 11 (Months 6, 12, and 24, respectively). Additional time/travel may be required for visits, depending on where the MRI is done.
- X-ray of the target knee will be performed at Visits 9 and 11 (Months 12 and 24, respectively).

You will be contacted by telephone by a member of the study staff once per month between clinic visits up to Month 24. They will ask you questions about your health status (for example, about any symptoms or side effects you may be having, and any medications you are taking).

Safety Follow-up. Subjects who take part in this study will be followed up for 15 years following receipt of study drug. At the 24 month visit (Visit 11) or final (early withdrawal) study visit; whichever occurs first, all subjects that were dosed with either TG-C or placebo will be asked to take part in a separate 15 year long term safety follow-up study. Participation in the separate long-term safety follow-up study is voluntary. If you agree to participate, the long-term safety follow-up study will include annual office visits and telephone interviews.

If you do not choose to participate in the separate long-term safety follow-up study, a separate cancer surveillance questionnaire will be provided for completion every year for a total of 15 years after study treatment. In the event that the questionnaires are not completed and returned, the study staff will contact you directly via phone to ensure the questionnaires are completed. If you cannot be reached during this long-term follow-up period, when possible, we will attempt to contact your primary care physician to ask about any cancer diagnosis.

Withdrawal. If you withdraw or are withdrawn from the study, you may be asked to have in-home visits through Visit 11 (Month 24) to get information about your response to study treatment. If you withdraw due to an adverse event (side effect) or study doctor decision before Visit 11 (Month 24), you will be asked to have the study procedures described for Visit 11 (Month 24) at the time that you withdraw from the study. Although you have the right to refuse these tests and procedures, the annual cancer screening questionnaire will be provided to you for completion every year for a total of 15 years following treatment with study drug.

Unscheduled visits. If your study doctor believes that you should have additional visit(s), (for example because of a new symptom, side effect, or laboratory result), you may be asked to come to the study center for additional tests or procedures. You may also be asked to have X-rays retaken or the MRI scan repeated if the image (picture) taken was unclear.

Arthroplasty (replace or repair joint). If you have no relief from your knee osteoarthritis symptoms, you, in consultation with your doctor, may determine to have an elective (optional) surgical procedure (including total knee replacement) 12 months or more after the injection of study treatment. If any knee surgery is planned within the first 12 months of the study you cannot participate as premature withdrawal from the study leads to a loss of scientific strength (important data to show the outcome) of the study. Knee surgery is at your own discretion, in consultation with your personal treating physician and/or the study doctor. Having surgery is not required for taking part in this study and is not considered part of the study. If you have surgery on your target knee through the end of the study (Month 24), assessments of your knee will be performed before surgery. As surgical treatment is not part of the study procedures, the risks related to arthroplasty or other surgical treatment will be provided by a specialist/consultant independent of this study.

5.3. Blood Tests and Urinalysis

Blood and urine samples will be taken at Visits 1, 2, 3, 4, 6, 7, 8, 9, 10, and 11 for routine tests of your general health or for other tests described below. You will be asked to fast (nothing to eat or drink except water) for at least 8 hours before some study visits when blood and/or urine samples are collected for certain laboratory tests (Visits, 2, 6, 7, 8, 9, 10 and 11). Urine screens for substance abuse will also be done at Visit 1 and 2. If you are a woman who may be able to have children, you will have a urine pregnancy tests at Visits 1, 2, 6, 7, 8, 9, 10, and 11.

At Visit 1, your blood sample will also be tested for human immunodeficiency virus (HIV; also called the AIDS virus) human T-lymphotropic virus 1 (HTLV-1), vesicular stomatitis virus (VSV-G) and hepatitis B and C. If the test result shows that you have HIV or hepatitis B or C (ie, result is positive), you will be referred to your primary care physician or a community health clinic for follow-up. Positive results for HIV and hepatitis B and C will be reported to health authorities according to local requirements. If the test results are positive for HTLV-1 or VSV-G, you cannot participate in this study. If you have any questions about these laboratory tests or results, please ask the study doctor or study staff.

The fasting blood and urine samples taken at Visits 2, 6, 7, 9, and 11 will also measure biomarkers. Biomarkers are a marker of a specific biological activity in the body. Biomarkers of osteoarthritis will be measured to see how biological differences are involved in the response to study treatment.

Blood samples taken at Visits 1, 2, 3, 4, 6, 7, 8, 9, 10, and 11 will be tested for vector (virus) DNA, which is related to the gene transfer into the GP2-293 cells to make TGF-β1, and the samples will also be tested for TGFβ1 expression. Blood samples taken at screening, Visits 6, 7, 9, and 11 will also be tested for the presence of replication-competent retrovirus. A replication-competent retrovirus is any virus that can copy itself in a human cell. Depending on the TGF-β1 results of the blood sample, another sample may be needed.

All your test results are confidential and will be disclosed only as required by law.

Except for urine drug tests, urine pregnancy tests, and blood tests for inflammation, all blood and urine samples taken for this study will be sent to a central laboratory. All urine drug tests, urine pregnancy tests, and blood tests for inflammation, are done at a local laboratory. Except for samples taken for measurement of biomarkers, urine samples will be destroyed after laboratory tests are complete and blood samples will be stored for up to 2 years for possible retesting. Blood and urine samples taken for biomarker measurements will be stored for up to 7 years after which they will be destroyed. Your biomarker samples may be studied at any time during the storage period.

Your blood and urine samples will be stored with similar samples from other people at a secure central laboratory, which has experience in storing and analyzing such samples. These laboratories may be located outside of the country in which the study is conducted. Your identity will be protected by the use of a code, which is a number specifically assigned to you (see Section 13).

The variations (changes) in your biomarkers may be compared with medical information collected in the study, but only as this information relates to the research goals described above. The results from this biomarker research may be analyzed (examined) along with results from other research. You should be aware that Kolon TissueGene might not conduct all research immediately and that your samples may be studied at any time before they are destroyed.

The purpose of biomarker analysis is not to provide you with test results or to make any results available to you, any insurance company, your employer, your family, the study doctor, or any other physician who treats you now or in the future.

No genetic research on your samples is planned. If the Sponsor considers genetic testing to be necessary, additional consent will be requested from you before any genetic testing is performed.

6. WHAT WILL I HAVE TO DO DURING THE STUDY?

First, you will be asked to sign this consent form if you agree to take part in this study. If you take part in this study, you should follow the study procedures and return to the study center for all the study visits. You should report any side effects to the study doctor.

You will be asked to fast (nothing to eat or drink except water) for at least 8 hours before some study visits when blood and/or urine samples are collected for certain laboratory tests (Visits 2, 6, 7, 8, 9, 10, and 11).

It is also important that you tell the study doctor or member of the study staff about any other medication you are taking or therapy you are receiving before and during the study.

You must not take NSAIDs (non-steroidal anti-inflammatory drugs) within 14 days before Visit 2 (Day 0) and for the initial 72 hours following the study treatment injection unless, in the opinion of the study doctor, they are medically necessary. You also should not begin use of any new herbal products during the study. You must not take any steroidal anti-inflammatory medications within 2 months nor receive any corticosteroid or other knee injections within 2 months before the study treatment injection visit (Visit 2).

You should not take any steroidal medications during the study unless, in the opinion of the study doctor, they are medically necessary.

Following the study treatment injection visit (Visit 2), you will need to:

1. Apply a gentle compressive dressing with a cotton roll and elastic bandage for the first 48 hours.
2. Ice the injected target knee periodically for the first 24 hours to help prevent swelling.
3. Avoid strenuous physical activities, especially sports-related activities such as running, biking, etc. for about 2 to 3 weeks, and restrict (limit) physical activities to walking.
4. Take over-the-counter acetaminophen for 3 to 5 days in the event of pain, swelling, or discomfort. Please talk with your study doctor prior to taking any medications.
5. Contact study staff to arrange further evaluation and treatment if pain, swelling, or discomfort persists and are not relieved by acetaminophen.

You are not to take medications (other than medications approved by the study doctor) for the target knee osteoarthritis pain relief.

You will be asked to not take any analgesics (pain medication) within the 24 hours before each study visit. You should contact the study doctor or study staff before taking other medications or therapies while taking part in this study.

On the day that you receive your study treatment injection, you will receive instructions on how to take care of your target knee for the first few weeks following the study treatment injection. It is important that you follow these instructions to help minimize possible side effects, such as swelling.

You must use an effective method of birth control during the initial 24 months of the study (approximately 2 years) as the risks of the study treatment on pregnant women, embryos, fetuses (unborn babies), and nursing infants are unknown. The effects of the study treatment on sperm are also unknown. More information about methods of birth control is provided in Section 7.

7. WHAT ARE THE POSSIBLE RISKS?

Study treatment: As with all research studies, the study treatment and study procedures may involve unknown risks. Any medication can have temporary and permanent side effects and can cause unforeseen (unexpected) adverse reactions and occasionally allergic reactions.

Because the study treatment is made of live cells, it is possible that abnormalities with blood test results or an immune reaction may occur. In previous clinical studies with TG-C, no clinically important blood test result abnormalities were seen. There have been no known immune reactions reported with the investigational study drug (TG-C) to date in the US.

In previous clinical studies with TG-C, the most common side effects seen were injection site pain, joint inflammation (such as joint redness, swelling, warming sensation, pain, stiffness, and/or loss of function), and joint effusion (fluid in the joint). Less common side effects seen were chills, fatigue, feeling cold, and feeling faint/fainting. Rarely, allergic reactions can be life threatening and may result in death. Treatment for allergic reactions will be available.

The study doctor will advise you on the right therapy for any problem or side effect that you might experience following the study treatment injection.

There is a slight risk that you may have abnormal tissue growth in your knee in response to the study treatment. However, this has not been seen in previous clinical studies with TG-C.

The study treatment is mixed and prepared by a pharmacist or other appropriately designated and trained staff at the study site (for example, nurse practitioner, physician assistant, or registered nurse) before it is injected into your target knee. When the study treatment is being prepared, there is a slight possibility that it will no longer be sterile (will get contaminated with bacteria or other substances that can make you sick). No contamination of the study treatment has been seen previously.

Because TG-C contains the growth factor TGF-β1, your blood levels of TGF-β1 may increase. In animal studies, increased blood levels of TGF-β1 caused heart problems (enlarged heart and abnormal thickening of the heart valves). In clinical studies involving humans, decreases in kidney function were seen, but they were reversible. TGF-β1 levels did not increase in subjects taking part in previous clinical studies with TG-C. Blood tests will be done throughout the study to check the levels of TGF-β1 in your body. Depending on these test results, you may be asked to return for repeat blood tests to confirm the results.

TG-C cells that are injected into the target knee are made with a special type of virus called a retrovirus. The TG-C cells are tested to make sure that no live retrovirus is found in the cells. If live retrovirus is present, there is a risk that the retrovirus may enter the normal tissue surrounding the joint or other places in your body. If this were to occur, there is the possibility that some of the DNA (the genetic material) from the retrovirus may join with your own DNA in

such a way that your DNA will be changed and, as a result, will not work properly and/or will make the cells cancerous. The risk of causing a new cancer related to TG-C is considered to be very small, and no cancers from retroviruses have been found in previous 2 studies with TG-C. Nevertheless, injection of irradiated GP2-293 cells does carry a potential risk of tumor formation requiring ongoing surveillance (or monitoring) throughout the study for the occurrence of cancer. Your immune system is expected to kill the retrovirus if it is present, so it should not be able to grow in your body. The study doctor will explain this to you. To help reduce the risk of live retrovirus in the TG-C cells, the cells are exposed to low-dose radiation, so that the cells die within 2 weeks after your study treatment dose is prepared. In previous clinical studies with TG-C, no live retrovirus or viral DNA were seen. Although GP2-293 cells expressing TGF-β1 are irradiated (exposed to radiation), it is also important to understand that anyone who receives the TG-C product is not receiving any form of radiation as a result of the injection of TG-C into the knee joint.

Although the long-term effects of TG-C are unknown, they are being monitored. At the 9-year time point of a 15-year follow-up study of TG-C in the US, no safety concerns related to the study treatment have been seen.

The risks of the study treatment on pregnant women, embryos, fetuses (unborn babies), and nursing infants are unknown, therefore, you must use an effective method of birth control during the first 24 months of the study (approximately 2 years). If you are a woman who may be able to have children, you will be given a urine pregnancy test at Screening and Visit 2 Day 0), and if the result is positive, you will not be able to participate in the study. If you are a male who is sexually active, you must inform your partner(s), if they are able to have children, that the effects of the study treatment on sperm are unknown. You or your partner(s) should use an effective method of birth control, so your partner(s) does not become pregnant.

If you are a sexually-active man or woman, you must use an accepted form of birth control for the first 24 months of the study (until Visit 11 [approximately 2 years]). Acceptable forms of birth control include:

- Men: abstinence, condoms with spermicide, or vasectomy.
- Premenopausal women: abstinence, intrauterine devices/systems, tubal ligation, hormonal methods (birth control pills, vaginal ring, transdermal birth control patch, Depo-Provera injection, and contraceptive implants), condoms, female cervical cap, and spermicidal methods (Today Sponge, diaphragm with contraceptive jelly or foam, vaginal contraceptive film, foam, inserts).

The study doctor will discuss methods of birth control with you if needed.

If you become pregnant or think you may be pregnant during the study, contact the study doctor's office immediately. You may be asked to withdraw from the study. You must not be breast-feeding an infant during the study. If your partner becomes pregnant or thinks she may be pregnant during the study, contact the study doctor's office immediately.

The study doctor must follow up and report on the progress and outcome of all pregnancies, even if you withdraw from the study or if the study has finished. If you or your partner becomes pregnant during the study, the study doctor or his/her staff will ask to contact you/your partner and your/your partner's physician for information about the pregnancy and the child until 1 year after the birth.

Blood draws: Blood samples will be taken from a vein (blood vessel) in your arm during the study. This may cause some discomfort and bruising, and there is a risk of infection. Other risks, although rare, include dizziness and fainting. The maximum amount of blood that will be taken on any day of the study is about 57 mL or 3.9 tablespoons. The total amount of blood that will be taken over the entire study is about 376.5 mL or 25.5 tablespoons.

Blood pressure and heart rate: An inflatable cuff will be placed on your arm and a machine will measure your blood pressure and heart rate. You may experience mild discomfort in your arm while the cuff is inflated.

X-ray: You will be exposed to a low level of radiation. You must not have an X-ray if you think you could be pregnant.

MRI: An MRI scan is painless and will not expose you to X-ray radiation. The MRI machine uses powerful magnetic waves to take pictures inside the body. The waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working. You should not have an MRI if you have metal or electronic devices inside your body (for example heart pacemakers and insulin pumps). You must tell the study doctor if you have metal in your body for any reason. Some people may feel frightened by the cramped space inside the machine or by the loud, repeated sounds the machine makes. You will be in the MRI machine for about 45 minutes. If you are concerned about feeling claustrophobic, your study doctor can recommend a medication to take prior to the scan.

You may be asked by your study doctor to have an additional short MRI scan following your first MRI test and again about 12 months later. If you withdraw from the study before 12 months the retest MRI scan will be done at the withdrawal visit. This is called an MRI test-retest scan and helps to make sure that MRI scans are consistent (the same). If you agree, you will be asked to change position and then be scanned for about 15 more minutes. If you are willing to participate, please sign and date below.

Ultrasound: An ultrasound is a painless and a non-invasive test using sound waves to make pictures of the inside of the body. During an ultrasound of your target knee, you will lie on a table, and a small amount of gel will be applied to your target knee. The transducer (a device sending and receiving the sound waves) will be moved around on your target knee. While the transducer is being moved around on your target knee, it may cause some temporary mild discomfort or pressure.

Topical anesthetic: The most common topical anesthetic (decreases pain sensitivity) for joint injections is ethyl chloride. Side effects are not common but may include freezing of the sprayed area with change in skin coloring, rash, hives, blistering, peeling, infection at application site, and delayed wound healing.

8. WHAT ARE THE POSSIBLE BENEFITS?

The possible direct benefits of taking part in this study are delayed progression of your knee osteoarthritis, longer preservation of your knee joint, and improved quality of life. However, you may not get any direct benefit from taking part in this study.

You will be given close attention by the study staff during the time you are involved in this study. You may also receive information about your health from physical examinations and medical tests done in this study.

This study is expected to benefit the Sponsor by providing information about TG-C.

If the results of this study are favorable and, along with additional studies, lead to approval by the regulatory authorities (such as the FDA) of TG-C for use in humans, there may be benefits in the future for people with osteoarthritis like you. These benefits may include delay in progression of osteoarthritis, which may lead to greater joint longevity, better mobility, and improved quality of life, including the ability to continue to work, participate in recreational activities, and remain active members of their communities. These benefits may also lead to decreased use of pain medication and fewer doctor visits for people with osteoarthritis like you.

9. WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?

You do not have to be in this study to get treatment for your knee osteoarthritis. Other prescription, non-prescription, and experimental therapies are available. Your doctor can discuss your treatment options with you.

10. WILL I INCUR ANY EXPENSES OR RECEIVE ANY PAYMENTS?

There will be no cost to you or your insurance company for the study treatment or the study-related procedures and examinations.

For your time and inconvenience related to your participation in this study, you will be paid for the study visits you complete according to the following schedule: You will be paid $100.00 for each completed visit (with the exception of Visit 5 for which you will not be paid). You will also be paid $100 for each completed X-Ray and MRI. You will also be paid $50.00 for the completion of the Cancer Surveillance Questionnaire at the Year 3 to Year 15 Visits. The Sponsor is paying the study doctor and/or study site for their work in this study. You will be paid following each completed visit.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete according to the schedule above.

Biomarkers

Any information derived directly or indirectly from this biomarker research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this biomarker research, are the sole property of the sponsoring company (and its successors, licensees, and assigns) and may be used for commercial purposes. You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this biomarker research. However, in signing this form and donating blood and urine samples for biomarker research, you do not give up any rights that you would otherwise have as a participant in research.

11. WHAT IF I AM INJURED DURING THE STUDY?

If you experience any unexpected symptoms or injury, and if emergency medical treatment is required, please report it promptly to the study doctor at the telephone number listed on page one of this consent form.

If you have a physical injury or illness directly related to the study treatment or study procedure which was properly performed in accordance with the protocol (referred to as a study-related injury), medical treatment will be provided to you. You will not be charged for this treatment. The Sponsor will cover the cost of reasonable and necessary medical treatment for a study-related injury and has insurance to cover the study-related injury. Study-related injuries do not include injuries that result from your own fault or intention. Additionally, payment for such things as lost wages, expenses other than medical care, or pain and suffering is not available. By signing this document, you will not lose any of your legal rights or release anyone involved in the research from responsibility for mistakes.

12. WHAT WILL HAPPEN IF THERE IS ANY NEW INFORMATION?

If any new information becomes available which may influence your decision to continue in the study, you will be told in a timely manner. It is possible that some new information will require that you sign another informed consent to continue in the study.

13. WILL INFORMATION ABOUT ME BE KEPT CONFIDENTIAL?

By signing this form you consent (agree) to the study doctor and his or her staff collecting and using your personal data for the study. This includes: your initials, date of birth (day, month and year), your sex, your ethnic origin and information on your physical or mental health or condition.

The information shared with the Sponsor is protected by the use of a code, which is a number specifically assigned to you. The study doctor is in control of the code needed to connect your data to you.

All medical records and research materials that identify you by name will be held confidential (confidential data) so far as permitted by law. However the study doctor, the Sponsor and its representatives, the study monitor (who checks how the study is going and makes sure that the information is being collected properly) and, under certain circumstances, the regulatory

authorities and ethics committees will be able to inspect confidential data that identify you by name.

All personal data from this study will be treated in accordance with national and local data protection laws.

By signing this consent form, you grant permission for medical information about you obtained during this study (your study data) to be made available to authorized representatives of the regulatory authorities and other government agencies. You also grant permission for your study data to be made available to the Sponsor, the study monitor, other study personnel, and ethics committees. The Sponsor may transfer your study data to countries outside of the US for the purposes described in this document. Please be aware that the laws in such countries may not provide the same level of data protection as in the US and may not stop your study data from being shared with others. The study doctor, the regulatory authorities, and the Sponsor may keep the study data indefinitely.

You have the right to request information about your study data held by the study doctor and the Sponsor. You also have the right to request that any inaccuracies in such data be corrected. If you wish to make a request, then please contact the study doctor, who can help you contact the Sponsor if necessary. You may be asked to provide this request in writing.

Your consent for the use of your study data as described above does not have an expiration date. If you withdraw your consent for participating in this study, your study data that were collected before you withdrew your consent may still be used as described above. You may be asked to provide written notification of your decision to withdraw from the study. Once you have withdrawn your consent for participating in the study, no further data will be collected about you for the purposes of this study unless you agree otherwise; for example, you agree to have further tests and examinations. If you do agree to have further data collected after you have withdrawn your consent, these study data may also be used as described above.

The results of this study may be published in a medical journal and shown at medical meetings. You will not be identified (by name or any other means, eg, photo) in any of these publications.

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.

14. WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00026070.

15. CONSENT STATEMENT OF SUBJECT

I have received verbal information on the above study and have read the attached written information. I have been given the chance to discuss the study and ask questions.

I voluntarily consent to participate in this study, including all assessments, lifestyle restrictions, contraception requirements, and taking of blood samples.

If asked to undergo additional scans during your first MRI scan and again 12 months later please indicate below if you agree or do not agree.

☐ YES - I agree to MRI test-retest during my first MRI scan and again in about 12 months. Initials: _____ Date: _____

☐ NO - I do not agree to MRI test-retest. Initials _____ Date: _____

☐ Not Applicable

I understand that I am free to withdraw at any time. I understand that I if I choose to not participate or to withdraw, my current medical care will not be affected by this decision.

If I withdraw, I agree to complete an annual cancer surveillance questionnaire for 15 years after I receive study drug. ☐ YES ☐ NO

I agree that my primary physician may be informed of my participation in this study.

I agree that my primary physician may be asked to provide information about my medical history and any cancer diagnosis.

Primary Care Physician Name: _____ Phone Number:( ) _____

I agree that my personal data, including data relating to my physical or mental health or condition, and ethnic origin, may be used as described in this consent form.

I understand that I will receive and may keep a copy of this signed and dated consent form.

By signing and dating this consent form, I have not waived any of the legal rights that I would have if I were not a participant in a medical research study.

		AM/PM	
Signature of Subject	Date (mm/dd/yyyy)	Time	Printed Name of Subject

ONLY COMPLETE THE BELOW IN THE EVENT THE SUBJECT IS UNABLE TO READ:

The study subject has indicated that he/she is unable to read. The consent document has been read to the subject by a member of the study staff, discussed with the subject by a member of the study staff, and the subject has been given an opportunity to ask questions of the study staff.

		AM/PM	
Signature of Impartial Witness*	Date (mm/dd/yyyy)	Time	Printed Name of Impartial Witness

Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent and any other written information supplied to the subject.* ***Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance*

16. STATEMENT OF PERSON CONDUCTING INFORMED CONSENT DISCUSSION

I, the undersigned, certify that to the best of my knowledge, the subject signing this consent form had the study fully and carefully explained and clearly understands the nature, risks, and benefits of participation in this research study.

		AM/PM	
Signature of Investigator (or other Person Obtaining Consent)	Date (mm/dd/yyyy)	Time	Printed Name of Person Obtaining Consent

Schedule of Study Procedures

Visit Number	1	2[b]	3	4	5[a]	6[b]	7[b]	8[b]	9[b]	10[b]	11[b]
Assessments	**Screen**	**Day 0**	**Day 1**	**Week 1**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 18**	**Month 24**
Informed Consent	X										
Inclusion / exclusion	X	X									
Medical history	X	X									
Physical exam and weight	X	X	X	X		X	X	X	X	X	X
Vital signs	X	X[e]	X	X		X	X	X	X	X	X
Knee exam/evaluations	X	X	X	X		X	X	X	X	X	X
Questionnaire(s)	X	X	X	X		X	X	X	X	X	X
X-ray (knee(s)[c]	X								X		X
MRI of target knee	X[d]						X		X		X
HIV, HTLV-1, VSV-G, and hepatitis B and C testing	X										
HbA1C Testing	X										
Blood and urine samples	X		X	X		X	X	X	X	X	X
Urine pregnancy test	X	X				X	X	X	X	X	X
Urine drug screens	X	X									
Injection of study treatment in target knee		X									
Review medications & therapies	X	X	X	X	X	X	X	X	X	X	X
Review of side effects		X	X	X	X	X	X	X	X	X	X
Between visit phone call	Monthly Interim Subject Contact at Months 2, 4, 5, 7, 8, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, and 23										

[a] *You will be contacted by phone by a member of the study staff and asked questions about your health and any changes in medications or therapies. An office visit may be scheduled if the study doctor believes it is medically necessary.*

[b] *You will be asked to fast (nothing to eat or drink except water) for at least 8 hours before some study visits when blood and/or urine samples are collected for certain laboratory testing (Visits 2, 6, 7, 8, 9, 10, and 11).*

[c] *X-rays of both knees at screening (Visit 1) and of target knee at Visits 9 and 11.*

[d] *MRI of the target knee must be performed at least 7 days prior to Visit 2, Day 0.*

[e] *Vital signs taken pre-dose, every 15±5 minutes for the first hour, and every 30±5 minutes for the second hour after dosing.*

Schedule of Study Procedures (24 months or Early Withdrawal through 15 years post dose – only applicable for subjects who do not consent to participate in the separate 15-year Long-Term Follow-up Safety Study):

Assessments	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11	Year 12	Year 13	Year 14	Year 15
Cancer Surveillance Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X

AUTHORIZATION TO USE & DISCLOSE MEDICAL INFORMATION

As part of this study, medical information about you will be collected and analyzed. This medical information will include (but is not limited to) your date of birth, gender, medical history (that is, data from your medical records such as past or present health conditions and medications, and the results of procedures and test you undergo during the study and had before the study), laboratory test results, physical exam data and data collected from the procedures described in your informed consent form for this study.

Under the Health Insurance Portability and Accountability Act (HIPAA), your health information cannot be used or disclosed (made known) by your study doctor for research purposes unless you sign this consent form. By signing this consent form, you authorize the study doctor and his/her staff to use this information in conducting the study and to disclose and provide access to or copies of this information to the following:

1. Sponsor (Kolon TissueGene, Inc.),
2. Contract Research Organization (CRO) conducting the study on the Sponsor's behalf and other organizations working with the Sponsor to monitor the progress of the study, collect, or analyze the study data,
3. Central laboratory, and other laboratory facilities working with them,
4. Central imaging laboratory, and quantitative or specialized MRI imaging analysis vendors,
5. The FDA or similar, foreign, regulatory authorities,
6. Institutional Review Board to ensure that a subject's safety and rights are protected, and
7. Institutional Biosafety Committee, if applicable.

Access to this information is necessary to ensure that the study is being done correctly, and to collect and analyze data about the safety and effectiveness of the study treatment.

In addition, this information may also be disclosed to the Food and Drug Administration or similar, foreign, regulatory authorities, for the purpose of attaining regulatory approval. The information may also be disclosed to the institutional review board (IRB). The purpose of this board is to ensure that a patient's safety and rights are protected.

You agree that, while the study is still in progress, you may not be given access to medical information about you that is related to the study. This may include, for example, information about whether you are receiving study treatment or placebo, or any other information that is "blinded" (that is, kept secret during the study to prevent bias). While a request for access to medical information can be denied, the study doctor and staff will consider whether it's medically appropriate under the circumstances to allow access. Your agreement that you may be denied access to your study-related medical information during the study will not be used to deny you access to that information after the study is completed at all locations and study results are analyzed.

You may decide not to sign this authorization, or you may revoke (withdraw) this authorization at any time. You can do this by giving written notice to your study doctor, informing him or her that you are revoking your authorization to use and disclose your medical information. The contact information for your study doctor is provided below.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You can only participate in the study if you authorize the use and disclosure of the information as described above. If you decide not to sign this authorization form, you will not be enrolled in the study. If you sign this authorization and decide later to withdraw this authorization, you will be not be permitted to continue your participation in the study. Information collected up to the time that you end this authorization may continue to be used and disclosed as described above, but only as necessary to protect the integrity of the research study.

You should know that, once information is disclosed under this authorization to someone who is not a health care provider; the information is no longer protected by federal law. The Sponsor and those working with the Sponsor on this study (such as the CRO) will only use and disclose your information as described in this Authorization. If reports or articles are written about the study, you will not be identified by name in them.

You will be given a copy of this authorization after you have signed and dated it.

WHO TO CONTACT IF YOU HAVE ANY QUESTIONS:

If at any time before, during or after the study, you have any questions about the use or disclosure of your study-related information or if you wish to withdraw your authorization to use or disclose your medical information, you should contact the study doctor at the telephone number listed on page one of this consent document.

Signature of Subject	Date (mm/dd/yyyy)	Time	AM/PM	Printed Name of Subject
Signature of Investigator (or other Person Obtaining Authorization)	Date (mm/dd/yyyy)	Time	AM/PM	Printed Name of Person Obtaining Authorization