copernicus group independent review board

Approved: 23Aug2016

SUBJECT INFORMED CONSENT FORM AND HIPAA AUTHORIZATION

TITLE: A Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of a Single Injection of rexlemestrocel-L Alone or Combined with Hyaluronic Acid (HA) in Subjects with Chronic Low Back Pain

PROTOCOL NO.: MSB-DR003

SPONSOR: Mesoblast, Ltd., c/o Mesoblast, Inc.
New York, New York
United States

INVESTIGATOR: **Michael Giovanniello MD**

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This is a clinical trial, which is a research study to answer specific medical questions. The information from this study may help future patients. The study doctor (the person in charge of the research) or a member of the study staff will explain the clinical trial to you. Clinical trials are voluntary, which means you can choose whether or not you want to take part. Please take your time and think carefully about whether you want to participate in this study. You may discuss your decision with family and friends. You can also discuss this with your health care team. If you have any questions, you can ask the study doctor or designee for more explanation.

INTRODUCTION

You are being invited to take part in this clinical research study by your doctor because you have low back pain and damage to a spinal disc, commonly called degenerative disc disease (DDD) and may require medical treatment. Before you decide to take part in this study, you should carefully read this consent form. This consent form gives you details about the study and may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision. If you decide to take part in this study and sign this consent form, it means that you have read and understood the information in this consent form. You will be given a signed and dated copy of this consent form to keep for your records.

DESCRIPTION OF CLINICAL INVESTIGATION

The purpose of this research study is to evaluate an investigational product called, rexlemestrocel-L. The study sponsor, Mesoblast Ltd. (Mesoblast), makes rexlemestrocel-L from a certain type of stem cell. Stem cells are unspecialized cells that can turn into various specialized cell types such as blood or vascular cells, muscle, cartilage, or bone. The stem cells used in making rexlemestrocel-L, called mesenchymal precursor cells (MPCs), are taken from the hip bone marrow of an adult human donor.

This Phase 3 study is designed to determine whether rexlemestrocel-L, used alone or in combination with a carrier material (hyaluronic acid), is safe and effective in treating low back pain by repairing damaged spinal discs. Rexlemestrocel-L is not approved for any use by the United States Food and Drug Administration (U.S. FDA) or other regulatory agencies. The carrier material, hyaluronic acid, is FDA legally marketed for certain other procedures, but its use in the human disc has not been approved.

This study will include up to 360 subjects, male or female, who are at least 18 years of age. If you qualify to be included in this study and agree to participate, you will take part in the study procedures below. Your participation in this study will last approximately 38 months. It is important that you come for all scheduled study visits and complete all activities required for the study.

If you choose to participate in this study, you will be randomly assigned (like drawing straws) to one of three groups. Depending on the group to which you are assigned, your study doctor will inject one of the following into the center of the damaged spinal disc that your doctor has determined is causing the pain:

1) rexlemestrocel-L alone
2) rexlemestrocel-L mixed with hyaluronic acid, or
3) Saline alone (no rexlemestrocel-L or hyaluronic acid at all)

Two of the groups will receive the investigational product (rexlemestrocel-L, either alone or with hyaluronic acid) and one group will receive placebo (saline). A placebo (saline) looks like the study drug, but does not contain any active ingredient(s).

You have an equal chance of being assigned to any one of the three groups.

You have a 2 out of 3 chance of being assigned to one of the two groups that will receive the investigational product, rexlemestrocel-L.

You have a 1 out of 3 chance of being randomly assigned to the placebo (saline alone) group.

If you are eligible to receive the study injection, you will be asked to return to the study doctor's office for study visits at 1, 3, 6, 12, 18, 24, and 36 months after your study injection. You will not be told to which group you were assigned until all subjects have completed 36 months of follow-up. This is to ensure that the study evaluates if the product is safe and if the product is working without any bias.

STUDY PROCEDURES

Screening, Visit 1 (Days -75 to Day 0)

Before any study procedures are performed, the study will be explained to you by the study doctor or a member of the study doctor's staff. The purpose of the study will be reviewed, and the potential risks and discomforts of your participation will be explained. After you have read, understood, and signed/dated this consent form, you will be asked for information about your health, and some additional tests will be done.

You will be asked about your health history and any medicines that you are currently taking, as well as any injections or surgeries for your spine. A physical examination will be performed. Your height, weight, and vital signs (blood pressure, heart rate, breathing rate, and body temperature) will be measured. Blood samples will be taken from you (about 3 tablespoons) for routine blood tests (including pregnancy test, for female patients) as well as testing for HIV and immunology tests. If required by state law, the results of positive tests for HIV will be reported to a local health agency. If you do not want to be tested, you should not take part in this research study.

You will also be asked whether you have ever been administered any blood products, whether you smoke or have smoked, whether you have been or are pregnant (females only) and what vaccinations you have received.

A magnetic resonance imaging (MRI) scan, a type of image, will be performed to evaluate the disc in your lower back (lumbar spine) that is causing your pain.

X-rays, another type of image, may be taken in different positions to evaluate your lower back disc.

You will be assessed for your risk of osteoporosis. If you are considered to be at risk, you will undergo a DEXA scan of your lumbar spine. The DEXA scan measures bone mineral density and determine whether you have osteoporosis.

As radiographic images may vary slightly depending on the time of day the images are taken, all imaging assessments should be done approximately at the same time of day if possible, preferably in the morning.

You will be asked to complete different questionnaires that ask questions about your pain and your health. The questionnaires are:

- Leg Pain Visual Analogue Scale (VAS): to measure your right and left leg pain, if any
- Low Back Pain VAS (average and worst over 24 hours): to measure your lower back pain
- Oswestry Disability Index (ODI): to measure your functionality (ability to do certain activities)
- EuroQoL (EQ5D): to measure your quality of life
- Institute for Medical Technology Assessment (iMTA) Productivity and Costs Questionnaire (iPCQ): to measure costs that arise due to you being either absent or present for work as well as any and unpaid work
- Patient Reported Utilization: to measure health-related costs due to your lower back pain
- Abbreviated DSM-V Self Rated Level 1 Cross Cutting Symptom Measure: to assess your mental state
- DSM-V Alcohol and Substance Abuse Questionnaires: to collection information on your alcohol and substance use
- Pain Catastrophizing Scale: to get more details on your pain

You may undergo a diagnostic injection of dye into your spinal disc. The purpose of this procedure is to determine if your disc is intact, and that leaking of the treatment will not occur, and/or to identify which spinal disc(s) are causing your back pain. Discography is the procedure used to determine which disc is causing your back pain and may also serve as the diagnostic injection. A neurological exam will be performed before and after the diagnostic disc injection. If this discography was completed within the last 6 months and enough information was obtained during the procedure, it may not need to be repeated.

The diagnostic injection of dye to determine if your disc is intact or discography will be in addition to the study injection during which either rexlemestrocel-L, rexlemestrocel-L mixed with hyaluronic acid, or saline will be administered.

Computed tomography (CT scanning), another type of imaging, may be done after a discography procedure to evaluate your lower back disc.

In order for you to be in this study, your study doctor will have to rule out some causes (other than degenerative disc disease) for your lower back pain.

A medial branch block will be performed to confirm that your lower back disc is causing your pain. Medial branch nerves are small nerves that feed out from the facet joints in the spine and carry pain signals from those joints. A medial branch nerve block temporarily interrupts the pain signal being carried from a specific facet joint and allows the study doctor to determine if your facet joint is causing your pain instead of the disc.

The sacroiliac (SI) joint is a located in your hip and supports your spine. In most cases, your study doctor will be able to conduct a specific type of physical exam to determine if your SI joint is causing your pain. However, if your study doctor is unable to confirm the cause of your pain by physical exam, an SI joint injection may have to be performed. Medicine is administered into your SI joint by injection and may interrupt the pain to help determine what is causing your low back pain.

During certain times of the study, you will be asked to complete a daily diary. The diary will be in the form of an electronic (e-diary) hand-held device that will be provided by the study site. Prior to receiving the study injection, you will be asked to complete the e-diary for 2 weeks to track certain medications you take to deal with pain and the reason why you are taking them. You will also complete low back pain VAS, leg pain VAS and ODI in the e-diary. You will be contacted, either by the study staff or computerized reminder system, approximately 2 weeks prior to each post-study injection visit as a reminder to complete your daily e-diary. You will need to complete your e-diary every day for 2 weeks during the Screening period and prior to each clinic visit from 1 month after the study injection (Visit 3) to 36 months after the study injection (Visit 9).

Visit 2 (Day 0, Study Injection)
At this visit, your height, weight, vital signs (blood pressure, heart rate, breathing rate, and body temperature) will be measured and a brief physical examination will be performed.You will be asked "How have you been feeling?" It is important that you report any new pains or illness as well as any new medications you are taking. If you are female and able to become pregnant, a urine pregnancy test will be done before your study injection.

You may receive a light sedative to help you relax during the study injection procedure. You will be asked to lie on your stomach on a table. Your skin will be wiped at the site of the injection with a cleansing antiseptic agent. The health care provider may inject an anesthetic into the skin to reduce the pain. In some cases, antibiotics might be given intravenously before and after the procedure; however your study doctor can discuss the standard practice and medications which are routinely used for spinal injections.

A needle is inserted through the skin and muscle and into the center of the disc. During the process of placing the needles, imaging studies called fluoroscopy (similar to X-ray) are used to help the health care provider see where the needle is located along the path to the disc. Depending on the group to which you are assigned, either rexlemestrocel-L alone, or rexlemestrocel-L with hyaluronic acid, or saline alone will be slowly injected into the center of the disc.

The injection procedure generally takes about 20 to 30 minutes. After the injection, you may be kept for observation for 30 minutes or more. A neurological exam will be performed after the study injection, before you are sent home. It is advisable that you have someone available to assist with your transport back to your home. In some cases, pain from the injection can persist for up to 1 week. There may be some muscle pain from passing the needle. The only experimental part of this study is the study injection.

When you are sent home, you will be given a set of instructions telling you what you may and may not do. You are to call the study doctor **immediately** if you experience increased pain, swelling, redness, fever, or drainage (fluid leaking) from the injection site.

Outpatient (Post-Injection) Follow-up Office Visits
You will be returning to the study doctor's office for several tests at the following times:

- Visit 3: 1 month ± 14 Days following the study injection
- Visit 4: 3 months ± 14 Days following the study injection
- Visit 5: 6 months ± 30 Days following the study injection
- Visit 6: 12 Months ± 60 Days following the study injection
- Visit 7: 18 Months ± 60 Days following the study injection
- Visit 8: 24 Months ± 60 Days following the study injection
- Visit 9: 36 Months ± 60 Days following the study injection

Tests that will be done during these scheduled Follow-up Visits
You will have a physical and neurological examination at each of these follow-up visits. Your height, weight, and vital signs (blood pressure, heart rate, breathing rate, and body temperature) will be measured. Also, you will have blood drawn (no more than 3 tablespoons) for laboratory tests at certain specified visits. X-rays and MRI scans of your back will be done at specific visits to see how your back is doing. You will be given questionnaires to complete that ask questions about your pain and your health.

You will be asked at each visit "How have you been feeling?" It is important that you report any new pains or illness as well as any new medications you are taking.

Below is a table of which of these tests will be done at each visit:

Assessment	Visit 3 1 Month (± 14 Days)	Visit 4 3 Months (± 14 Days)	Visit 5 6 Months (± 30 Days)	Visit 6 12 Months (± 60 Days)	Visit 7 18 Months (± 60 Days)	Visit 8 24 Months (± 60 Days)	Visit 9 36 Months (± 60 Days)
Physical examination	X	X	X	X	X	X	X
Vital signs (blood pressure, heart rate, breathing rate, temperature)	X	X	X	X	X	X	X
Height and weight	X	X	X	X	X	X	X
Neurological exam	X	X	X	X	X	X	X
Blood tests	X			X		X	X
MRI scans				X	X	X	X
X-rays	X	X	X	X	X	X	X
Questionnaires about your pain and general health/wellbeing	X	X	X	X	X	X	X
Questions about medications you take	X	X	X	X	X	X	X
"How have you been feeling?"	X	X	X	X	X	X	X
Completion of the pain medication, VAS and ODI on the e-diary	Pain medication, leg and low back VAS and one (1) ODI questionnaire should be completed on the e-Diary approximately 2 weeks prior to each scheduled clinic visit.						

Tests that will be done during unscheduled Follow-up Visits

You are still allowed to see your study doctor for any reason even at a time that is not required by the study (unscheduled visits). Additionally, if you are prescribed additional spinal injections or are to undergo lower back surgery during the study, your study doctor may ask that you return for an unscheduled visit. If you should see your study doctor during unscheduled visits, you will be asked at a minimum:

- To complete questionnaires about your lower back and general health/wellbeing
- Questions about medications you take
- "How have you been feeling?"
- Any other tests your study doctor feels is necessary as your study doctor may ask that you complete additional tests (for example x-rays, blood work, etc.) based on the reason for your unscheduled visit.

ECONOMIC DATA COLLECTION

Information about your medical bills, medical records and the medical charges relating to your medical care (i.e., doctor's visits) or complimentary services (i.e., acupuncture, etc.), diagnostic imaging uses (CT, MRIs, x-rays, etc.), and any hospitalizations you have for up to 12 months before, 12, 24, and 36 months after the study injection will be collected. This includes copies of your hospital medical bills, access to your medical records and the explanation of benefits documents that are sent to the hospital by your third party payer. Other information will also be collected about your usage of pain

medication, if you have had any spine surgeries or injections, and number of days you have missed work. This data will be collected to understand what impact study participation has on your overall medical care and your ability to perform your usual work. However, this is optional and will not impact your participation in the study. There are no medical risks to this part of the research but there is always the possibility of loss of confidentiality of your private health information. Steps have been taken to minimize this risk as described in the confidentiality section below.

RISKS AND DISCOMFORTS

Risks Associated with Magnetic Resonance Imaging (MRI) Scanning

An MRI scan will be performed at Screening and at 12, 18, 24 and 36 months.

MRI stands for magnetic resonance imaging. An MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to create images of the inside of your spine. Electromagnetic radiation is not the same as ionizing radiation used, for example, in x-rays or computerized tomography (CT scans). The potential risks of MRI are minimal.

MRI is generally a well-tolerated procedure and your study doctor will determine whether or not these will cause any harm to you before any imaging is started. You will also be asked to leave all metal objects, such as keys and jewelry, in a locker outside of the scanning room. You may feel claustrophobic (fear of enclosed places) inside of a scanner because the space is small. This is a loud scanner, which is why you will be given earplugs and/or earmuffs to decrease the noise. You may feel slight tingling sensations, usually along your arms or your lower back. If you move your head while the machine is doing the scan, you may feel dizzy or nauseous.

Risks Associated with X-rays

X-ray evaluations will be done at Screening, and at 1, 3, 6, 12, 18, 24 and 36 months.

There are risks from ionizing radiation resulting from the x-ray evaluation. During the conventional x-ray examination of your lumbar spine, the effective radiation dose is approximately equivalent to 6.4 years of the natural environmental background radiation for the average U.S. citizen. The additional radiation exposure is at each individual visit at which x-rays are being taken.

There is also some exposure to radiation associated with the image amplifying during the initial injection of dye or discography and at the time of study injection. The risk from the radiation dose received from this procedure is too small to be detected. If you are especially concerned about radiation exposure, you may discuss this thoroughly with the study doctor. The lowest dose of radiation and appropriate lead shielding is used.

Risks Associated with DEXA Scan

If you are considered to be at risk of osteoporosis, a lumbar DEXA scan will be done at Screening.

The risk from the radiation dose received from this procedure is negligible. The effective radiation dose is approximately equivalent to 1.4 hours of the natural environmental background radiation for the average US citizen.

Risks Associated with Computed Tomography Scanning
Computed tomography (CT scanning) may be done after a discography procedure. The amount of radiation from CT scanning is higher than that of standard x-rays.

CT scanning involves ionizing radiation. There are minimal risks to you from ionizing radiation resulting from CT scanning. The minimal dose of radiation and appropriate lead shielding is used. During the lumbar spine CT scanning, the effective radiation dose is approximately equivalent to 54 months of the natural environmental background radiation that a person receives in a city such as New York City each year. The risk from the radiation dose received from this procedure is very remote. If you are especially concerned about radiation exposure, you may discuss this thoroughly with the study doctor.

Risks Associated with Blood Tests
You will have blood taken for this study to assess your health. Blood samples will be taken from a vein in your arm during the study. Taking a blood sample may cause some temporary discomfort and other side effects such as the following: fainting, redness, pain, bruises, bleeding, and/or infection. If you feel faint, tell the study staff right away.

There also may be other side effects that cannot be predicted.

Risks Associated with Local Anesthetic
Since a local anesthetic is a part of your study injection, you may experience the following side effects: low blood pressure, heart rhythm disturbances, confusion, and/or seizures.

Risks Associated with Sacroiliac Injections
Risks associated with injection of an anesthetic in the sacroiliac join to determine if that joint is causing your back pain may include, allergic reaction to the medication used, bruising and/or soreness at the injection site, leg weakness or numbness or infection at the injection site, deeper tissues, or in the joint.

Risks Associated with Spinal Disc Injections
Risks associated with the discography procedure or disc injection to confirm that the disc is intact used for screening potential participants and the study injection procedure are the same as they both involve placing a needle into the center of the spinal disc and then injecting fluid.

There is a risk of complications associated with spinal disc injections. The most common is discitis (an infection of the disc space). On average, this occurs in less than 1% of patients undergoing discography. Discitis usually results in very intense pain, but can be treated with antibiotics. Other complications that have been reported (but are

rare) include nerve root injury, urticaria (a skin rash or hives), injection into the dural sac (surrounding the spinal cord), bleeding, blockage of the central area of the disc (called a nucleus pulposus pulmonary embolism), nausea, headache, and increased pain. If the area surrounding the spinal cord is damaged, a minimally invasive procedure called a "blood patch" may be required to seal the damaged area. Pain and bruising at the injection site have also been observed. Other cases of infection/inflammation of the brain, bones, and spinal cord have been noted.

Additionally, there is a risk that some or all of the study injection (investigational product or saline) may leak out of the disc during or after the injection procedure. If some or all of the study injection leaks out of the disc, it may reduce or prevent potential healing of the disc. This could prevent you from experiencing the potential benefits associated with the investigational product, including improvement in your back pain or physical function. The effect of rexlemestrocel-L and/or hyaluronic acid on spine structures outside of the disc has not been studied. There is a potential risk that if the study injection leaks out, it could affect nearby structures and cause damage that may need surgery to correct.

Some studies suggest that placing a needle into the disc might cause disc degeneration or speed up progression of disc degeneration as a result of puncturing the disc.

Risks Associated with Injection of Contrast Media into Your Symptomatic Disc

Contrast media (sometimes called contrast agents or dye) are chemical substances used during an injection procedure to determine if the disc is intact (the diagnostic injection) or in discography. Contrast media enhance and improve the quality of these images so that your study doctor can have a more accurate diagnosis of your symptom or condition, to assist in deciding what treatment will be most appropriate for you.

The most common used contrast media is Iodine-containing contrast medium (ICCM). A commonly used type of ICCM is Omnipaque. ICCM is generally very safe. Side effects or reactions are uncommon but may occur. The most common side effects of ICCM include: headaches, mild to moderate pain, backache, neckache, stiffness, nausea, and vomiting. These reactions usually occur 1 to 10 hours after injection and are usually mild to moderate. They may last for a few hours, and they usually disappear within 24 hours.

Allergic (anaphylactic) reactions to ICCM have occurred but are extremely rare. These severe reactions occur within minutes of the ICCM being given. However, 2 to 4 in every 100 people have a late reaction (up to 1 week but usually within 2 days) after an ICCM injection, consisting usually of an itchy rash, swelling of the face, or nausea. These delayed reactions generally require only treatment of specific symptoms and they resolve promptly. Severe reactions generally respond very well to emergency drug treatment. This treatment is given while in the radiology department of the hospital or private radiology practice. If you have had a mild, moderate, or severe allergic reaction to ICCM in the past, you must tell the radiology facility when you are making your appointment.

In patients with normal kidney function, most of the ICCM injected is almost entirely passed out in the urine within 24 hours.

If you are a patient with reduced kidney function or kidney failure (either chronic or acute), and hepato-renal syndrome (a condition involving reduced function of liver and kidneys), you should avoid use of this contrast media.

Nephrogenic systemic fibrosis (NSF) is another rare condition, which causes extensive patches of thickened and hardened skin, associated with ICCM administered to patients with severe kidney disease. Its onset occurs days or weeks after administration of the agent with almost all cases occurring within six months of the last dose. The use of these agents is generally avoided in patients at risk of NSF.

Risks Associated with Stem Cell Products like Rexlemestrocel-L

Possible risks associated with the study procedures and the most common side effects associated with rexlemestrocel-L are listed below. There may be risks that are not known. Your condition may not improve or may worsen while participating in this study.

If the study injection leaks out of the disc space, there is a theoretical possibility that it might cause changes at another disc level. Such changes have not been observed in previous rexlemestrocel-L studies. Since stem cells are believed to react in response to inflammation, they are unlikely to affect normal tissue.

If any fluid or blood accidently causes pressure on a nerve, it might be necessary to have an operation to remove any pressure on the nerve. In general, most of the fluids would likely be absorbed naturally by the body.

Reaction to Fetal Calf Serum or Murine (Mouse) Antibody

The MPCs used in rexlemestrocel-L are grown in a solution that includes a murine-(mouse) derived antibody, as well as fetal calf serum. As a result, subjects with known severe allergic reactions to murine (mouse) and/or bovine (cow) products may not participate in this study. The risk of developing an allergy (sensitization) to this type of cell product is small.

Reaction to Dimethyl Sulfoxide (DMSO)

Dimethyl sulfoxide (7.5%) is a preservative used as part of the cell freezing and preservation process. The systemic toxicity of DMSO is considered to be low. The DMSO exposure in this therapy is minimal and is locally applied which means it does not spread throughout your body. If you are allergic to DMSO, you will not be allowed to be included in this study.

Potential Cell Contamination

Rexlemestrocel-L could become contaminated, which could cause you to develop an infection. This risk is greatly decreased by the use of a production facility that follows a set of standards called Good Manufacturing Practice (GMP) that are accepted by the government health agencies. Before rexlemestrocel-L is released from the

manufacturing facility, screening tests for a number of agents that can cause infection are performed. As with any blood or marrow-derived product, infectious risks from unknown pathogens are possible.

Potential Immunological Responses
As the MPCs are taken from another person's bone marrow (allogeneic), your body may see the cells as foreign or not "belonging" to you and may develop a type of antibody (a substance naturally produced in your body) as a reaction to them as the development of antibodies has occurred in another study. The body may have a similar reaction when it receives a blood transfusion. The development of such antibodies may or may not be harmful, but it could change a diagnostic test called a panel reactive antibody (PRA) which if high, could delay or limit you from having an organ transplant (such as a heart, kidney, etc.) in the future (should you need one) because of the chance of increased rejection after transplant. You will be monitored throughout the study by having blood PRA tests done at study visits.

Potential Inflammatory Responses
MPCs may cause local inflammation or swelling. While possible, this response was not seen in the animal studies that have been performed with the MPCs. You will be monitored for these responses with blood inflammatory marker tests at study visits.

EFFECTS ON TREATED AND ADJACENT DISCS
It is unknown at this time what (if any) the long-term effects of the study injection are. Over the long-term, adverse effects could potentially develop at the treated disc or at disc(s) above or below the treated disc. Adverse effects could cause additional or recurrent pain and may need treatment through medication and/or injections or surgery. In a previous clinical study, no significant adverse effects on the treated disc, adjacent spine levels or surrounding neurological structures were observed through 24 months after the injection of rexlemestrocel-L.

Potential Risk of Tumor
MPCs are living cells and there is a risk that these cells could directly or indirectly cause unwanted tissue growth or a tumor. MPCs have been tested in animals to see if it causes unwanted tissue growth or tumors. So far, no unwanted tissue growth or tumor has been seen in human studies or in any other animal study with MPCs.

Reaction to Hyaluronic Acid
Pain, swelling, heat, redness, and/or buildup of fluid around the knee have been reported worldwide after hyaluronic acid was injected into the knee. These reactions have been generally mild and have not lasted long. Rare cases of joint infection have been reported after hyaluronic acid injections. The most common reactions are local knee joint pain and injection site pain. Other common events are joint swelling, joint stiffness and injection site reaction. Rashes, hives, and itching have also been seen.

Other less common adverse events have been:

- muscle pain/cramps,
- flushing and/or swelling of the face,
- fast heartbeat,
- nausea,
- dizziness,
- fever,
- chills,
- headache,
- difficulty breathing,
- swelling of the arms and legs,
- prickly feeling of the skin,
- increased liver enzymes, and
- in rare cases, a low number of platelets in the blood.

These medical events occurred under circumstances where a direct causal relationship to hyaluronic acid is uncertain.

Rare cases of allergic/non-allergic reactions accompanied by cold sweat, paleness, and low blood pressure which may be potentially serious have been reported.

In addition to Hyaluronic acid being injected in the knee, Hyaluronic acid alone was administered intradiscally as a control treatment in the Phase 2 study of chronic discogenic low back pain to 20 subjects. .One subject experienced mild rash which subsequently resolved, and another subject experienced 2 events of back pain.

SUBSEQUENT SURGICAL INTERVENTIONS
You may need additional pain medication(s) or surgery if the study injection fails to alleviate your low back pain. Types of surgery may include discectomy, fusion, disc replacement or other surgical interventions.

PREGNANCY
This research study may involve risks to you or your unborn child, which are currently not known. If you are a woman, you must not get pregnant for 24 months after injection. The only way to not get pregnant is to not have sex. If you are a woman whom is able to have children and choose to have sex, you must use a type of birth control listed below.

Methods of birth control for this study include:

- Abstinence (not having sex)
- Hormonal (examples are birth control pills or patches, progestin implant, or injection)
- Barrier method (examples are diaphragm with spermicide, intrauterine device [IUD], condom, and foam)

Even if you use birth control during the study, there is a chance you could become pregnant.

You cannot enter into the study if you are pregnant or breastfeeding. The procedure and study injection, or the tests that need to be done, may have unknown risks to breastfed babies. You must inform your study doctor immediately if you think you may be pregnant. In addition, the study doctor must report to the sponsor, Mesoblast Ltd., follow-up information regarding the course of the pregnancy, including during the pregnancy and the outcome of the pregnancy (i.e., birth). You will continue to be monitored until conclusion of the pregnancy.

Possible Effects on Fetus

Because of potential or unknown side effects of the study on the fetus, if you are a woman able to have children, you must have a negative blood pregnancy test before entering the study as well as a negative urine pregnancy test immediately before injection on the day of the injection. Women who are able to have children will be allowed to participate in this study provided that they agree to use adequate contraception (hormonal or barrier method or abstinence) from the time of screening and for a period of at least 24 months after injection.

BENEFITS

This product is intended to reduce chronic low back pain, improve quality of life, and increase function, such as personal care, lifting, walking, sitting, standing, sleeping, social life, ability to work, and traveling. However, there is no guarantee that you will benefit. Your participation may provide important information about this type of investigational product that could help others with your disease.

COSTS

Any lab tests and radiology scans (x-rays and MRI scans) that are not standard of care for people having spinal injections will be paid for by the sponsor of this study, Mesoblast Ltd.

Costs related to your spinal injection procedure(s) will be paid for by the sponsor of this study.

Standard of care procedures not directly related to this research study will be your financial responsibility. To ensure that you understand the expenses that you might incur as a result of participation in this study, ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include the costs of treating possible side effects.

There may be costs associated with your transportation to and from the study doctors' office or to the radiology office for MRIs and x-rays. You may discuss these costs with your study doctor.

PAYMENT FOR PARTICIPATION

There is no cost for participating in this research study. The study sponsor pays all the study costs. You will not be paid for participating in this study; however, reasonable travel expenses will be reimbursed to you for study visits. The amount you receive will depend on the number of visits you complete. You will receive $64.00 for each visit that you complete. You will not receive any compensation for visits that you do not complete.

ALTERNATIVE PROCEDURES OR TREATMENTS

Other treatments for the type of back pain that you have include continued non-operative treatment (medications, physical therapy, acupuncture, dry needling, nutrition, magnets, activity modification, and many others), epidural steroid injection, fusion surgery, disc replacement, discectomy (surgical removal of disc material), or other surgical interventions. You may discuss your other options with your study doctor.

CONFIDENTIALITY

All information that you give will be kept strictly confidential. The information collected about you usually will not directly identify you (for example, by name, address, or social security number). Instead, your initials and a code number will be used for your information.

Your records may be reviewed by:

- The study sponsor.
- People who work with the sponsor on the study.
- Government agencies, such as the FDA.
- Copernicus Group Independent Review Board (IRB). The IRB is a group of scientists and non-scientists who review the ethics of research. The goal of the IRB is to protect the rights and welfare of study subjects.

These people may look at your records to make sure the study has been done the right way. They also want to make sure that your health information has been collected the right way, or for other reasons that are allowed under the law.

If information about this study is published, you will not be identified.

COMPENSATION AND MEDICAL TREATMENT IN EVENT OF INJURY

Mesoblast will reimburse you for reasonable medical expenses incurred by you for treatment of any physical injury or illness that you may suffer as determined by Mesoblast to be a direct result of administration of rexlemestrocel-L or the protocol procedures followed in this study. However, such reimbursement by Mesoblast will be limited to your medical expenses not otherwise covered by existing healthcare programs or insurance policies. Mesoblast will not reimburse for future procedures if the investigational procedure does not relieve your back pain. No other compensation will be provided by Mesoblast except as provided in this consent form, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

CONTACTS

If you have questions, concerns, or complaints about this study, your condition, and/or investigational product; if at any time you think you have experienced a research-related injury or reaction to the study drug; or if you do not feel well or have been seen by another doctor, contact:

Study Doctor/Contact Name: **Michael Giovanniello MD**

Daytime Telephone Number(s): 801-352-9228, 801-676-7627

24-hour Contact Number(s): 801-676-7627

You should contact the study doctor first if you have questions, complaints or concerns about the study.

Please call Copernicus Group IRB at 1-888-303-2224 if:

- You want to talk to someone other than the study doctor or study staff.
- You have a hard time reaching the study doctor or study staff.
- You have questions about your rights as a research subject.

Please visit the Copernicus Group IRB website www.cgirb.com for more information about research studies and the role of a research subject.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to participate in this study, you will receive a signed and dated copy of this consent form for your records.

VOLUNTARY PARTICIPATION

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

SOURCE OF FUNDING

Funding for this research study will be provided by Mesoblast Ltd., a biopharmaceutical company.

UNFORESEEABLE RISKS

As the study injection is still being tested to understand if it is safe and if it works to treat your back pain, there may be risks which are not yet known or cannot be estimated. Unforeseeable risks are usually caused by anesthesia, blood clots, undiagnosed medical problems such as silent heart disease, and rare allergic reactions. Most of these risks can be treated once they are detected, but sometimes they require a longer period of recovery and additional medications. There is also an unknown risk to pregnant women as discussed previously in this consent form.

INVOLUNTARY TERMINATION OF PATIENT'S PARTICIPATION

Your participation in the study may also be ended at any time by the study doctor or the sponsor without your consent for any of the following reasons:

- If your study doctor feels that it is in your best interest;
- If the study doctor feels that the number or severity of side effects is excessive;
- If you do not follow the study instructions;
- If the sponsor cancels the study;
- You do not later consent to any future changes that may be made in the study plan.

If your participation in this study – or the study overall – is ended, you will be notified by your study doctor. Ongoing medical management of your back disease and other treatment options may be available to you. You may discuss these with your study doctor at that time.

CONSEQUENCES OF SUBJECT'S DECISION TO WITHDRAW

You may withdraw from this study and/or withdraw your permission to use and disclose your health information at any time by notifying the study doctor. If you withdraw your permission to use and disclose your health information, you will not be able to continue in this study. When you withdraw your permission and you have had your final study visit, no new health information that might identify you will be gathered for the research study after that date. Information that has already been gathered may still be used and given to others.

Withdrawal from the study will involve no penalties or loss of benefits to which you are otherwise entitled, and will not affect your future medical care from your study doctor.

If you withdraw, or are withdrawn from the study before it has been completed, you will be asked to complete an early termination follow-up appointment with your study doctor to conclude your participation of the study. If the testing results were outside of the expected range at the last visit, you may be asked to return to your study doctor's office to repeat the tests.

SIGNIFICANT NEW FINDINGS

You will be told if any new information, good or bad, is learned about the investigational product being studied that may affect your decision to continue to participate in the study. If new findings arise, you may be asked to sign a revised consent form.

APPLICABLE CLINICAL TRIALS

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.

Posting to other websites in other countries may also be required; however these web sites will not include information that can identify you.

CONSENT SIGNATURE

I have read and understood the information in this consent form. I have been given plenty of time to ask questions and to decide whether or not to participate. I freely consent to participate in this research study. I understand that I need to attend all scheduled study visits and perform all activities required by the study. I understand that I should notify my study doctor of any changes in my medical status or the medications I am taking.

I will receive a copy of this signed informed consent form.

By signing this consent form, I have not given up any of my legal rights.

_____

Subject's Name (printed)

_____ _____

Subject's Signature Date

The information about the study was described to the subject in language he/she understood.

_____

Name of Person Conducting Informed Consent Discussion (printed)

_____ _____

Signature of Person Conducting Informed Consent Discussion Date

ECONOMIC DATA COLLECTION

Do you agree to allow the study doctor to collect information about your medical bills, medical records, and the medical charges relating to any spinal interventions you have during the course of the study for up to 12 months before the study and 12, 24 and 36 months after the study injection?

_____ **YES**, my billing information and medical records can be collected.

_____ **NO**, my billing information and medical records cannot be collected.
(Please "X" either YES or NO above, initial and date your entry)

HIPAA AUTHORIZATION

Federal laws give you certain rights related to your protected health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.

If you choose to be in this Research Study, you must authorize (i.e., allow) Physicians' Research Options, LLC, your doctors, and your other health care providers (together "Providers") to use and disclose private health information about you as described below, which includes "Protected Health Information" as defined in federal laws called the Privacy Regulations developed under the Health Insurance Portability and Accountability Act of 1996 as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (as amended, "HIPAA") as necessary and appropriate to carry out the Research Study and as otherwise specified here in this Authorization. In general terms, you understand that Protected Health Information is health information that identifies you or that could reasonably be used to identify you.

a) The health information about you that may be used and disclosed in connection with the Research Study includes:

- Pre-existing medical records as may be necessary or appropriate to use in connection with the Research Study, and medical records created during the Research Study.
- Your medical bills and administrative or other billing information related to treatment you may receive during the course of the Research Study.
- Other records that contain your Protected Health Information, such as your medically-related phone calls and study visits.

Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of the study site. For records disclosed outside of the study site, you will be assigned a unique code number (i.e., an identifier) to protect your confidentiality. You may ask the study staff for more information about when identifiers might be used.

b) The Providers may disclose your health information:

- To the contract research organization for this Research Study or its designated agents or representatives (collectively, the Contract Research Organization). The Contract Research Organization for this Research Study is an independent contractor with the sponsor of the Research Study (Mesoblast, Ltd.) that is obligated to carry out one or more of the sponsor's obligations related to the Research Study such as design of the research protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the U.S. Food and Drug Administration.
- To the sponsor of this Research Study (Mesoblast, Ltd.) or its agents or representatives other than the Researchers, but only where your health information is de-identified and/or aggregated (i.e., combined) with the results of other participants in the Research Study and as otherwise permitted by the Informed Consent, the Institutional Review Board, and applicable law.
- For future research and analysis, such as other medical research-related to the further development of the technology in the Research Study, development of other study protocols, cost/benefit analysis, development of new medical products or procedures, system analysis, and other similar purposes, unless prohibited by law.
- To representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of Research Study and/or which have authority to approve new products or new indications resulting from the Research Study, including but not limited to the U.S. Food and Drug Administration, the U.S. Department of Health and Human Services and similar state agencies, governmental agencies to whom certain diseases must be reported, the Institutional Review Board governing this Research Study, and government agencies in other countries (collectively, Government Agencies or Review Boards). This information may also be disclosed to the Government Agencies or Review Boards by the Contract Research Organization and/or on behalf of the sponsor as permitted or required by the Informed Consent, the Institutional Review Board, and applicable law.
- To maintain the integrity of the Research Study such as to account for your withdrawal from the Research Study, as necessary to incorporate the information as part of a marketing application

submitted to the U.S. Food and Drug Administration, to conduct investigations of scientific misconduct, or to report adverse events.

- For the Research Study's proper management and administration or to carry out the legal or compliance responsibilities of the Providers, the Researchers, or the sponsor, as otherwise permitted by the Informed Consent, the Institutional Review Board, and applicable law.
- You acknowledge that by participating in this Research Study, your health information may be used in publications in scientific journals or presentations at medical meetings, but only where your health information is de-identified and/or aggregated (i.e., combined) with the results of other participants in the Research Study, unless your specific written authorization is obtained to identify you in such studies or presentations.

c) Once your health information has been disclosed to a third party, federal laws may no longer protect it from further disclosure. However, the Providers agree to protect your health information by using and disclosing it only as permitted by you in this Authorization.

d) Other rights and obligations:

- You do not have to sign this Authorization, but if you do not, you cannot participate in the Research Study.
- You may change your mind and revoke (i.e., take back) this Authorization at any time and for any reason. To revoke this Authorization, you must write to your study doctor at:

Michael Giovanniello MD
Physicians' Research Options, LLC
96 E Kimballs Ln Ste 405
Draper UT 84020

However, if you revoke this Authorization, you will not be allowed to continue taking part in the Research Study, which means that the sponsor will no longer cover your medical costs related to the Research Study as specified in the Informed Consent Form. Also, even if you revoke this Authorization, the health information about you that has already been collected based on this Authorization may still be used and disclosed in accordance with this Authorization.

- You acknowledge and agree to that while the Research Study is in progress, you will not be allowed to see your health information that is created or collected by the Providers. After the study is completed, however, you may see this information as described in Physicians' Research Options, LLC Notice of Privacy Practices.

e) This Authorization does not have an expiration date. If you do not withdraw this Authorization in writing, it will remain in effect indefinitely. Your study doctor will keep this Authorization for at least 6 years.

AUTHORIZATION

I authorize the use and disclosure of my health information to the parties listed in the HIPAA Authorization for the purposes described above. I will receive a signed and dated copy of this Authorization.

_____

Printed Name of Subject

_____

Signature of Subject **Date**