University of California, San Diego
Consent to Act as a Research Subject

The Effects of Glucagon Antagonism on Insulin Sensitivity, Cardiovascular Risk, and Ketogenesis in Type 1 Diabetes

WHO IS CONDUCTING THE STUDY, WHY YOU HAVE BEEN ASKED TO PARTICIPATE, HOW YOU WERE SELECTED, AND WHAT IS THE APPROXIMATE NUMBER OF PARTICIPANTS IN THE STUDY?

Dr. Jeremy H. Pettus and his associates are conducting a research study to learn more about a study drug called REMD-477 in subjects with Type 1 diabetes. REMD-477 is investigational, which means it has not been approved by the U.S. Food and Drug Administration (FDA). All study related visits will occur at the UCSD Altman Clinical and Translational Research Institute (ACTRI).

This study is being conducted in people 18 to 65 years of age who have been diagnosed with Type 1 diabetes and who are currently using an insulin pump and continuous glucose meter (CGM), and who meet other specific study eligibility criteria. The eligibility criteria will be reviewed with you by the study doctor or a member of his research team and will include physical assessments and laboratory assessments. This study will enroll about 40 participants over approximately 2 years. If you are a female and plan to become pregnant during the course of the study, you are not eligible to participate.

Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take as much time as you need to decide whether or not to participate and discuss your participation with family, friends, or your doctor, if you wish.

This document provides you with information about the study. Please read this informed consent form carefully and ask any questions you have about the study so you can make an informed decision about your participation. You are under no obligation to take part in this study and, if you decide not to, your future medical care will not be affected in any way. If you have questions at any time while reading this document, please ask a study doctor or study staff member to explain any words or information you do not understand. If after reading this document, you are interested in participating, you will be asked to sign this informed consent form. You will receive a copy of this form to keep.

WHY IS THIS STUDY BEING DONE?

Controlling blood glucose levels is part of the overall management of diabetes. Two primary hormones regulate the level of glucose in your body: insulin and glucagon.

Insulin is a hormone that is produced by cells called beta-cells, located in the pancreas. Insulin suppresses liver glucose (sugar) production and stimulates glucose uptake by tissues. Glucagon is a hormone that is produced by cells called gastric alpha cells located in the pancreas. Glucagon stimulates liver glucose production. Type 1 diabetes is an autoimmune disorder. An autoimmune disorder is a condition in which your immune system mistakenly attacks the healthy cells in your body. In Type 1 diabetes the body's immune system mistakenly destroys the cells within the pancreas responsible for producing insulin (beta-cells). The absence of circulating insulin results

in increased levels of glucagon and increased blood glucose concentrations. The main purpose of this research study is to test how REMD-477 affects the cardiovascular system (heart and blood vessels), the body's sensitivity to insulin, and ketone production in subjects with Type 1 diabetes after 10-12 weekly doses. Ketones are chemicals that your liver makes. The body produces ketones when there is not enough insulin in the body to turn sugar (glucose) into energy.

Your glucose levels will be closely monitored after repeated doses of the investigational product, and the study will look to see if your body is able to maintain normal glucose levels. In addition, we will see how your body responds to high blood sugars (hyperglycemia) after taking REMD-477.

During this study, each subject will receive up to 12 doses of REMD-477. A study doctor or study nurse will inject the investigational product subcutaneously (under the skin) on your abdomen once per week for up to 12 weeks. Each single dose of investigational product will be divided into two injections (1 dose = 2 injections). You will only receive one dose-strength of REMD-477 (35 mg) during the study.

Funding Source:

The JDRF foundation is funding this study through a research grant. REMD Biotherapeutics, Inc. is providing the study drug at no cost, but is not providing any other financial support.

WHAT WILL HAPPEN TO YOU IN THIS STUDY AND WHICH PROCEDURES ARE STANDARD OF CARE AND WHICH ARE EXPERIMENTAL?

All of these procedures are done for research purposes only. These procedures are not procedures for standard of care with exception of your current anti-diabetes care which is standard of care.

If you agree to take part in this research study you will be asked to sign this consent form and you must meet specific entry criteria. Additionally, you must be available to visit the UCSD ACTRI Clinic located in La Jolla, CA on multiple occasions.

During your participation in this study, you will be responsible for taking only the medications approved by a study doctor. It is important that you tell the study doctor(s) what medications you are currently receiving or have received in the recent past. It is also important that you notify the study staff before taking any new medications during this study, including other investigational products, over-the-counter medications, vitamins or herbal remedies/supplements. This includes any changes to your current medications.

If you have any questions about the medications you are presently taking, ask to speak with a study doctor.

Screening (Approximately 1 – 1.5 hours)

Within 1 to 6 weeks prior to the Baseline Visits, you will undergo a screening appointment at the ACTRI Clinic. Before the start of any procedures associated with this study, you will need to sign this Informed Consent document to consent to your participation in the study, the study restrictions and the study procedures themselves. You will be asked to fast for 8 hours (nothing to eat or drink except water) before attending the visit.

Following this, you will undergo a complete medical examination (which should take approximately 1 hour) which will include medical, surgical and family history, an assessment of any medications that you have recently taken are currently taking, vital sign measurement (blood pressure, pulse, breathing rate and temperature), height, weight and physical examination. A physical examination by a study doctor will include listening to your heart, checking your ears, eyes, throat and checking overall your physical condition. You may be required to remove your outer clothing for this examination.

Blood samples will be collected from a vein in your arm using a needle and syringe (venipuncture) and the following tests will be performed: complete blood examination, including blood glucose, blood fats and some hormones, chemicals and enzymes. A urine sample will be taken for safety assessments and a pregnancy test (for all female subjects). The amount of blood collected at the screening visit will be 1 tablespoon (16 mL).

Baseline Period

The Baseline visit assessments will take place on 2 separate days at our UCSD La Jolla research clinic (ACTRI). On each day, you will be asked to arrive in the morning after an overnight fast of at least 8 hours. The visits can occur on 2 consecutive days or spread out over a 1-week period. Each day of procedures lasts about 2-8 hours.

The following will occur:

Cardiovascular Visit #1 (about 2 hours):

- Vital signs (Blood pressure, Heart Rate, Respiratory Rate, oral temperature)
- Fasting blood collection for cardiovascular biomarkers and safety labs (40 ml of blood about 3 tablespoons)
- Download your personal CGM data for study physician review
- Collect insulin usage from your pump data
- RH-PAT procedure (EndoPAT)
- Flow Mediated Dilation (FMD)
- Study staff will ask if you have had any changes to your health or medications.

⇒ **FMD, EndoPAT (RH-PAT)**

You will undergo two complementary procedures to measure endothelial function: flow mediated dilation (FMD) and reactive hyperemia-peripheral arterial tonometry (RH-PAT). The endothelium is a thin membrane that lines the inside of the heart and blood vessels. Endothelial function is a possible predictor of cardiovascular health. These procedures are being done for research purposes only and are not being used as diagnostic tools.

These procedures are non-invasive and take about 30 minutes (each) to complete. You will be laying in a bed, in a resting state. A blood pressure cuff is placed on your arm just above the elbow. The cuff is inflated to at least 50 mmHg above your systolic blood pressure to occlude blood flow for five minutes, then quickly deflated.

During the EndoPAT procedure, small inflatable finger probes are placed on both your right and left index fingers. These probes are inflated during the entire procedure. During

the FMD procedure, an ultrasound technician will be examining the blood vessels in your arm with an ultrasound probe.

Insulin Sensitivity Visit #1 (8-9 hours):

- Physical examination
- Weight and Bioimpedance
- Vital signs (Blood pressure, Heart Rate, Respiratory Rate, oral temperature)
- Fasting blood collection (200 ml or about 13.5 tablespoons)
- Urine sample for pregnancy test (females only)
- Insulin Sensitivity Test
- Resting Energy Expenditure
- Muscle and fat biopsies
- Adverse Event monitoring

⇒ **Insulin Sensitivity Test (2-step Hyperinsulinemic/Euglycemic Clamp with tracer):**

This Insulin Sensitivity Test (also called a Clamp) is a method for measuring insulin secretion and resistance in the body. It is used to measure either how well your body metabolizes glucose or how sensitive your body is to insulin.

What will happen during the Insulin Sensitivity Test:

The term "clamp" involves keeping or holding your blood glucose at a certain level during this procedure. The term "euglycemic" means that your blood glucose will be kept in a normal range (between 90-120 mg/dL) throughout the procedure. Early, on the morning of the test day, you will receive an intravenous (IV) infusion of non-labeled glucose (20% dextrose) with tracer and human regular insulin. A non-radioactive glucose tracer will be administered during this procedure. There are no known risks associated with the non-radioactive glucose tracer (6,6-$^{2}H_{2}$ glucose). Your insulin pump will be stopped prior to the start of the insulin infusion.

Dr. Pettus' research nurses will insert a small tube into a vein of your arm for infusion of the glucose and insulin. Another tube will be placed into a vein on or near your hand of the opposite side (if possible) for intermittent blood sampling of glucose, hormones and other substances. This hand will be placed in a heating pad to help with collection of blood. This procedure is done to determine how your body responds to insulin for production and use of glucose and it will last approximately 7 hours.

After the clamp procedure is over, you will be given a meal and resume your insulin pump basal rate. The study nurse and doctor will continue to monitor your blood sugar for about 1 hour until it remains stable without the use of IV glucose. When this occurs, your IVs will be removed, and you will be discharged from the research unit to go home.

⇒ **Muscle and Fat Tissue Biopsies:**

A muscle and fat tissue biopsy will be completed the morning of Day 2. To obtain the muscle and fat tissue, a trained study doctor and nurse will clean one side of your abdomen (for fat) and one side of your upper thigh (for muscle), numb the areas with

lidocaine, and make a small incision (0.5 cm) in the skin with a scalpel. A small liposuction tool will be inserted into the incision in the abdomen (lower stomach area) to collect about 1 ½ teaspoons of fat tissue. A separate small puncture tool will be inserted into the incision in your upper thigh to collect about 1/2 teaspoon of muscle tissue. These procedures are done under sterile conditions and from start to finish takes about 1 hour to complete. You will also need to stay in bed after the procedure is over for several hours.

You should wear loose clothing that allows access to your lower stomach area and your upper thigh. You will also have the option to wear a hospital gown during the procedure.

⇒ **Resting Energy Expenditure (REE):**

Your resting energy expenditure is the number of calories you burn while at rest. This procedure will be performed 3 separate times during the Insulin Sensitivity Test. The REE measurement will be done using Indirect Calorimetry and involves lying quietly in bed, while breathing normally with a clear canopy (a large plastic hood) placed around your head; the hood is ventilated with fresh room air. This test measures how much oxygen you breathe in and how much carbon dioxide (CO_2) you breathe out. From these measures, we can calculate how many calories you burn at rest. Each REE procedure lasts about 15-30 minutes.

⇒ **Bioimpedance Body Composition:**

Your body composition is made up of your muscle, bone, fat, organs, skin and fluids. The bioimpedance scale uses a low voltage electrical current that you cannot feel to provide a breakdown of your overall body composition. It provides the results in percentages (for example 15% fat, 20% skeletal muscle) and also calculates an estimate of your resting energy expenditure (similar to the Calorimetry test described above, but not as accurate). To complete the test, you simply stand on a special scale, like when you weigh yourself. However, this scale has metal sensors where you place your feet and then you hold handles that also have metal sensors. After approximately 20 seconds of standing still, the scale calculates your body composition. For the test, you will be asked to wear very light clothing (for example a t-shirt and shorts) or you can also wear a hospital gown (you will not need to remove your underwear if wearing the gown).

◊ A total of about 240 ml (16 tablespoons) of blood will be collected over the 2 days of these Baseline procedures.

◊ A meal will be provided to you on each day following completion of the procedures.

Randomization: 1:1 (REMD-477 or placebo)

You will randomized (like the flip of a coin) to receive either REMD-477 (35 mg) or placebo (no active ingredients). You will have a 50% chance of receiving active REMD-477 and a 50% chance of receiving the placebo. The randomization is blinded, meaning you and the study team will not know whether you are receiving REMD-477 or placebo. In case of emergency the research pharmacy may unblind the randomization. The first dose of REMD-477 will be given on the second day of baseline testing after the completion of all other procedures.

Study Dosing Visits (Week 2-12)

Dosing will last at least 10 weeks and up to a maximum of 12 weeks. At dosing visits weeks 2, 4, 6, 8, 10, 12 fasting blood collection will occur. A total of 10 ml (2 teaspoons) of blood will be collected at each visit. Each of these dosing visits will take about 1 hour of your time.

At each of these visits, study participants will have their vital signs taken, study drug administration, downloading participant's CGM data to evaluate glycemic control and time-in-range metrics including time-below-range (hypoglycemia), collection of and review of insulin usage, concomitant medication and adverse event monitoring. The study doctors will closely monitor and manage your diabetes, including adjustments of insulin pump settings, as necessary, to prevent hypo- and/or hyper-glycemia.

Repeat Baseline Studies

Following completion of up to 10-12 weeks on study drug, you will return to the ACTRI clinic to repeat all the baseline procedures,(except randomization and study drug administration), in addition to the Insulin Withdrawal Visit (described below).

You will be asked to arrive in the morning after an overnight fast of at least 8 hours on each day. The visits can occur on 3 consecutive days or spread out over a 2-week period beginning after week 10.

Insulin Withdrawal Visit (8 hours):

- Vital signs (Blood pressure, Heart Rate, Respiratory Rate, oral temperature)
- Insulin Withdrawal Procedure
- Adverse Event monitoring
- Randomization
- First dose of study drug administered in clinic

⇒ **Insulin Withdrawal Challenge:**

Upon arrival to the ACTRI Clinic, and under the direction and supervision of a study doctor, you will be asked to suspend and remove your insulin pump for up to 8 hours. An intravenous catheter (IV) will be temporarily placed into a vein in your arm to collect blood samples. During the challenge a study doctor and research nurse will be closely monitoring your blood glucose and ketones and will stop the test if your glucose goes above 400 mg/dL and/or your ketones go above 3.0 mmol/L. 150 ml of blood will be collected during this procedure which is about 10 tablespoons.

◊ A total of about 390 ml (26 tablespoons) of blood will be collected over the 3 days of these procedures.

Final Safety Follow-up visit (1 hour visit)

A final safety follow-up visit will occur about 2-4 weeks after the repeat baseline procedures, and the following procedures will occur:

- Vital signs (Blood pressure, Heart Rate, Respiratory Rate, oral temperature)
- Physical exam
- Concomitant Medication monitoring
- Adverse Event monitoring

Genetic Sample Collection

Contained within our genes {DNA (deoxyribonucleic acid) and RNA (ribonucleic acid)} are the traits which we inherited from our parents, for example the color of our hair, skin, and eyes. DNA contains all our genes and instructs each cell in our body how to behave. RNA moves within our cells delivering the instructions provided by DNA to the various cell parts. Other characteristics affected by our genes are the likelihood of getting certain diseases. In addition, some of these genes may also influence how the body responds to drugs.

As part of this study, only **RNA analysis** will be done on the tissue samples collected during the fat biopsy on Day 2 of the Baseline and Repeat Baseline visits. If you do not want to provide samples for RNA analysis you should not participate in this study. These samples will not contain any identifiable information about you.

The total amount of blood collected from you during the course of the entire study will be approximately 720 mL (about 49 tablespoons) over a period of about 12 weeks. You are advised not to donate any additional blood during the study, or for 60 days after completing the study. As with all studies requiring blood draws, adequate rest and good eating habits are also advisable.

The study team is allowed to provide you with results of any testing completed during the study. Please contact the study coordinator or a study doctor and we will provide the results you requested. Should any of the testing reveal abnormal findings, the study investigator, Jeremy Pettus, will explain the results and recommend any follow-up medical treatment.

HOW MUCH TIME WILL EACH STUDY PROCEDURE TAKE, WHAT IS YOUR TOTAL TIME COMMITMENT, AND HOW LONG WILL THE STUDY LAST?

This study includes a screening period (that may last up to 6 weeks), a 10-12 week treatment period and a final safety follow-up visit. The total time that your participation in this study will be is approximately 4-5 months.

There will be a total of 18 visits to the research site. Each visit is described in this consent form and the amount of time each visit lasts is listed.

If you have problems during the study, you may have to come in for an unscheduled visit in addition to those planned.

WHAT RISKS ARE ASSOCIATED WITH THIS STUDY?

Participation in this study may involve some added risks or discomforts. These include the following:

The administration of any investigational product involves a general risk of side effects. Since REMD-477 is an investigational product, not all the potential side effects in humans are known.

REMD-477 may cause all, some, or none of the side effects listed below. Side effects are undesirable medical conditions or a worsening of a pre-existing medical condition that may occur while you are in a study. In addition to the possible adverse effects listed below, unexpected, or uncommon side effects, which could be serious or life threatening, may occur when REMD-477 is given alone or when it is combined with other medicines. Dr. Pettus will monitor you closely during the study and discuss with you any questions regarding risks, discomforts, and adverse effects.

If you participate in this study, you or your family members should tell the study staff or a study doctor immediately if you have any unusual health experiences, injuries or side effects while you are in this study. If you have any concerns about the study at any time, then you should contact Dr. Pettus and/or the study staff.

Side effects of the investigational products:

Risks of REMD-477:

REMD-477 has been tested in healthy subjects and patients with type 1 diabetes and type 2 diabetes. A single subcutaneous (under the skin) injection of REMD-477 or placebo was administered to 40 healthy subjects without diabetes at dose levels between 0.3 mg/kg to 2.5 mg/kg and to 20 patients with type 1 diabetes at a dose of 70 mg. A single subcutaneous injection followed by 28-day washout (time without study drug) and 8 weekly injections of REMD-477 at dose levels between 14 mg and 70 mg has been administered to patients with type 2 diabetes. Overall, REMD-477 appeared to be generally well tolerated. Side effects that were seen included increased liver function test values, headache, constipation, muscle strain, joint aches, bloating, abdominal (belly) pain, abnormal dreams, dizziness, back pain, neck pain, chest pain, nausea, and sore throat. Some mild to moderate increases in the liver enzymes (AST and ALT) levels in the blood were observed. The reasons for such changes in liver enzyme levels are still under investigation but could be related to changes in the metabolic process in the liver. When the cells in the liver become inflamed or damaged, ALT (alanine transaminase) and AST (aspartate transaminase) enzymes can be leaked into the bloodstream, causing higher than normal levels. Enzymes are proteins that act as catalysts within living cells. No deaths, side effects requiring a change in dose, or subjects leaving the study due to adverse events were reported. No clinically significant findings in electrocardiograms (readout of the heart's electrical activity), safety laboratories (aside from increases in liver enzymes noted below), or vital signs were reported. Hypoglycemia (low blood sugar) was not observed for any subjects in the studies. Mild increases in liver enzymes were observed in some subjects, but the liver enzymes returned to normal afterwards. The significance of these changes is unknown. Routine monitoring of adverse effects and changes in vital signs and laboratory findings will be conducted.

In the studies with laboratory animals that were given REMD-477, increases were seen in the pancreas cell size, and increased glucagon was measured. These changes decreased when treatment was stopped. The potential significance of this finding in relation to treatment of humans with REMD-477 is unknown. Routine laboratory tests will be completed throughout the study.

Administration of some drugs like REMD-477 have been associated with infusion, allergic, or injection site reactions. You will be observed in the clinic for signs of infusion, allergic, and injection site reactions.

As with many other medications, you may experience an allergic reaction to REMD-477. Symptoms that may occur include headache, rashes, flushing, swelling, shortness of breath, nausea, and sometimes vomiting. Allergic reactions may also be severe or life threatening, such as dizziness, difficulty breathing or swallowing, or a decrease in blood pressure. If you experience any of these symptoms during the study, you should notify a study doctor immediately.

REMD-477 has not been studied in combination with other medications. The risk of interactions of REMD-477 with other medications is not known. That is why we want to closely monitor all medications you are currently taking.

List of REMD-477 (35 mg dose) documented adverse events in order of severity and likelihood of occurrence based on current studies:

Most common:

- Elevated Liver Enzymes (AST and ALT)
- Nausea
- Headache
- Anemia (low red blood cell count)
- Nasal Congestion

Less common:

- Low blood sugar (hypoglycemia)
- Diarrhea
- Cough

Least common:

- Vomiting
- Sinusitis
- Sore throat

Risks of Study Procedures:

HYPERGLYCEMIA: Typical signs of hyperglycemia (high blood sugar) are feeling thirsty, dry mouth, and a need to urinate often. Other signs include a loss of appetite, blurred vision, dizziness, stomach pain, nausea, or vomiting, warm, dry or flushed skin, difficulty breathing, weakness, sleepiness, fruity smell on the breath and, in rare instances coma. With high blood sugar, you may also be at increased risk of an infection.

HYPOGLYCEMIA: Because the study drugs may also result in excessively low blood sugar (hypoglycemia), you should be aware of its signs and symptoms including hunger, increased heart rate, sweating, dizziness, lightheadedness, shakiness, nausea, vomiting, mental confusion, drowsiness, and, rarely, coma, seizures, and death.

Fasting Risks: Fasting for 8 hours may cause dizziness, headache, stomach discomfort, hypoglycemia, or fainting. Overnight fasting risks:

- You will be asked to keep your normal eating pattern and requested not to eat after 10:00 pm as per your usual eating pattern. Since you are on insulin or other diabetes medications which reduce blood sugar, you will be seen first thing in the morning to complete study procedures and blood collection. You will be allowed to eat and take your medications right after the study procedures are finished. You will be asked to please inform a study doctor if your eating habits are different, if you have a usual midnight snack, or if you are unable to fast overnight.

Blood Draw and Catheter Risks: You will have your blood drawn periodically throughout the study. Possible side effects of blood draws are tenderness, pain, bruising, bleeding and/or infection at the site of the needle puncture. Having your blood drawn may also cause you to feel nauseated and/or lightheaded.

In some cases, you may have a venous catheter (a thin, hollow tube) placed into a blood vessel, most commonly in the wrist or arm. The catheter is used to get repeated blood samples, without repeated needle sticks.

Possible side effects of a venous catheter include bleeding and pain at the place where the catheter is inserted, infection, or blood clot.

Electrocardiogram (ECG): You may experience some discomfort such as redness or itching from the sticky pads used during the ECG**.**

Risk of Insulin Sensitivity Study (HEC)

IV catheters will be used for the HEC. There is a small risk of infection, irritation to skin, veins and/or nerves or the formation of blood clots from the insertion of IV catheters. These catheters will be inserted under sterile conditions and the puncture sites will be carefully dressed and checked.

There is a small risk of hypoglycemia during the HEC. Blood sugar samples during the HEC will be drawn at approximately 5–10 minute intervals and will be tested by trained study staff (i.e. physician and nurse). Should hypoglycemia occur that cannot be corrected by the Dextrose 20%, the insulin infusion will be stopped and the attending physician will be notified immediately. Rescue agents such as Dextrose 50% and Glucagon will be available at all times.

There are no known risks associated with the non-radioactive glucose tracer (6,6-$^{2}H_2$ glucose).

Risk of Resting Energy Expenditure (REE):

A transparent, ventilated hood will be placed on your head. You will be lying down and breathing normally while under the ventilated hood. This procedure is safe but in rare cases, some people may experience claustrophobia.

Risk of the FMD, EndoPAT (RH-PAT):

A blood pressure cuff will be placed on your arm (above the elbow) and will be inflated tightly and kept tight for a total of up to a maximum of 6 minutes for each procedure (FMD and RH-PAT). This is safe, but your arm and fingers may feel tingly and have a sensation of "falling asleep".

Risk of Muscle and Fat Biopsies:

Possible side effects of the muscle and fat biopsy procedures are pain during and for some time after the procedures. The biopsy sites may also be tender or sore for two to three days after the biopsies. Swelling and/or bruising may occur at the biopsy sites. Lidocaine injection may be painful during the injection followed by numbness in the area injected (see lidocaine risks below).

Fat biopsies can cause temporary numbness or loss of sensation in the skin in the region of the biopsy sites.

Risk of Local Anesthetic (Numbing Medication):

Inform the doctor or nurse if you have a known allergy to Lidocaine.

It is common to feel some mild discomfort when the lidocaine is first administered. Rarely, an allergic reaction may occur that would result in minor swelling or irritation at the injection site.

Very rarely people may feel light-headed and nauseated due to the pain at the injection site.

An allergic reaction is very rare, but may be severe and cause itching, swelling of the face or extremely low blood pressure or difficulty breathing may occur.

Insulin Withdrawal Challenge Risks:

An IV catheter will be used for the challenges. There is a small risk of infection, irritation to skin, veins and/or nerves or the formation of blood clots from the insertion of an IV catheter. Your blood sugars will purposefully be elevated during the challenges, so you may experience hyperglycemic symptoms as described above.

Reproductive Risks:

It is not known if REMD-477 is harmful to an unborn baby. If you have intercourse during this study, you should understand that even with the use of effective birth control there is still a small chance that a pregnancy could occur. Potential risks include loss of the pregnancy (a miscarriage) and birth defects.

Females

Because the investigational product in this study may affect an unborn baby, you should not be pregnant or become pregnant while in this study.

You must confirm to a study doctor that, to the best of your knowledge, you are not pregnant now, and that you do not intend to become pregnant during the study.

You must use two clinically acceptable and effective methods of contraception/birth control during the entire study and for an additional 3 months after the end of dosing with the investigational product. Examples of these include not having sex, hormonal birth control, a condom in combination with barrier methods or if your male partner has a vasectomy.

If you are uncertain of what form of contraception is acceptable for use during the study, then please ask your study doctor.

Males

The long-term effects on sperm and the ability to father a child are unknown. The potential for REMD-477 to be transferred via semen is unknown. If you are male and you have a partner of childbearing potential, you should inform her of your participation in this clinical study and use highly effective, clinically acceptable methods of birth control during the study and for an additional 6 months after the end of treatment. Examples of highly effective methods of birth control include abstinence, vasectomy, or a condom in combination with hormonal birth control or barrier methods used by the woman. You and your doctor must discuss your method(s) and agree that they are effective.

Pregnancy

If you are female and become pregnant or suspect you are pregnant during this study, you must tell the study staff member immediately and treatment with study drug will be stopped. You will not be able to continue participation in the study if you become pregnant. A study doctor will ask for your consent to obtain information on the pregnancy outcome for you and the baby.

If you are male and your partner becomes pregnant during this study, you must tell a study staff member immediately. A study doctor will ask you for contact information and consent to obtain information on the pregnancy outcome for the mother and baby. Male study subjects whose partners are pregnant must use effective methods to ensure that an unborn child is not potentially exposed to REMD-477 via semen.

Risk of Providing Genetic (RNA) Samples

Some individuals feel anxiety or stress when having genetic samples collected. For example, some people involved in genetic studies have felt anxious about the possibility of carrying an altered gene that they could possibly pass on to their children.

Instances are known in which a subject in research has been required to furnish genetic information as a precondition for in applying for health insurance and/or a job. Participation in this study does not mean that you have had genetic testing. Genetic testing means having a test performed and the results provided to you and your doctor. If you are interested in having genetic testing performed you should consult your doctor, as some commercial tests are available. Your doctor can provide you with the necessary information to determine if such a test would be appropriate for you.

Risk of Potential Loss of Confidentiality

Participation in this study may involve a loss of privacy, but information about you will be handled as confidentially as possible. We will keep confidential all research and medical records that identify you to the extent allowed by law. However, you should know that there are some circumstances in which we may have to show your information to other people. For example, the FDA, the UCSD Human Research Protections Program, and federal compliance officers may look at or copy portions of records that identify you.

Risk of Placebo:

You may not be given active study drug and your condition may become worse, stay the same or improve. However, you will remain on your prescribed insulin treatment for Type 1 diabetes.

UNFORESEEN RISKS

Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings. Some side effects may not be known yet. Also, the risks or discomforts described may occur more often or be more severe than has been seen before. Tell a study doctor or the study staff right way if you have any problems.

Randomization Risks

You will be assigned to a study group at random (by chance). Your assignment is based on chance rather than a medical decision made by the researchers. The study group you are assigned to might not be the group you would prefer to be in. Your assigned study group might also prove to be less effective or have more side effects than the other study groups(s), or other treatments available for your condition.

WHAT ARE THE ALTERNATIVES TO PARTICIPATING IN THIS STUDY?

You do not have to participate in this study in order to be treated for your condition. If you decide not to participate in this study, or study participation is stopped, a study doctor will discuss with you alternative treatments for your condition that are available to you as well as the important risks and benefits associated with each.

WHAT BENEFITS CAN BE REASONABLY EXPECTED?

There may or may not be any direct benefit to you from being in this study. Your condition may become worse or you may benefit from the study if you receive a treatment that proves to be effective.

CAN YOU CHOOSE TO NOT PARTICIPATE OR WITHDRAW FROM THE STUDY WITHOUT PENALTY OR LOSS OF BENEFITS?

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without penalty or loss of benefits to which you are entitled. In that case, we ask you to notify a study doctor or study personnel.

If you decide that you no longer wish to continue in this study, you will be requested to complete the Final Safety visit described on page 6 of this form. There are no consequences to you as a result of withdrawing from the study.

You may also choose to withdraw partial consent, which means that you can choose not to take investigational product any longer but still provide further data by participating in all subsequent study visits or procedures.

CAN YOU BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT?

Doctor Jeremy Pettus can stop your participation at any time without your consent for the following reasons:

- if it appears to be medically harmful to you,
- if you do not follow directions for participating in the study,
- if it is discovered that you do not meet the study requirements,
- if the study is stopped/cancelled.

WILL YOU BE COMPENSATED FOR PARTICIPATING IN THIS STUDY?

In compensation for your time and travel, you will receive up to $1,800 for participating in this research.

Payments will be prorated for each visit completed as follows:

- Screening - $50
- Cardiovascular Visit #1 - $300
- Insulin Sensitivity Visit #1 - $300
- Week 2-12- $50 (each visit)
- Cardiovascular Visit #2 - $200
- Insulin Sensitivity Visit #2 - $300
- Insulin Withdrawal Visit - $300
- Final Safety Visit - $50

In the event that an unscheduled visit may occur, subjects will be compensated $25.00 for the unscheduled visit.

Payments will be in the form of cash or a Visa gift card (like a credit card).

In agreeing to participate in this study, you will be acting in an individual capacity, not as an employee of the University of California, San Diego (UCSD). No taxes are deducted from the payment. You will be responsible for paying any state, federal, or Social Security taxes if payments are more than $600 in any one calendar year.

ARE THERE ANY COSTS ASSOCIATED WITH PARTICIPATING IN THIS STUDY?

There will be no financial cost to you as a result of your participation in this study. The cost of REMD-477, and all study-related tests performed as a result of taking part in the study, will be paid for.

WHAT IF YOU ARE INJURED AS A DIRECT RESULT OF BEING IN THIS STUDY?

If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

WHAT ABOUT YOUR CONFIDENTIALITY?

The handling of medical information obtained in clinical research is governed by national and international data protection regulations and medical confidentiality. The medical information collected during this study will first be checked to make sure it is accurate. It will then be transferred into the study database(s) and processed to allow the results of this study to be analyzed and reported or published for scientific purposes.

The confidentiality of your clinical research medical records will be maintained to the extent permitted by the applicable laws. If results of the trial are published, your identity will remain confidential. The results and other information from the study may be reported to regulatory agencies in countries where the investigational product may be submitted for approval.

Neither your results nor your samples will be identified with your name, they will be coded with a study number (001, 002, etc.), date of visit, year of birth, time of collection, and sex. The list matching your name and number will be held in a separate locked file cabinet as the rest of the study records. All research records will be kept in locked offices, inside locked cabinets where only Dr. Pettus and his study staff will have access. Any electronic data stored on a computer will be encrypted and password protected and also be within a locked office.

Laboratory samples sent to the central vendor for analysis will be destroyed once the analysis is completed. Quest Diagnostics is the Central Vendor being used for this study. Any samples collected and processed on site (for example, urine pregnancy test, bedside blood glucose samples) will be immediately destroyed once the results are available.

Federal and State laws generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways: a) Health insurance companies and group health plans may not request your genetic information that we get from this research. b) Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. c) Employers with 5 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that these laws **do not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Your clinical research medical records may also be reviewed and copies made by members of the UCSD Human Research Protections Program, the UCSD Research Compliance Office, or an authorized federal representative. These individuals will see your name, other personal information such as date of birth and gender, and your medical information, but shall not disclose your name to anyone else.

Some of the data collected from you, including laboratory samples, which may contain confidential information, will be sent to a central vendor for analysis, interpretation, and reporting results back to Dr. Jeremy Pettus. The confidentiality of your information provided to the central vendor will be maintained by the central vendor staff members.

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. If the study results are presented at meetings or printed in publications, your name will not be used.

Who can you call if you have questions?

Jeremy H. Pettus, M.D. and/or a member of his research team has explained this study to you and answered your questions.

The names and telephone numbers of the study staff to contact are listed in the table below.

Main study doctor	Jeremy H. Pettus, M.D.	858-246-2160
Other study doctor	Schafer Boeder, M.D.	858-246-2161
Study Coordinator	Todd May	858-246-2169
Study Coordinator	Adrienne Armstrong	858-246-2151
After hours phone (cell)	Erin Giovannetti, NP-C	949-698-2169

You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) to inquire about your rights as a research subject or to report research-related problems.

NEW INFORMATION

During the study, new information about the risks and benefits of the study drug or type 1 diabetes may become known. Your study doctor will discuss with you any important new information developed during the course of the study that may affect your willingness to continue to participate in the study. This new information may also mean that you can no longer participate in this research. In all cases, your study doctor will offer medical care to suit your needs and/or medical condition.

YOUR SIGNATURE AND CONSENT

In signing this document, you are confirming that:

1) All of your concerns and questions about this research study have been answered to your satisfaction.
2) You have had alternative treatments discussed with you.
3) In signing this document, you agree to be part this study and that you have received your own copy of this document.
4) You have been told that your participation in the study is voluntary and that you are free to withdraw at any time, without giving any reason, and without your medical care or legal rights being affected.

You have received a copy of this consent document and a copy of the "Experimental Subject's Bill of Rights" to keep.

You agree to participate.

PRINT **Subject's** Name	Date	**Subject'**s Signature
PRINT Name of Person Who Conducted the Informed Consent Discussion	Date	Signature of Person Who Conducted the Informed Consent Discussion