INFORMED CONSENT FORM

TITLE OF STUDY: Treatment with Romosozumab versus Denosumab to Improve Bone Mineral Density and Architecture in Subacute SCI

NCT# NCT05101018

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PI: Christopher Cardozo, MD

Co-investigators: Michael LaFountaine, Ed.D; Ann M. Spungen, Ed.D; Christopher M. Cirnigliaro, Ph.D; Noam Y. Harel, MD, Ph.D; John Handrakis, PT, DPT, Ed.D

INTRODUCTION

You are being asked to participate in a research study that is supported by the James J. Peters Veterans Affairs Medical Center (JJPVAMC). This research study is being performed at JJPVAMC and at Kessler Institute for Rehabilitation (KIR). JJPVAMC and Kessler are separate Institutions and independent of one another. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

You will read the information below closely, and you will discuss it with your family and friends if you wish. You can also ask one of the study staff members if there is anything that is not clear to you or if you would like more details. You will take your time to decide. If you do decide to take part in this study, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

1. Purpose of study and how long it will last:

You currently have a spinal cord injury, and you are being asked to participate in a research study. The purpose of this study is to compare two drugs used to treat osteoporosis (thinning and weakening of bone): romosozumab and denosumab. Romosozumab is a recently FDA-approved bone anabolic (promotes bone growth) drug. Romosozumab is FDA approved to treat osteoporosis in women after menopause who have an increased risk for fractures. Denosumab is FDA approved to treat osteoporosis in women after menopause who have an increased risk for fractures, to treat women receiving certain treatments for breast cancer who have an increased risk of fractures, and to treat bone loss in men receiving certain treatments for prostate cancer who have an increased risk for fractures. These two drugs are considered experimental for the purpose of this study. If you decide to take part in this research, your study participation will last for approximately 24 months (7 study visits total plus 12 visits for romosozumab/denosumab injections). Visits will range from 1- 4.5 hours depending on the number of tests that need to be completed. A copy of this form will be given to you and a copy will be kept by the JJPVAMC research team. There may be words in this consent form that you do not understand. If you do not understand a word or sentence, please ask the person who is reviewing this document with you to explain. This study is funded by the New York State Department of Health (Grant # DOH01-34461GG-34500)

Participants:
You will be one of 40 participants with a subacute, motor complete or incomplete SCI (6 months or less). The study is a two-drug clinical trial in which you will be randomly assigned (like the flip of a coin) to one of two groups; romosozumab treatment for 12 months (20 subjects) or denosumab treatment for 12 months (20 subjects). Following romosozumab or denosumab administration, both groups will receive a denosumab injection once every 6 months for 12 months.

Inclusion Criteria
1. Traumatic motor-complete or incomplete SCI C4-L2 {International Standards for Neurological Classification of Spinal Cord Injury (ISNSCI) grade A-C (wheelchair dependent 100% of the time)};
2. Duration of SCI ≤6 months; and
3. Males and females (e.g., premenopausal) between the ages of 18 and 55 years old;

Exclusion Criteria
1. Active and/or history of coronary heart disease or stroke;
2. Osteosarcoma (bone cancer);
3. Long-bone fracture of the leg within the past year;
4. History of prior bone disease (Paget's hyperparathyroidism, osteoporosis, etc.);
5. Postmenopausal women;
6. Men with known hypogonadism (low functioning testes) prior to SCI;
7. Anabolic therapy (drugs geared toward increasing BMD) longer than six months duration after SCI;
8. Glucocorticoid administration longer than three months duration within the last year;
9. Endocrinopathies (hyperthyroidism, Cushing's disease or syndrome, etc.);
10. Severe underlying chronic disease (e.g., COPD, end-stage heart disease, chronic renal failure);
11. Heterotopic ossification (OH) of the distal femur (the knee end of the thigh bone) HO is a condition where bone tissue forms outside of the skeleton. If HO is found in any other area than the distal femur it will not prevent study participation.;
12. History of chronic alcohol abuse;
13. Diagnosis of hypercalcemia (high calcium levels in the blood);
14. Pregnancy;
15. Prescribed a bisphosphonate for heterotopic ossification (HO), or prescribed any other agent to treat osteoporosis other than calcium and vitamin D;
16. Current diagnosis of cancer or history of cancer;

17. Prescribed moderate or high dose corticosteroids (>40 mg/d prednisone or an equivalent dose of other corticosteroid medication) for longer than one week, not including drug administered to preserve neurological function at the time of acute SCI; and
18. Life expectancy less than 5 years.

2. Description of the Study Including Procedures to be Used:

You are aware that if you agree to participate in this study you will be asked to visit the JJP VAMC 7 times (Month 0, 1, 3, 6, 12, 18, 24). You will also be asked to visit the JJP VAMC to receive injections of your study drug at the following intervals when randomized (a method based on chance alone used to determine group assignment like the flip of a coin) to one of the 2 treatment groups:

Romosozumab + denosumab (Romo + Deno) group: If you are randomly selected to receive romosozumab treatment followed by denosumab treatment, you understand that you will be asked to visit JJP VAMC once a month for 12 months to receive injections of romosozumab. After those first 12 months of romosozumab treatment, you will be asked to visit JJP VAMC twice (once every 6 months for 12 months) to receive injections of denosumab.

Denosumab (Deno) group*:* If you are randomly selected to receive denosumab treatment for 24 months, you will be asked to visit the JJP VAMC 4 times (once every 6 months for 24 months).

Vitamin D levels will be measured at baseline to exclude a vitamin D deficiency state. A deficiency of vitamin D will not disqualify a patient from study participation. If a deficiency in vitamin D is diagnosed, supplemental vitamin D (4000 IU/day) will be administered until vitamin D levels are within normal range. You understand that if you are <u>not</u> vitamin D deficient, you will receive supplemental vitamin D (2000 IU/day) over the course of the study. If you consent to participate in this study, romosozumab or denosumab will be administered to you as soon as possible, but up to 6 months, after acute SCI. You understand you will be studied for measurements of chemical markers of calcium and bone metabolism, bone mineral density (BMD), which will be performed by a method called dual energy x-ray absorptiometry (DXA), and bone structure, performed by a method called peripheral quantitative computed tomography (pQCT), as indicated in the work schedule below.

Study Timeline:

		Month						
		Baseline (0)	1	3	6	12	18	24
Studies/Tests	DXA	X			X	X	X	X
	pQCT	X			X	X	X	X
	Bioelectrical Impedance Spectroscopy (BIS)	X			X	X	X	X
	Biomarkers of Bone Formation/Resorption	X	X	X	X	X	X	X
	Calcium Metabolism	X	X	X	X	X	X	X
	General Laboratories	X	X	X	X	X	X	X
	24 Hour Urine Collection	X	X	X	X	X	X	X
	Endocrine Laboratories	X				X		X
	Pregnancy Test (if applicable)	X	X	X	X	X	X	X

Study drug injection timeline																
Month		Baseline (0)	1	2	3	4	5	6	7	8	9	10	11	12	18	24
Treatment group	Romo(*) +Deno(X)	*	*	*	*	*	*	*	*	*	*	*	*	X	X	
	Deno (X)	X						X						X	X	

Romosozumab 210 mg will administered at baseline and then each month subcutaneously (SQ (under your skin)) for 12 months followed by denosumab for 12 months; in the comparator group, denosumab 60 mg SQ will be administered at baseline and 6, 12, 18, and 24 months. Bone Biomarkers: serum C-telopeptide, serum osteocalcin, bone alkaline phosphatase, and carboxyterminal propeptide of type 1 procollagen. Calcium Metabolism: serum total and ionized calcium concentrations, 24-hour urine calcium, 25 OH-vitamin D (performed monthly during supplementation therapy), 1,25 $(OH)_2$-vitamin D, and intact PTH. Endocrine Labs: serum thyroid function tests (T_3, T_4, & TSH), cortisol, total testosterone, calculated free testosterone, estradiol, growth hormone, insulin-like growth factor-1.

Vitamin D Administration: (Visit months: 0, 1, 3, 6, 12, 18, 24):
Your baseline vitamin D status will be assessed. If your vitamin D levels are found to be in the normal range, you will receive 2000 IU of vitamin D/day. If your blood levels of vitamin D are below the normal level (30 ng/mL), you will be given 4,000 IU/day vitamin D for 4 weeks, before reducing the dose to 2000 IU/day. Regardless of group assignment, you will be instructed to consume a normal calcium diet of 700-1,000 mg/day.

Dual Energy x-ray Absorptiometry (DXA): (Visit months: 0, 6, 12, 18, 24):
You will be asked to lie on a semi-padded, fixed table-top to complete a bone density measurement with a DXA scanner. Two machines, one above and one below, will move together passing over and under you. You will complete a DXA scan of both hips and knees, and this will take no more than 60 minutes to complete.

Peripheral Quantitative Computed Tomography (pQCT) (Visit months: 0, 6, 12, 18, 24):
You understand scans will be performed using a Stratec XCT 3000 scanner pQCT (STIM designs, Carmel, CA) that is on a specialized lift enabling it to be used for measurements of the bones you hip, knee, and ankle. This will be done by placing your legs into the chamber of the machine. This machine will use a low dose of radiation, which will determine the amount of bone in your legs and take approximately 60 minutes to complete. The XCT 3000 is accessible to people with SCI and has a wider gantry than other pQCT instruments, which makes it uniquely suited to measure the knee region in persons with SCI.

Bioelectrical Impedance Spectroscopy (BIS) (Visit months: 0, 6, 12, 18, 24):
Using a small electrical current that you will not feel, you will have your body fat and muscle measured using another non-invasive technique known as bioelectrical impedance spectroscopy (BIS). You will be lying down for 5 minutes on the DXA table, 2 electrodes will be placed on both your hands and your feet.

Chemical Markers for Bone Formation and Breakdown, Calcium Metabolism, and General Laboratories (all seven visits):
A routine blood sample will be drawn from a vein as outlined above in the work schedule. Approximately 75 ml of blood (5 tablespoons) will be drawn from a vein in your arm. You understand the investigators are obtaining chemical markers of bone formation and breakdown, calcium metabolism and vitamin D levels, and a complete chemistry panel.

Endocrine Laboratories (Visit months 0, 12, 24)
A routine blood sample will be drawn from a vein as outlined above in the work schedule at baseline (Month 0), month 12 and month 24. An additional 12 ml of blood (2 teaspoon) will be drawn from a vein in your arm. You understand the investigators are obtaining levels of certain circulating hormones to ensure levels are not different between the treatment groups.

24-hour Urine Collection (All seven visits):
You will complete a 24-hour urinary calcium collection into a container provided by the investigators. This collection will be used to measure the calcium in your urine as well as other chemical markers of bone health.

Romosozumab Injection (Once a month for 12 months):
You understand that a subcutaneous (under the skin) injection of the 210mg of the drug romosozumab (EVENITY®) will be administered in the upper arm by the study physician or designated clinical personnel. You will only receive romosozumab injections if you are randomly assigned to this treatment group.

Denosumab Injection (Once every 6 months for 12 – 24 months):
You understand that a subcutaneous (under the skin) injection of the 60 mg of the drug denosumab (Prolia®) will be administered in the upper arm by the study physician. You will receive denosumab injections for 12 or 24 months depending on the treatment group you are randomly assigned to.

Pregnancy Test - (all seven visits)***:***
If you are female with childbearing potential, you will be asked to complete a pregnancy test to ensure that you are not pregnant. You will have the choice to provide urine sample or a blood sample to complete this test. If you choose to give urine you will be asked to fill a urine sample cup which will be used to assess pregnancy. If you choose to give a blood sample, you will have a total of 5 ml (1 teaspoon) blood drawn from a vein inside your elbow to confirm that you are not pregnant. If the test shows that you are pregnant then you will be withdrawn from the study.

All specimens obtained during this study will be stored in the Basic Science Laboratory at The Center of Excellence on the Medical Consequences of Spinal Cord Injury located at the JJPVAMC, Bronx, NY. All samples will be labeled with a number randomly assigned to you, along with the date and information regarding the study. Samples will be stored for analysis specifically related to this study. Samples will

be stored until all data related to this study has been analyzed and at the end of this period specimens will be destroyed.

3. Description of any Procedures that may Result in Discomfort or Inconvenience:

Vitamin D Supplementation: You may feel that taking Vitamin D supplementation (4,000 IU/day for 4 weeks, if you're vitamin D deficient, followed by 2000 IU/day for 18 months; or 2000 IU/day for 18 months if you're not vitamin D deficient) is a burden and inconvenient to take on a daily basis while participating in this study.

Bone Density Studies: You may feel discomfort when you are asked to transfer or when you are transferred by appropriate staff from your wheelchair to the DXA and pQCT table. You might find the padded DXA table uncomfortable for the hour it takes to complete the DXA scanning. Each DXA scan will expose you to a small amount of radiation (approximately ½ of a routine chest x-ray).

Blood Collection: You understand you may feel discomfort, pain, lightheadedness, dizziness, blurred vision, nausea, and in rare cases, temporary loss of consciousness (syncope) during the needle insertion. There is also the potential risk of developing a bruise or infection at the site of skin puncture

Study Drug Administration: You may feel inconvenienced by the administration of the study medications. You understand that you will receive either romosozumab injections monthly for 12 months, and denosumab every 6 months for 12 months, or denosumab every 6 months for 24 months. You understand that you will need to visit the JJP VAMC once a month for 12 months to receive your romosozumab injection, or once every six months to receive your denosumab injection, depending on the group you are randomly assigned to, which you may feel inconvenienced by. You are also aware that there may be some slight discomfort at the site of injection.

Since this research may have unknown effects on an unborn child and should not be done during pregnancy, it is necessary for a pregnancy test to be done first. To your knowledge you are not pregnant at the present time. If you agree to avoid becoming pregnant (use highly effective contraceptives e.g. hormonal contraception or an intrauterine device) throughout the treatment period until 6 months after the final injection. Specific risks to the fetus may include increased perinatal mortality, and impaired development of bones, teeth and or lymph nodes.

4. Expected Risks of the Study:

***Blood Draws*:** You may feel discomfort, pain, lightheadedness, dizziness, blurred vision, nausea, and in rare cases, temporary loss of consciousness (syncope) during the needle insertion. There is also the potential risk of developing a bruise or infection at the site of skin puncture.

Bone density studies: A DXA scan carries a small risk associated with low levels of radiation used in the scan. You understand that all of the DXA measurements combined will be approximately 30-45 μSv of radiation (for comparison, a routine chest x-ray is approximately 60 μSV). All of the pQCT measurements combined will result in less than 1 μSv of radiation. Also, this quantity of radiation exposure is approximately 4 to 6 times the amount of radiation received daily from normal background radiation.

Bioelectrical Impedance Spectroscopy (BIS): You understand that if you have an implanted medical device such as a pacemaker, you will let the researchers know. There are no other risks associated with BIS.

***Vitamin D Supplementation*:** Even though the amount of vitamin D that you will receive daily for this study is clinically safe (2,000 IU to 4,000 IU per day), it is important that you understand high doses of vitamin D (greater than or equal to 40,000 IU per day) are considered to be potentially toxic. Vitamin D toxicity can cause non-specific symptoms such as weight loss, polyuria (excessive urine production), and irregular heartbeat. You also understand that vitamin D toxicity can be associated with an increase in calcium levels in the blood, which may lead to vascular and tissue calcification (deposits of calcium in the vessels and body's organs), with resultant damage to the heart, blood vessels, and kidneys.

Study Drug (Romosozumab) Side Effects: You understand that the most common side effects of romosozumab (EVENITY®) are joint pain and headaches. Other possible side effects include: serious allergic reactions, low calcium levels in your blood (hypocalcemia), severe jaw bone problems (osteonecrosis) and unusual thigh bone fractures. Symptoms of a serious allergic reaction may include rash, hives, swelling of the face, lips, mouth, tongue, or throat which may case difficulty swallowing or breathing. Symptoms of low blood calcium levels (hypocalcemia) include spasms, twitches, or cramps in your muscles, and numbness or tingling in your fingers, toes or around your mouth. Symptoms of unusual thigh bone fracture include new or unusual pain in your hip, groin, or thigh. The most serious side effects of romosozumab are increased risk of heart attack or stroke. Symptoms of heart attack may include chest pain or pressure, shortness of breath, feeling light-headed or dizzy. Symptoms of stroke

may include headache, numbness or weakness in arm or legs, difficulty talking, or changes in vision or loss of balance. If you have had a heart attack or stroke, especially if it happened in the past year, please inform the research team.

***Study Drug (Denosumab) Side Effects*:** You understand the most common adverse events are back pain, pain in the extremities, musculoskeletal pain, high cholesterol, and cystitis (bacterial infection of the bladder and/or urinary tract). You also understand that rare but possible adverse events include: pancreatitis (inflammation of the pancreas), dermatitis (inflammation of the skin), eczema and rashes, serious infections leading to hospitalizations, skin infections, infections of the abdomen, urinary tract and ear infections, and endocarditis (inflammation of the inside lining of the heart layers). Osteonecrosis of the jaw (ONJ) is an extremely rare condition that occurs after giving the medication to be used in this study (e.g., denosumab). ONJ is a condition where part of the bone of the jaw rapidly deteriorates after receiving this medication. When ONJ occurs, it most often happens in persons who have a history of or are identified as having severe dental problems or who are also on drugs that adversely influence their immune system, such as steroids or other such medications.

You understand that in the general able-bodied population, those who have received denosumab therapy for extended periods of time (much longer than that proposed to be administered in this study) may infrequently have fractures of the leg below the hip region. This is an uncommon condition that has been reported in women receiving denosumab for postmenopausal osteoporosis and cancer patients. Prior to the occurrence of the leg fracture, this condition may be associated with new or unusual hip or groin pain. Causality with the administration of this medication often is not definitively established because these fractures also have occurred in osteoporotic patients who have not received this drug. In addition to these hip fractures in the general able-bodied population, the risk of multiple vertebral fractures has been shown to increase to that of the pre-treatment level approximately 19 months after discontinuing treatment with denosumab.

There also may be risks and discomforts that cannot be foreseen.

5. Expected Benefits of the Study:

There may be no direct benefit to you from this study, but any information that the researchers get from this study may help others. The study medication has the potential to prevent the loss of bone in your legs and elsewhere in your body. If an abnormality that may be clinically treated is identified during the study, it will be brought to your and/or your physician's attention.

6. Other Treatments Available:

Participation in the study is voluntary and the alternative to this study is to not participate and seek clinical advice from your doctor.

7. Use of Research Results:

The researchers will let you and your physician know of any significant new findings made during this study which may affect your willingness to participate in this study. All research material generated from the study will remain in the possession of Dr. Christopher Cardozo and his study team at the JJP VAMC.

Your research records will be maintained according to the requirements of the JJPVAMC as follows:

Data Collection, Storage, and Transfer:

- Your coded electronic data will be collected on VA computers that are not connected to the internet.
- Your coded electronic data without your name, or other identifying information, will be stored on secured networks, behind electronic security systems, in access-restricted folders.
- Hard copies of your data will be stored in a locked file cabinet behind 2 locked doors.

Access to the research materials generated from the study will be restricted to Dr. Christopher Cardozo and his study team. Records will be retained according to National Archives and Records Administration, in accordance with Records Schedule RCS-10-1. If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent. No information by which you can be identified will be released or published unless required by law. In order to comply with federal regulations, research records identifying you may be reviewed by the following:

Authorized representatives of the JJPVAMC (e.g. Institutional Review Board, Research Compliance Officer) and VA, including the Office of Research Oversight (ORO), Federal Agencies such as the Government Accounting Office (GAO), VA Office of Inspector General (OIG), and Office for Human Research Protections (OHRP) may have access to your research records. If this research involves articles regulated by the FDA, the FDA may choose to inspect and copy research records that identify individual research subjects.

Clinical Trials:

Because this research involves articles regulated by the FDA, the FDA may choose to inspect and copy medical or research records that identify individual research subjects. If this study was initiated on or after March 7, 2012, a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. You can search this website at any time.

8. Special Circumstances:

If you are a patient, a copy of this consent form will be placed in your medical record.

9. Compensation and/or Treatment in the Event of Injury:

The VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. Further information about compensation and medical treatment may be obtained from the medical administration service at this VA medical center.

10. Voluntary Participation:

You are not required to take part in this study; your participation is entirely voluntary you can refuse to participate in this study or withdraw your participation in this study after you consent without penalty or loss of VA or other benefits to which you are entitled.

11. Termination of Participation:

You can refuse to participate now, or you can withdraw from the study at any time after giving your consent. This will not interfere with your regular medical treatment, if you are a patient. The investigator also has the right to withdraw you from the study at any time for reasons including, but not limited to, medical concerns (your health and safety are in jeopardy with continued participation in the study), non-compliance (you miss several scheduled appointments without notification) and protocol deviations (exclusion/inclusion criteria change and you are no longer eligible to participate).

12. Costs and Reimbursements:

As a veteran or non-veteran, you will not be charged for any treatments or procedures that are part of this study. For veterans who are required to pay co-payments for medical care and services provided by VA, these co-payments will continue to apply for medical care and services provided by VA that are not part of this study. You have been told that you will receive $525 for your participation in the 24-month main study: $100 each for the study visits in months 0 (Baseline), 12, and 18, $75 for study visit in month 6, and $50 each for study visits in months 1, 3, 24. You understand that payment process for

each time point will be initiated after you complete the respective visit. The reimbursement will be sent in the form of a check. Reimbursement typically takes 8-10 weeks to arrive by check.

Payment Schedule:
Baseline: $100
Month 1: $50
Month 3: $50
Month 6: $75
Month 12: $100
Month 18: $100
Month 24: $50
Total: $525

13. Contact Person(s):
To obtain answers to questions about the research, report or seek treatment for a research-related injury, or to voice concerns or complaints about the research contact the following:

- **During the Day: [Dr. Christopher Cardozo at (718) 584-9000 ext.1828]**
- **After Hours: [Dr. Christopher Cardozo at (917) 923-3569]**

I understand that should I wish to discuss my participation in this study with any other doctor or layperson, I can contact Mary Sano, Ph.D., Associate Chief of Staff (ACOS) R&D Program at the JJP VAMC by requesting an appointment at (718)741-4228 hospital extension 4228, first floor in the research building, Room 1F-01. If I have questions, concerns, and/or complaints or to offer input.

RESEARCH SUBJECTS' RIGHTS: I have read or have had read to me all of the above. Dr. Christopher Cardozo or his delegate has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but my records will not be revealed unless required by law. This study has been explained to me. I have had a chance to ask questions. I voluntarily consent to participate in this study. I will receive a signed copy of this consent form.

Subject Signature	Date	Time
Person Obtaining Informed Consent (Print Name) (Investigator or Delegate as indicated on Assurance Page)	Signature of Person Obtaining Informed Consent	Date

VERBAL CONSENT IF THE PARTICIPANT LACKS UPPER LIMB FUNCTION TO COMFORTABLY WRITE

_____ is unable to sign the consent form due to impaired arm function. I certify that I have carefully explained the purpose and nature of this research to him/her in appropriate language and he/she has had an opportunity to discuss it with me in detail. I have answered all of his/her questions and he/she has consented to participate in this research. I, therefore, am signing the consent form to document that he/she has given his/her consent to participate in this research study.

Person Obtaining Consent:

Name: _____

Signature: _____

Date: _____

Witness Name: _____

Signature: _____

Date: _____