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PROTOCOL TITLE: Effects of Romosozumab on Bone Health in Women with Spinal Cord Injury and Osteoporosis (Amgen ISS-#20197268)

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	Romosozumab (Evenity®) Alendronate (Fosamax®)
IND / IDE / HDE #	149486
ClinicalTrials.gov ID	NCT04708886
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	12
Funding Source	Amgen, Inc.
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☒ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☒ Yes ☐ No
DSMB / DMC / IDMC	☒ Yes ☐ No

OBJECTIVES:
1. Assess the effect of romosozumab on bone mass and bone strength in women with SCI
2. Evaluate differences in bone response at different skeletal sites
3. Evaluate the effects of romosozumab on serum bone markers

BACKGROUND:

Rationale:

1. Spinal cord injury results in acute bone loss that is rapid and profound.

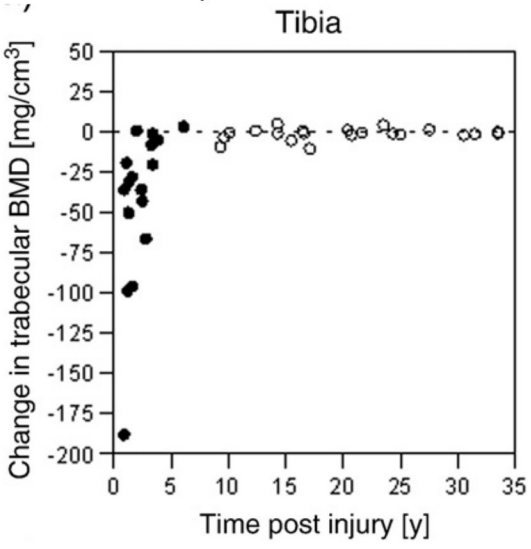
Spinal cord injury (SCI) results in marked acute loss of bone, primarily limited to those bony structures that are below the level of the neurologic lesion and non-weight-bearing with little or no loss of bone at the spine and in bony structures that are supra-lesional.[1, 2] The bone loss occurs rapidly, with the greatest decrease in bone density observed during the first 6-18 months after SCI, and is profound in magnitude, commonly being in the range of 15-30% at the hip, and potentially even higher at sites of less weight-bearing and of greater trabecular content below the hip.[1, 2] The degree of bone loss has been shown to be highly dependent on the degree of loading, with individuals having incomplete motor lesions and capable of some degree of weight-bearing having less bone loss than those with motor complete lesions. Lower extremity bone loss is similar in people with paraplegia and quadriplegia with similar motor function loss; upper extremity bone mass is unaffected in individuals with paraplegia, but variably affected in those with quadriplegia, dependent on the degree of impairment of upper extremity function. Age, weight, and gender are not important determinants of bone loss. Initially, bone mineral density (BMD) decline is most marked in areas rich in trabecular bone, with relative sparing of cortical bone.[2-6] The length of time that this enhanced rate of bone loss can be observed has been estimated at between 2 and 5 years after SCI, at which time a new steady state is reached and bone resorption and bone formation become once again tightly coupled, but now at a new "set point" with bone mass that is 30-50% below the level prior to the injury.[2-5] After this point in time, there is little further decrease in bone mass based on consequences of SCI though other secondary causes of bone loss, e.g., estrogen withdrawal, endocrinopathies, remain potentially important contributors to further changes in bone status.

The exact factors contributing to the rapid and profound bone loss after SCI have not been fully defined. Lack of normal weight-bearing is clearly an important component, but likely not the sole contributor, with neural as well as endocrine dysregulation being hypothesized to potentially play other important roles. Thus, correction of weight-bearing alone may not be adequate to restore normal bone mass in this setting. Regardless of which factors are at play, when bone metabolism has been studied, the consequences, again in the acute setting, are both highly up-regulated bone resorption reflecting increased osteoclast activity with elevated levels of bone resorption markers such as NTX coupled with an inadequate bone formation osteoblastic response.[1, 7] This decrease in bone mass is coupled with a decrease in bone quality, with trabecular bone being particularly impacted.[3, 5]

2. Chronic SCI is associated with low bone mass and increased risk of fracture.

Individuals with chronic SCI have been documented in a number of cross-sectional epidemiologic studies to have low bone mass, specifically at infra-lesional sites. The magnitude of the bone loss has been shown to vary by site and by type of bone. Studies utilizing peripheral Quantitative Computed Tomography (pQCT) have documented greatest bone loss in distal femur and proximal tibia, areas rich in trabecular bone and the most common site for fracture in these individuals. Bone mass (measured by dual-energy X-ray absorptiometry or DXA) and bone volume (measured by QCT) have been reported to be reduced in the femoral and tibial epiphyseal areas by 50% and 60-70%, respectively, with cortical bone loss being less profound

but still quite significant, 25% and 35% respectively.[8-11] Bone loss at the hip has been of lesser degree, and no bone loss was reported in the spine or the upper extremities of individuals with paraplegia. Correlation of bone loss with a number of demographic and clinical parameters has been evaluated with greatly varying results (review by Jiang[1]). To some extent, this is a function of the fact that the majority of the studies have involved small numbers of subjects, almost all have been cross-sectional and/or retrospective in nature, and many were not optimally controlled. However, it appears that in chronic SCI, bone mass is independent of age at time of injury, gender, and weight. Many studies have claimed a relationship between time since injury and BMD, suggesting that there is continued bone loss that occurs after the initial, acute period of rapid reduction in bone. This is an important point, as it would suggest that there is on-going bone resorption that exceeds bone formation and that a new "set-point" has not been reached. However, the majority of studies examining this point have been cross-sectional in nature, while the few longitudinal studies undertaken have not extended beyond 2-5 years, a period during which there may continue to be net bone loss.



BMD change over 30 months with regard to time since injury

Recently, Frotzler et al[3] have specifically examined this issue in detail, utilizing pQCT to determine changes in bone over a 30 month period (baseline, 15 months, 30 months) in 39 males with complete SCI and paralysis. Time of injury varied from 0.9 years to 39 years prior to study start. They report that BMD reached a new steady-state in the femur and the tibia within 3 to 8 years after onset of SCI, with the time scale depending on bone parameter and skeletal site, and that once the initial rapid phase of bone loss had occurred, bone status was stable and unrelated to time from injury (see Figure 1). In the few studies in which bone markers were examined in those with chronic SCI, levels were reported to be elevated many years after the acute injury, though markedly lower than in the immediate post-injury period.[12, 13] As with the majority of the studies evaluating BMD, these studies were also cross-sectional and not longitudinal in design.

The clinical consequences of the decrease in both bone mass and bone quality in chronic SCI are reflected in a markedly increased rate of fracture, reported to be in the range of 1.2 to 3.4 per 100 patient years at risk.[4, 14, 15] This rate is similar to the rate of non-vertebral fractures occurring in post-menopausal osteoporotic women treated with placebo in the most recent anti-fracture efficacy trials.[16, 17] The fractures occur primarily at periods more than 5 years after the initial injury and involve the lower extremities and those areas that have had the greatest bone loss, e.g., distal femur and proximal tibia, areas not generally subject to fracture in people with post-menopausal osteoporosis or male osteoporosis.[4, 15, 18] Not only do fractures occur at a higher rate, but they also lead to longer hospitalization (7 times the length of non-fracture related admissions for SCI) and frequent medical complications with a higher rate of discharge to a second facility rather than home, all these factors resulting in significantly increased medical costs and loss of independence.[19] Risk of fracture was found to be related to extent of motor

loss (motor complete higher than incomplete) and alcohol consumption, with a non-significant relationship to time after injury.[19]

3. Animal models to understand mechanisms involved in SCI-associated bone loss.
Attempts to assess the basic endocrine and cellular mechanisms involved with SCI-associated bone loss have often turned to animal models. One widely used animal model to study the effects of loss of normal mechanical input has been the hindlimb-unloaded rat model (or tail suspension model)[20], though others utilizing mechanical immobilization also exist.[21, 22] The hindlimb unloading model has been used extensively to provide a laboratory surrogate for events happening during weightlessness[20, 21], and by extension has been used in studies to provide understanding in situations of disuse osteoporosis, including SCI. In summary, what has been found is under these experimental conditions, there is a marked increase in osteoclastic activity with significant loss of bone mass in the unloaded limbs with a concomitant decrease in osteoblast activity. Interventions with various agents have been evaluated (ovariectomy, bisphosphonates, PTH, etc), permitting studies at a biochemical, cellular, metabolic and structural level.[23-27]

To what extent this model which reduces mechanical stimulation mimics the clinical situation in SCI has been debated as the role of the nervous system in bone metabolism has become further defined.[28-32] For this reason, specific animal models have also been investigated to define changes in bone biology after injury to the spinal cord.[33, 34] Although these models have not been extensively studied for bone-related changes, what has been reported at this point is similar to what is known after removal of mechanical stimulation, namely that shortly after injury there is a marked decrease in trabecular and cortical bone mass with increased osteoclastic activity and decreased new bone formation with evidence for osteoblastic dysfunction.[34] Importantly, these animal models permit a means of evaluating both the mechanisms and effects of various interventions in a pathologic state that has similarities to that seen in SCI and are the basis for studies described below. It should be noted, however, that almost all models have focused on changes shortly after SCI or changes in mechanical loading and few studies, if any, have evaluated states equivalent to what is observed in human chronic SCI.

4. Considerations for treatment intervention to reduce fracture risk reduction in chronic SCI.
Based on the above data, interventions that could result in a decreased risk of fracture warrant investigation. With a rate of clinical fractures similar to that seen in an osteoporotic post-menopausal population, the size of study required to definitively demonstrate anti-fracture efficacy would be large, on the order of 5,000-10,000 subjects, which makes it highly unlikely that this will be undertaken in the SCI population. Therefore, it would be reasonable to investigate the effects of agents on surrogate measures of bone strength, with the most widely studied and best accepted being BMD, determined by either DXA or QCT. Additionally, because of the extensive bone loss that occurs in SCI, attention also needs to be paid to restitution of bone microarchitecture as well as simply bone mass, as bone structure has been shown to also be an important determinant of overall bone strength and fracture risk.[35, 36]

Given the extensive bone loss seen in chronic SCI (50-70% loss in locations of most common fractures[8-11]), optimal intervention would be one that would lead to robust increases in bone mass (on the order of a minimum of 10-20%) and would also restore bone microarchitecture.

This degree of increase in bone mass would be expected to be only achievable by interventions which result in a strong bone formation (anabolic) response, stimulating osteoblast differentiation and/or function, and having a major impact on bone microarchitecture (trabecular number, thickness, connectivity). Inhibition of bone resorption, the other mechanism that has been demonstrated to increase bone mass and decrease fractures in osteoporotic individuals, results in relatively quantitatively smaller increases in bone and less dramatic changes in bone microarchitecture.[37, 38] Increased bone mass occurs as a consequence of decreased osteoclast activation and activity[39], with a reduction in bone turnover and partial refilling of the remodeling space, and over time, increased mineralization of bone.[40] Rather than any increase in bone formation, a decrease in bone formation markers is typically seen, particularly with the use of the most potent anti-resorptive agents.[41]

5. Anti-resorptive agents have not been effective at increasing bone mass in chronic SCI.
Bisphosphonates, potent anti-resorptive agents, have been evaluated in animal models of disuse/immobilization and shown to be effective at preventing acute bone loss,[42, 43] but no studies have evaluated these agents in chronic settings of bone loss. The most recent study evaluating zoledronic acid in hindlimb suspended mice demonstrated the ability to prevent both bone loss and microarchitectural change (trabecular number, thickness), but with associated decrease in bone formation rate and no increase in bone mass from baseline.

In people with SCI, there have been 8 trials utilizing bisphosphonates[42, 44-50] with only 2 trials evaluating these agents in people with chronic SCI. In the acute setting, there was evidence of efficacy compared to placebo, in preventing bone loss, though this prevention was not necessarily complete nor sustained. In the 2 studies of people with chronic SCI, the largest by Zehnder et al also included subjects with acute injury.[50] In this study, BMD at the distal tibia was measured over 24 months and found to remain similar to baseline in the alendronate-treated group (-2.0±2.9%) compared to the placebo-treated group, which showed a significant decrease from baseline (-10.8± 2.7%), though as noted this also included subjects only months after SCI. Similar, though less marked differences were observed at the hip. The other study in patients with chronic SCI enrolled 19 subjects, randomized to alendronate or placebo, and failed to find any significant differences when evaluated at the study endpoint after 6 months of treatment, which may have been too short a period of time to be able to assess effects in a study of this size.[46] Thus, from available data in both animals and man, anti-resorptive agents appear able to prevent further bone loss in acute and possibly chronic SCI. However, there is no evidence of any increase in bone mass during treatment as seen in able-bodied individuals treated with the same agents.

6. PTH, a potent anabolic bone agent, has been shown to be effective in disuse models of osteoporosis (OP) in animals but has not demonstrated efficacy in people with SCI.
Parathyroid hormone (PTH), when administered exogenously and in an intermittent manner, has been shown to be a potent anabolic agent in bone, whose activity is due to direct and indirect effects on osteoblasts, including differentiation, proliferation and anti-apoptotic activity.[51] It binds to osteoblasts through the type 1 PTH receptor, resulting in downstream activation via G-coupled receptors of PKC and PKA signaling pathways. The exact mechanisms by which exogenous PTH results in its anabolic actions are not known, but believed to include some combination of direct effects on number and activity of osteoblasts coupled with indirect effects

to stimulate osteoblast growth factors or decrease levels or activity of osteoblast inhibitors, e.g., sclerostin.

In bone, exogenous PTH has been shown to have a marked anabolic effect with increase in mass that is more marked in trabecular than cortical bone, and is associated with a decrease in fracture risk. In studies in man, exogenous PTH, in the form of teriparatide (the N terminal 34 amino acids of native PTH, or 1-34 PTH) or full-length recombinant PTH (1-84 PTH) have been shown to result in increases in spine BMD, measured by DXA, of 9.7±7.4% in post-menopausal women after 12-24 months of 20 ug/day in the study by Neer et al[52] and 13.5±3.0% after 18 months in osteoporotic men.[53]

PTH has been studied extensively in animal models of disuse bone loss as it would be expected to prevent or reverse many of the changes observed. In one of the early studies, Ma et al demonstrated in rats undergoing hindlimb immobilization that exogenously administered teriparatide 30ug/kg/day could completely reverse the immobilization-induced cortical bone loss, even without mechanical loading, and that when added to a regimen of remobilization resulted in a synergistic anabolic effect on periosteal bone formation with an increased cross-sectional area that would be expected to result in increased bone strength.[22] Similar effects of PTH, independent of mechanical loading, were also reported by Turner et al.[54] The synergistic activity between teriparatide and loading was confirmed in two subsequent studies[55, 56] in which histomorphometric parameters of bone formation as well as bone strength were demonstrated to be increased by the combination of mechanical loading and exogenous PTH. In these studies, PTH was given concurrently with mechanical loading; however, in the study of Ma et al, PTH was administered after bone loss had already been established, which more closely approximates what occurs in the clinical setting.

Given these animal findings and the clinical efficacy of PTH in postmenopausal OP as well as male OP, PTH would seem a logical agent for use to reverse the bone loss seen in people with SCI. Our group tested this hypothesis in a study completed several years ago in which 60 people with chronic SCI and bone loss were treated with teriparatide 20 ugm administered subcutaneously (sc) daily for 12 months with and without vibration (administered via a vibrating platform).[57] This study was extended an additional 12 months with completers receiving teriparatide 20 ugm sc daily.[58] The results of these studies showed an increase in aBMD at the spine in the teriparatide group but no increase in aBMD was seen at the hip or femoral neck. CT analysis at the knee also demonstrated no consistent increase in either volumetric BMD or BMC at the distal femur or proximal tibia, the skeletal sites most prone to fracture in this population. Treatment with a second year of teriparatide did not alter these findings. Thus, in the only study of teriparatide in people with SCI, no clinical benefit on bone structure could be determined.

<u>7. Antibodies to sclerostin, a different anabolic agent, have been shown to be effective in animal disuse models of OP and in OP in man but not tested in people with SCI</u>.

A number of studies have demonstrated the pivotal role of sclerostin in mediating the response to loading and weight-bearing in murine models of bone disease. Early studies demonstrated clearly a marked increase in sclerostin upon unloading of bone and in the number of osteocytes, both in vivo and in vitro.[59-61] Furthermore, mutant mice lacking the *Sost* gene (*Sost* (-/-);

lacking sclerostin expression), failed to show the rapid bone loss seen in the *Sost* competent mice after mechanical unloading. Furthermore, treatment with antibody to sclerostin prevented the bone loss seen with both loss of normal weight-bearing and estrogen deficiency.[62, 63] These studies were complemented by studies in man in which sclerostin was also shown to be responsive to mechanical effects, seen in response to both physical activity and bed rest.[64, 65]

In man, treatment with antibody to sclerostin has been shown to result in significant increases in BMD in both post-menopausal women and men with OP. Specifically, romosozumab, a monoclonal antibody against sclerostin developed by Amgen, has not only shown increases in BMD but also reduction in fracture risk compared to both placebo and alendronate in randomized, controlled trials in post-menopausal women.[66, 67] In both trials, romosozumab was administered at a dose of 210 mg monthly for 12 months, followed by 12 months of either alendronate[67] or denosumab[66] treatment. Both BMD and fracture efficacy were evident after 12 months and maintained at 24 months. Compared to alendronate, both spine and hip BMD were greater at 12 months; and in a separate study, romosozumab treatment for 12 months resulted in greater increases in both spine and hip bone strength, determined by finite element modeling, than with teriparatide treatment.[68]

STUDY ENDPOINTS:

Primary Endpoint:
Change in integral vBMC at the knee (distal femur) at Month 12
Secondary Endpoints:
Change in DXA BMD at the total hip and femoral neck at Month 12
Change in vBMC at the hip at Month 12
Change in BMC/BMD at regions of interest around the knee at Month 12
Change in serum bone biomarkers at Month 12

Change will be assessed as both percent change from baseline and absolute change in all instances (see Statistical Analysis section below).

INVESTIGATIONAL AGENTS:

Romosozumab is a monoclonal antibody which inhibits sclerostin. It is marketed in the United States for the treatment of osteoporosis in post-menopausal women at high risk of fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or who have failed or are intolerant to other available osteoporosis treatments**.** For this study, Amgen will provide romosozumab and a letter of cross-reference to their IND to satisfy CMC (Chemistry, Manufacturing, and Controls) and other documentation for FDA. Romosozumab will be stored in the locked and temperature-monitored refrigerator used solely for investigational drug products (IP) in our research space. The refrigerator is maintained in a locked room accessible only to research staff. All staff are required to sign in and sign out when opening the refrigerator, and a log is maintained of all activity. Dispensing of IP (both romosozumab and alendronate) is under the supervision of Thomas Schnitzer, MD, PhD, principal investigator (PI) of this study.

For injections performed at a local clinic site, study drug will be shipped from Northwestern with a temperature monitor. The local clinic will be trained on the receipt, storage, accountability, administration, and disposal of study drug.

Alendronate is a bisphosphonate compound that inhibits bone resorption and leads to increases in bone mineral density. It is marketed in the United States for the treatment of osteopenia and the treatment of osteoporosis in post-menopausal women and men as well as for the prevention and treatment of glucocorticoid-induced osteoporosis. Alendronate will be sourced from NorthStar Rx LLC. Alendronate will be stored in the same locked room as romosozumab and be dispensed under PI's supervision. Participants will receive oral alendronate 70 mg once weekly in pill form. The study coordinator will explain how the medication is to be taken: first thing in the morning; sitting upright; on an empty stomach with a full glass of water; no other liquids, food or medication for at least 30 minutes. We have considerable experience with bisphosphonates in clinical trials and providing adequate instruction.

Vitamin D: Supplemental 25-OH vitamin D will be provided to all participants. This vitamin is required for intestinal absorption of calcium. Because hypocalcemia can occur with treatment of osteoporosis, it is important for adequate vitamin D to be available. At study entry, all participants will have to have a normal serum 25-hydroxyvitamin D level. Cholecalciferol 1000 IU/day to all participants to assure normal levels during the course of the study. For individuals who are already taking vitamin D supplements, the dosage of study cholecalciferol may be adjusted so as not to exceed 2000 IU per day, unless prescribed as such by the subject's primary physician.

Calcium: Calcium carbonate will be supplied to all participants. Because hypocalcemia can occur with treatment of osteoporosis, it is important for adequate calcium to be available. All participants will be given supplemental calcium (1000 mg/day) to be taken as 500 mg tablets, one tablet twice daily. For individuals who are already taking calcium supplements or obtain sufficient calcium through their diet, the dosage of study calcium may be reduced in order not to exceed 1000 mg of exogenous calcium per day. We recognize that there may be a preference for calcium citrate due to the lack of interference with absorption with concomitant use of proton-pump inhibitors, but our experience has been that calcium carbonate is well tolerated and does provide adequate calcium intake in most clinical settings.

The FDA has issued a Safe to Proceed Letter on 08May2020 for IND#149486 for romosozumab and alendronate tablets.
IND holder: Thomas Schnitzer, MD, PhD
The IND holder will comply with all sponsor requirements (reporting of SUSARs, annual reporting, etc).

PROCEDURES INVOLVED:

This is an open-label study of romosozumab 210 mg administered subcutaneously every month over a 12 month period followed by 12 months of oral weekly alendronate 70 mg treatment. Visits will occur as noted in the Study Procedures Flowsheet (Appendix A) and will take place at our research clinic in Abbott Hall, 10th floor, at Northwestern University building at 345 E.

Superior, and at nearby buildings. For participants who live more than 100 miles away and wish to receive monthly injections closer to their home, arrangements will be made with a local clinic to provide romosozumab injections for visits M7, M8, M9, M10, and M11.

Romosozumab will be administered by a licensed health care practitioner in the research clinic as outlined below or at a local clinic after month 6. At follow up visits during year 1, bone marker collection will occur prior to the romosozumab injections. During the Covid-19 pandemic, all Covid precautions will be followed per the Northwestern University policy and the research team's SOPs.

Childbearing potential will be determined based medical history and FSH results from the screening visit labs. Only subjects with childbearing potential will need documentation of a negative pregnancy test prior to imaging with DXA, CT, and/or injections of romosozumab.

The local clinic will be responsible for study drug receipt, storage, administration, collection of vital signs during the visit, and documentation of visit details on source documents. The rest of the study visit, including adverse event follow up, concomitant medications, questionnaires will be performed by the study coordinator over the phone. For Month 9, participants will be asked about their study supplement compliance over the phone instead of performing a physical compliance check. For participants of childbearing potential, a negative urine pregnancy test will be done at home by the participant and results will be shared with the study coordinator prior to the subject receiving an injection. Participants will receive supplies to perform a urine pregnancy test at home and will be trained on the proper procedure at Month 6.

Visit 1: Screening
At this visit, after the study is explained and consent is obtained, a medical history will be recorded and the Spinal Cord Injury & Lifestyle Information (SCILI) will be collected. Vital signs (VS) and physical examination performed, EKG, and blood and urine obtained for screening testing (hematology, chemistry, endocrine parameters, pregnancy, vitamin D levels). A DXA scan will be performed and the Walking Index for Spinal Cord Injury II (WISCI) administered at this visit. If needed, screening procedures may be completed in multiple visits.

Those individuals with low vitamin D levels will be given an eight-week supply of 50,000 IU vitamin D to be taken once a week. Participants will be asked to return to for a blood draw to establish adequate levels of vitamin D prior to initiation of romosozumab.

Visit 2: Baseline (within up to 8 weeks after screening)
At this visit, inclusion/exclusion criteria will be checked. Urine pregnancy test will be done, if applicable. CT of the hip and knee will be performed and blood obtained for serum bone marker determination. Participants will then receive their first doses of IP and be dispensed vitamin D and calcium with instructions for their daily administration. WISCI will be performed and SCIM will be collected.

Visit 3 (Month 1)
VS will be obtained and AEs and concomitant medications recorded. Urine pregnancy test will be done, if applicable. IP will be administered by trained study staff. Participants will have

serum calcium and vitamin D levels checked at this visit. If the results are abnormal, these labs will be repeated at Visit 5 (Mo 3).

Visit 4 (Month 2)
VS will be obtained and AEs and concomitant medications recorded. Urine pregnancy test will be done, if applicable. IP will be administered by trained study staff.

Visit 5 (Month 3)
VS will be obtained and AEs and concomitant medications recorded. Urine pregnancy test will be done, if applicable. IP will be administered: vitamin D and calcium will be provided. WISCI will be performed. DXA and CT of the knee will be performed and blood obtained for serum bone markers. If serum calcium and/or vitamin D levels were abnormal at Month 1, participants will be retested at this visit.

Visit 6 (Month 4) and Visit 7 (Month 5):
VS will be obtained and AEs and concomitant medications recorded. Urine pregnancy test will be done, if applicable. IP will be administered by trained study staff.

Visit 8 (Month 6):
VS will be obtained and AEs and concomitant medications recorded. DXA and CT of the hip and knee will be performed and blood obtained for serum bone markers. Urine pregnancy test will be done, if applicable. IP will be administered by trained study staff. Vitamin D and calcium will be provided. WISCI will be performed.

Visits 9-13 (Months 7-11):
VS will be obtained and AEs and concomitant medications recorded. Urine pregnancy test will be done, if applicable. IP will be administered by trained a licensed health care practitioner either at the research site or at a local clinic. At Visit 11 (Month 9) vitamin D and calcium will be provided.

Study Injections at a Local Clinic:

- Prior to receiving a romosozumab injection, the participant will send a photo to the study team of the pregnancy test results which must be negative.
- Local clinic will administer the injection and document details of the injection, vital signs, and any other pertinent information.
- The study team at the research site will be responsible for obtaining data on AEs, concomitant medications, questionnaires over the phone.

Visit 14 (Month 12):
VS will be obtained and AEs and concomitant medications recorded. Urine pregnancy test will be done, if applicable. DXA and CT of the hip and knee will be performed and blood obtained for serum bone markers. WISCI will be performed. Basic hematology, chemistry laboratory tests, and vitamin D levels will be assessed.

Alendronate, vitamin D and calcium will be dispensed with instructions for use. This will be the beginning of Year 2 and beginning of the treatment with alendronate.

Visits 15 and 16 (Months 15 and 18):
VS will be obtained and AEs and concomitant medications recorded. Urine pregnancy test will be done, if applicable. Alendronate, vitamin D and calcium will be provided. Visit 15 (Month 15) may be completed over the phone with supplements mailed to participant's home, if needed.

Visit 17 (Month 24):
VS will be obtained and AEs and concomitant medications recorded. DXA and CT of the hip and knee will be performed and blood obtained for serum bone markers. Urine pregnancy test will be done, if applicable. WISCI will be performed.

Subjects who discontinue the study who have completed 6 months of treatment with romosozumab will be offered the opportunity to immediately enter into the alendronate phase of the study (months 12-24).

DATA OBTAINED:

Clinical and Demographic Information
Clinical and demographic information will be obtained by personal interview and, if necessary, review of medical records. This information will include a complete medical history, including demographic information, with specific emphasis on bone-related issues (history of fracture, endocrinopathy, vitamin D intake, etc.) utilizing a bone health questionnaire used by our group to acquire baseline data for our in-house bone registry (Spinal Cord Injury & Lifestyle Information Form). They will also complete the Spinal Cord Independence Measure (SCIM) prior to initiating study drug. In order to assess ambulatory ability and status, participants will be asked to complete the Walking Index for Spinal Cord Injury II (WISCI) at each visit. This is a validated instrument to assess activity levels that affect bone loading and may be expected to have an impact on the effects of treatment that participants will be receiving.

DXA BMD
BMD will be determined by DXA at various skeletal sites: bilateral total hip, bilateral femoral neck, and spine. The DXA scans will be performed at Screening, 3 mos, 6 mos, 12 mos, and 24 mos by a trained DXA technician using a Hologic densitometer. Standard acquisition and analysis protocols will be used to quantify areal bone mineral density (aBMD) of all skeletal sites.

We have had extensive experience in DXA imaging of individuals with SCI. There have been no technical problems with DXA imaging though positioning has been challenging for some participants due to contractures and spasticity, and orthopedic hardware has also prevented the full set of images from being obtained. As much as possible, positioning is reproduced at subsequent visits to allow appropriate comparisons.

CT determined bone parameters
CT imaging will permit determination of volumetric integral BMD at the knee (distal femur and proximal tibia) and hip as well as definition of compartmental BMC and BMD (trabecular and

cortical). The non-dominant knee and hip will be scanned (based on handedness), unless metal or other artifacts are present. We also have extensive experience in this technique, with >200 knees imaged and analyzed. The CT scans will be performed using a Siemens Somatom machine (120kVp, 280 mAs, pixel resolution 0.352 mm, slice thickness 1 mm). Each CT scan will include a phantom – placed on the side of, or underneath, the subject's knee (for knee scans) or hip (for hip scans) – with known calcium hydroxyapatite concentrations of 0, 0.4, and 0.8 g/cm^3 (QRM, Moehrendorf, Germany). The phantom will serve as an interscan calibration, allowing for the conversion of CT Hounsfield units to bone equivalent density.

Three regions of bone will be analyzed corresponding to 0-10%, 10-20%, and 20-30% of segment length, as measured from the distal end of the femur or proximal end of the tibia. These regions were chosen based on their anatomical correspondence to epiphyseal (0-10%), metaphyseal (10-20%), and diaphyseal (20-30%) locations. The CT Hounsfield units will be converted to bone equivalent density and femora and tibiae will be segmented from CT images using a 0.15 g/cm^3 threshold to identify the periosteal surface boundary. Methodology for CT measurement of the hip has been previously published.[69]

The CT scans will be performed at Baseline, 3 mos (knee only), 6 mos, 12 mos, and 24 mos.

Determinants of bone strength

Measurements of distal femur and proximal tibia geometry and strength indices will be calculated along the longitudinal axis of the bone and subsequently averaged within each region. Cross-sectional area will be calculated as the cumulative sum of voxel area within the periosteal surface boundary. Bone volumes of integral and cortical bone will be quantified for each region and used as surrogate measures of periosteal and endosteal expansion. Both a compressive strength index and a torsional strength index will be calculated. Measurement of bone strength at the hip will utilize methodology previously published.[70]

Clinical chemistry evaluation (bone markers)

At Baseline, 3 months, 6 months, 12 months, and 24 months, 20 ml of blood will be obtained from each participant for determination of serum bone markers. Serum bone markers will include P1NP, osteocalcin (bone formation markers), CTX (bone resorption marker) as well as other bone-related serum markers to be determined. Serum will be separated and aliquots placed in vials individually labeled with the subject's study number and date; vials will be stored at -70°C in a locked freezer in a University maintained freezer repository.

At the end of the trial, samples will be sent for assay to the Maine Medical Center Research Institute Laboratory, Scarborough, Maine. This laboratory has extensive experience in performing these assays. Shipping will meet all federal, state and local regulations; all individuals involved in shipping biologic samples will have completed a training course provided the Northwestern University Office of Sponsored Research and will have received certification from them that they are aware of IATA/DOT regulations. Specimens will not be maintained for non-bone-related use.

Adverse events

Adverse events will be obtained by asking participants regarding changes in their health status during the course of the study. A MedDRA database will be used to document all adverse events. Reports of safety outcomes will be generated for use by the data and safety monitoring committee (DSMC) to review. DSMC meetings will occur at least every 6 months or more frequently depending on the activity of the protocol. All serious adverse events (SAEs) will be reported as required to the local IRB, Amgen, and FDA.

SHARING RESULTS WITH PARTICIPANTS

Results of the baseline laboratory testing and DXA data can be provided to the participants and/or their physician based on their providing permission. The CT data are not interpreted clinically and will not be provided. At the end of the study, the aggregate and individual participant's study results will be provided to the participant in a letter.

STUDY TIMELINES

It is anticipated that participants will require 25 months to complete the study. This includes a screening period of up to one month (can be extended to a second month), 12 months' treatment with romosozumab and 12 months' treatment with alendronate.

Recruitment will take 6-9 months for enrollment of all participants. The primary analyses should be completed within 3 months of the last subject completing IP treatment.

INCLUSION AND EXCLUSION CRITERIA

Eligibility criteria will be determined by the study coordinator at the screening visit after the participants has provided informed consent to participate in the study. Data will be obtained from the participants directly and from medical records if available. The Investigator will verify that a participant meets all study criteria prior to first dose of IP.

<u>Inclusion criteria</u>

- Age ≥18 years
- Female sex
- SCI 6 or more months prior to enrollment
- Non-ambulatory status (WISCI score of 3 or less)
- Osteoporosis by DXA defined as a t-score of ≤-2.5 at any skeletal site (lumbar spine, total hip, or femoral neck) or a t-score of ≤-2.0 plus a history of a fragility fracture
- Good general health, as determined by the study investigator
- Able to understand and agree to informed consent in English
- Able and willing to complete all the study visits
- Females of childbearing potential must be willing and able to use an effective method of contraception or practice abstinence throughout the course of the study and up to 90 days after the last use of study drug.
- Vitamin D 25-OH levels ≥ 20 ng/ml (subjects may be repleted and retested prior to baseline)
- Normal serum calcium levels (based on current local laboratory normal range)

- No known endocrinopathies (diabetes type 1 or 2, treated thyroid conditions can be included)
- Normal serum TSH and/or T4 levels (based on current local laboratory normal ranges)
- Able to take oral medication sitting upright for at least 30 minutes

Exclusion criteria

- Have Paget's disease of the bone
- Have abnormal laboratory values that in the judgement of the investigator would put the participant at increased risk of treatment
- Any active gastrointestinal condition that results in malabsorption
- Abnormalities of the esophagus which delay emptying such as stricture or achalasia
- Known hypersensitivity to romosozumab or alendronate
- Increased risk of aspiration
- Osteonecrosis of the jaw (ONJ) or risk factor for ONJ, such as invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery in the past 6 months), poor oral hygiene, periodontal and/or pre-existing dental disease, or planned invasive dental procedure over the next two years
- Heterotopic ossification of the knee region that interferes with CT analysis
- History of bone metastasis and skeletal malignancies
- History of alcoholism or drug abuse within the 2 years prior to study screening, which in the opinion of the investigator may affect subject's health and/or study commitment
- Other medical conditions that in the opinion of the investigator would preclude the subject from completing the study
- Currently being prescribed anticonvulsants at a dose or frequency that is determined to interfere with bone metabolism as determined by the investigator
- Currently being prescribed glucocorticoids, other than inhaled glucocorticoids
- Current or use during past 5 years of any bone-active agents, including any FDA approved treatment (e.g., teriparatide, abaloparatide, denosumab, any bisphosphonate (oral or IV), raloxifene, bazedoxifene, hormone therapy (estrogen and estrogen/progestin) and calcitonin) as well as any strontium-containing compounds.
- Pregnant, planning to become pregnant, or lactating
- Any history of stroke or cardiovascular disease other than controlled hypertension
- Renal insufficiency (calculated creatinine clearance less than 35 ml/min)
- Any other neurologic impairment that may impair ambulation or muscle function

VULNERABLE POPULATIONS: N/A

RECRUITMENT METHODS

Participants will be recruited from multiple sources:

A list of female patients having been treated at the Shirley Ryan AbilityLab (SRAlab) (previously known as the Rehabilitation Institute of Chicago (RIC)) with a diagnosis of SCI will be requested from their medical record system. Permission from their attending physician will be obtained prior to contact by phone or email.

Similarly, a list of female patients with SCI will be requested from the Northwestern Medicine's Enterprise Data Warehouse (EDW), which contains and makes accessible for researchers the electronic medical records of all individuals who are seen by clinicians within the NM system and who provide consent. Prior to phone contact, a letter will be ent by email or post to the identified patients allowing them to opt out of being contacted.

Social media (primarily Facebook, but others also possible) will also be used for recruitment, as well as non-public registries such as the Clinical Neuroscience Research Registry (STU00013948) and Clinical Research Registry (STU00212893). Patient referrals from other local institutions and organizations will be welcomed. Additionally, flyers, ads, brochures, and consent cards may be posted/provided in SRAlab, NM and/or other public areas.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

As all the participants will not be ambulatory, we will provide reimbursement for transportation costs or will pay directly for transportation (e.g., ride share) to bring them to the clinic.

We will provide $25/visit for screening and each clinic visit. Participants will receive $50 for Month 3 and 6 visits with imaging (DXA, CT) and $100 for Month 12 and 24 visits with imaging. All payments will be in cash other than the $100, which will be by check or debit card. For participants completing visits at a local clinic, a check will be mailed to them after each completed visit, per the reimbursement schedule.

WITHDRAWAL OF PARTICIPANTS

All participants will be informed as part of the consent process that their participation in the protocol is entirely voluntary and that they are free to discontinue at any time. Furthermore, such discontinuation will in no way prejudice any medical care they may be receiving from the institution or any clinician involved, or interfere in any way from their receiving on-going or future care.

If individuals elect to withdraw from the study, a termination visit will be scheduled, if possible, at which time the reason for their discontinuation will be solicited to allow appropriate action. If withdrawal is due to medical reasons, related to the protocol, appropriate medical referral and follow-up will be recommended, which could include further safety visits until the event has passed. Participants may be withdrawn from the study by the principal investigator if in his judgment continuation in the protocol would be detrimental to the health or safety of the participant, if the participant is not compliant, or if funding no longer exists for the project.

Although every attempt will be made to retain subjects in this study, we do not plan to replace withdrawn subjects. If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator will not access the participant's medical record or other confidential records requiring the participant's consent for purposes related to the study. However, the investigator may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

Female subjects who become pregnant will be withdrawn from the protocol and will not be allowed to continue participation.

RISKS TO PARTICIPANTS

Romosozumab
Romosozumab may increase the risk of cardiovascular events of myocardial infarction, stroke and cardiovascular death. Therefore, romosozumab should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Hypocalcemia and clinically significant hypersensitivity reactions including angioedema, erythema multiforme, dermatitis, rash, and urticaria have occurred in romosozumab-treated patients. Romosozumab is contraindicated in patients with uncorrected hypocalcemia and history of systemic hypersensitivity to romosozumab or to any component of the product formulation. Other potential risks include osteonecrosis of the jaw and atypical subtrochanteric and diaphyseal femoral fractures. These risks are rare and can occur spontaneously. The most common adverse events reported with the use of romosozumab includes: arthralgia, headache, muscle spasm, peripheral edema, asthenia, neck pain, insomnia, paresthesia, and injection-site reactions.

Alendronate
Risks associated with alendronate include osteonecrosis of the jaw, atypical femoral fractures and the possibility of severe bone, joint and muscle pains. These are seen in less than 1% of people taking alendronate. The most common adverse reactions reported with the use of alendronate are abdominal pain, dyspepsia, nausea, constipation, diarrhea, acid regurgitation, esophageal ulcer and headache.

Radiation Exposure: Risks of radiation exposure will be listed in the study consent form per the Radiation Safety Officer's assessment based on DXA and CT imaging.

Vitamin D and calcium. The doses administered in this study are significantly below the safe upper limit defined by the Institute of Medicine's recent report.[71, 72] Overdose of either can result in hypercalcemia, which is associated with nausea and vomiting, loss of appetite, excessive thirst, constipation, abdominal pain, muscle weakness and pain, confusion, lethargy and fatigue.

POTENTIAL BENEFITS TO PARTICIPANTS

The participants may have an increase in bone mass and bone strength as a result of their participation in this study. The probability and magnitude of this increase are not known. Participants will also have the advantage of screening laboratory values which may be useful.

Findings of this research will be shared with the participants at the end of the trial after analysis of all the results. This will be accomplished by sending a letter to each of the participants with a lay-person summary of the key results, including both benefits and any risks that may have been identified.

STATISTICAL ANALYSIS AND SAMPLE SIZE DETERMINATION

As this is a proof of concept study with a study population that has never been previously studied with this agent, the goal is to be able to identify a favorable change in bone parameters from baseline. It is well described that individuals with chronic SCI do not show an increase in bone density or bone content over time, rather there may be a small decrease though bone density tends to stay fairly constant over a 12 month period.

To reduce the number of people exposed, we have limited the sample size to 12. This should allow us to detect an effect size (ES) = 0.8 with 80% power and an alpha = 0.05 (or 90% power and an alpha = 0.10). This is based on using a Wilcoxon signed rank test (one sample) in G*power. If we increase the sample size to 15, we could detect an ES = 0.6 with 80% power and an alpha = 0.10. These ES estimates are based on changes in absolute BMD values (gm/cm^2).

In order to study our primary and secondary endpoints, we will evaluate absolute changes from baseline to Month 12 for each using a non-parametric approach (primary analysis). An analysis evaluating percent changes from baseline to Month 12 will also be performed. The null hypothesis being tested for each outcome is the median difference between pairs of baseline and post-treatment values is zero. Assuming the expected sample size (12 subjects), we anticipate that the distribution of baseline and post-treatment scores across endpoints will not approximate a normal distribution. Given the dependency of the measures from each other, we will test the hypothesis that the average signed rank of the two samples is zero (Wilcoxon Signed Rank test) for each outcome for the primary analysis. The primary and secondary endpoints will also be assessed at Month 24 and compared to values at Month 12 and baseline.

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6) and the Code of Federal Regulations on the Protection of Human Participants (45 CFR Part 46). The Northwestern University IRB will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. All personnel involved in the conduct of this study will have completed human subject protection training. Informed consent will be obtained before any clinical trial-related procedures are conducted and will be on-going throughout the study.

DATA MANAGEMENT AND CONFIDENTIALITY

Data management will be coordinated by the PI, with direct management by the study data manager. A REDCap database will be developed for the study and maintained on a secure server. Whenever possible, study results will be electronically uploaded. Double entry will be used for data that must be manually entered to track entry errors. The database provides transaction logs (i.e., records of who accesses the database) and audit trails (i.e., records of all changes to the database, at the cell level), thereby maintaining the highest level of data security. The master table linking patient names and other Protected Health Information (PHI) with identification numbers will be maintained in a separate password-protected file, accessible only by designated members of the research team. Hard copies of participants' records will be kept in individual study charts that are stored either in locked cabinet or in a locked office. If any participant-level

information is provided to third parties, including Amgen, this information will not include participants' identifiers unless required by law. Data records may be destroyed by deleting them from electronic media and by shredding paper documents, but some of the deidentified data records may be retained indefinitely. The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

Adverse events will be collected at all study visits. SUSARs will be reported to the IRB, FDA, and Amgen. Other sponsor required reporting responsibilities are described below.

The study will have an independent medical monitor to assist in the evaluation of safety. Because of the small number of participants, a statistician will not be part of the initial safety evaluation. Aggregate summary safety reports of all AEs will be generated every 6 months during the course of the study and reviewed by the PI and the medical monitor. If there should be need for additional input, clinical or statistical, this will be requested by the independent medical monitor and provided.

Participants will be discontinued from treatment if they experience a serious adverse event believed to be related to the study medication. Participants will be encouraged to continue to be followed with visits for safety and imaging visits.

Participants will be told to call the research coordinator or principal investigator if at any time in the study they have a change in their medical condition, particularly if they believe this may be related to the study interventions. They will be given a telephone number to call that will reach a study member at any time (24 hours/day) during the course of the study.

Specific Safety Reporting to Amgen

Safety Data	Timeframe for submission to Amgen	Send to
Suspected Unexpected Serious Adverse Reaction (SUSARs)	At time of regulatory submission	Amgen Safety
Pregnancy/Lactation exposure and any associated reports/outcomes (i.e. unexpected pregnancy, spontaneous abortion, congenital anomaly, etc.)	Within 1 business day of Sponsor awareness, for reports meeting serious criteria Not to exceed 15 calendar days of Sponsor awareness, for non-serious reports	Amgen Safety

Safety Data	Timeframe for submission to Amgen	Send to
Serious Adverse Device	Within 1 business day of Sponsor	Amgen Safety

Effect[c] (SADE)	awareness	
Adverse Device Effect (ADE)	Not to exceed 15 calendar days of Sponsor awareness	Amgen Safety
Product Complaint[d]	Immediately, not to exceed 1 business day of Sponsor awareness	Amgen Quality

Safety Data	**Timeframe for submission to Amgen**	**Send to**
Listing for Safety data reconciliation[b]	Once per year and at the end of the study	NASCR Manager
Annual Safety Report (eg, EU Clinical Trial Directive DSUR and US IND Annual Report)	Annually	NASCR Manager
Other aggregate analyses (any report containing Safety data generated during the course of the study)	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.)	NASCR Manager
Final (End of Study Report, including): • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.) but no later than 1 calendar year of study completion	NASCR Manager

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

We are committed to respect participant privacy and to keep personal information confidential. When choosing to take part in this study, participants are giving us the permission to use their PHI that includes health information in their medical records and information that can identify them. For example, PHI may include name, address, phone number or social security number. Health information that we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history
- Lab tests, or certain health information indicating or relating to a particular condition as well as information collected by PROs
- Records about study medication or drugs

The following groups of people may give the researchers information about research participants: All current and previous health care providers, including but not limited to Northwestern Medicine Faculty Foundation (NMFF), Northwestern Medicine Practice Group (NMPG), Northwestern Memorial Hospital (NMH).. Once we have the health information listed above, we may
share some of this information with the following people.

Importantly, any research information shared with people outside of NU and its clinical partners (or affiliates) will not contain subject's name, address, telephone or social security number or any other direct personal identifier unless disclosure of the direct identifier is required by law

- Authorized members of the NU workforce, who may need to see information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study),
- Clinical affiliates, including but not limited the NMFF, NMH, and NMPG. Individuals' participation in this clinical trial will be tracked in an electronic database and may be seen by investigators running other trials and by other healthcare providers having access to this database.
- Other University research centers and University contractors who are also working on the study,
- Study monitors and auditors who make sure that the study is being done properly,
- Government agencies and public health authorities, such as the FDA and the DHHS.

The results of this study may also be used for teaching, publications, or presentation at scientific meetings. However, the individual's name and personal information will not be used.

COMPENSATION FOR RESEARCH-RELATED INJURY

There will be no compensation provided by Amgen or by Northwestern University for any research-related injury. Participants will be told to obtain care from their regular providers as necessary and to seek reimbursement from their insurance company.

ECONOMIC BURDEN TO PARTICIPANTS

Participants will not be charged or have to pay for any study-related activities, medications, or supplements.

INFORMED CONSENT PROCESS

The study staff will speak to the potential participant in person or over the phone and do a brief screening to be certain that the person could potentially qualify for the study and then schedule a time for a screening visit. Potential participants will be offered the opportunity to have family

members or others with them during the consent process or to postpone making a decision if they feel they wish to get advice from another person not immediately available. In cases where the participant is not able to print her name, sign and date the consent form document, the accompanying person may also act as a witness of the consent process. A consent form may be sent to the potential participant if there is time prior to his/her scheduled appointment.

At the screening session, which generally will take approximately 3-4 hours, the participant will be given a consent form to read or review again if they had already received one. After they have had adequate time to read the form completely, the study coordinator will review all the elements of the study again with the participant. The study coordinator will assess whether the potential participant demonstrates the ability to provide informed consent by asking her to describe the goals of the study and what is expected of her, explore her motivation for being involved in the study and her expectations, and ask about any logistical issues and determine how they can be dealt with (transportation to the clinic, travel out of town for long periods of time). Questions will be answered by the study coordinator if possible; for those questions that cannot be answered by the study coordinator, the principal investigator will be available to provide them or suggest how an answer can be obtained.

The consent process, occurring in the consult room of the clinic or at the patient bedside, is expected to take approximately 30-45 minutes. Only English-speaking participants will be enrolled. If a patient is unable to print her name, sign and date the consent, the presence of a witness during the consent process will be required. The witness will document by signing the consent form that the study was thoroughly explained to the participant, all questions were answered, and that the participant freely gives her verbal permission to enter the study. Study staff will make a note in the source documentation describing the consent process. Two copies of the consent form will be fully executed; one copy is given to the subject and the other is put into the study chart.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

PHI will be obtained and HIPAA does apply. HIPAA Authorization will be obtained from all participants prior to their enrollment into the study.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

Thomas J. Schnitzer, MD, PhD: Principal investigator is responsible for overall management of all activities for this project. Dr. Schnitzer has managed clinical trials for over 20 years and has undertaken investigations in people with SCI for over 10 years. Dr. Schnitzer will provide supervision and direction to the study coordinator for all clinical and regulatory aspects of the study, assist in recruitment, do physical examinations, be available to answer questions and evaluate changes in clinical status, evaluate adverse events and report serious adverse events to appropriate authorities, prepare annual reports and protocol updates/amendments, interact and coordinate with co-investigators, interact with DXA technician to assure quality of DXA scans, interact with the other site investigators to assure recruitment and quality of CT evaluations, interact with Research Monitor on regular basis, help in preparation of safety reports, interact

with data manager to assure quality and integrity of data, evaluate data with the statistician and remainder of research staff, prepare manuscript and submit for publication.

James W. Griffith, PhD: Dr. Griffith is a faculty member and a clinical psychologist at Northwestern University in the Department of Medical Social Sciences. Dr. Griffith has extensive experience in research biostatistics and will be the primary statistician working with faculty in the Department of Physical Medicine and Rehabilitation. He will provide the statistical input for this project.

W. Brent Edwards, PhD: Dr. Edwards is an assistant professor at the University of Calgary and will be responsible for ensuring that CT data is collected according to a standard protocol. Dr. Edwards will be responsible for processing and analyzing all CT data. This includes segmenting images, obtaining architectural parameters and generating and running subject-specific finite element models. Working with Dr. Schnitzer, Dr. Edwards will intellectually contribute to the dissemination of this data.

Roles and responsibilities of other study personnel

Study Coordinator: The study coordinator will be responsible for all interactions with study participants, including recruitment, obtaining informed consent, scheduling all DXA, CT and follow-up clinical visits, collecting adverse event information at all visits from the participants, being available to answer queries and concerns from participants, providing telephone contact to all participants, reporting all safety reports, maintaining all regulatory documents and entering clinical data into the appropriate databases. He/she will work closely with all the key personnel to assure that everyone is aware of each participant's study status and any changes that occur during the study will be communicated to the PI.

Research Monitor: Dr. Elliot Roth has agreed to be the independent Clinical Monitor for this study. Dr. Roth is the Chairman of the Department of Physical Medicine and Rehabilitation at Northwestern University Feinberg School of Medicine and has significant clinical and administrative experience overseeing research projects.

The Research Monitor will review on an individual basis all unanticipated problems involving risk to participants, serious adverse events, and all participant death associated with the protocol, and provide an unbiased written report of the event to the IRB. For any event determined to be an unanticipated problem involving risk to subjects or others, this AE will be promptly reported by telephone, email, or facsimile to the FDA and Amgen. A complete written report will follow the initial notification.

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APPENDIX A

Study Procedures Flowsheet

Event	Screening	Baseline	Study Visits														
Study Day		0	Mo 1	Mo 2	Mo 3	Mo 4	Mo 5	Mo 6	Mo 7	Mo 8	Mo 9	Mo 10	Mo 11	Mo 12	Mo 15	Mo 18	Mo 24
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15*	V16	V17
Procedures:																	
Informed Consent	X																
Demographic Data	X																
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																
Weight	X																
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X																
Physical Exam	X																
EKG	X																
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm Patient Meets Incl/Excl Criteria	X	X												X			
Administer/Dispense Study Drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Calcium/Vitamin D		X			X			X			X			X	X	X	
Assess Compliance with calcium/vit D			X		X			X			X			X	X	X	X
WISCI	X	X			X			X						X			X
DXA Lumbar Spine (A-P View)	X				X			X						X			X
DXA Hip ROIs	X				X			X						X			X
CT Distal Femur/Proximal Tibia		X			X			X						X			X
CT Hip		X						X						X			X
Labs:																	
CBC	X													X			
Chemistry Panel/Serum Calcium	X		X		X**									X			
FSH and Estradiol	X																
TSH	X																
25(OH) Vitamin D	X		X		X**									X			
iPTH (I-84)	X																
Urinalysis	X																
Bone Markers		X			X			X						X			X
*may be replaced with telephone call																	
**Serum Calcium and Vitamin D will be repeated at Mo 3 only if Mo 1 labs are abnormal.																	