Cover Page for	**Protocol**
Sponsor Name	**Viking Therapeutics Inc.**
NCT Number	02578095
Sponsor Trial ID	VK5211-201
Official Title	A Phase II, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multi-Center Study to Explore the Efficacy, Safety and Tolerability of VK5211 in Subjects with Acute Hip Fracture
Document Date	December 23, 2015

Clinical Study Protocol: VK5211-201

Study Title:	A Phase II, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multi-Center Study to Explore the Efficacy, Safety and Tolerability of VK5211 in Subjects with Acute Hip Fracture
Protocol Number:	VK5211-201
Study Phase:	Phase IIa
Name of Test Drug:	VK5211
Formulation:	0.5 mg, 1.0 mg, or 2.0 mg capsule
Indication Studied:	Hip fracture
Study Design and Subject Population:	Approximately 120 subjects admitted for acute hip fracture will be screened and randomized to one of four treatment arms (VK5211 0.5 mg, 1.0 mg, 2.0 mg, or placebo) in a 1:1:1:1 ratio. Subjects will receive treatment for 12 weeks and be assessed for efficacy, safety and tolerability in comparison to placebo.
Sponsor:	Viking Therapeutics, Inc. 12340 El Camino Real, Suite 250 San Diego, CA 92130
Sponsor's Responsible Medical Officer:	Steven Schoenfeld, MD 12340 El Camino Real, Suite 250 San Diego, CA 92130 Email: sschoenfeld@vikingtherapeutics.com Tel: 858-704-4677 Mobile/cell: 858-208-9127
Protocol Dated:	Amendment 2: December 23, 2015

SPONSOR APPROVAL PROTOCOL SIGNATURE PAGE

The undersigned have reviewed and approved the following protocol:

Steven Schoenfeld, MD
Senior Vice President, Clinical Development
Viking Therapeutics, Inc.

Signature

23 Dec 2015
Date

AUTHOR SIGNATURE

The undersigned have written, reviewed and approved the following protocol:

Jillian L. Whidby, PhD
Medical Writer
Integrium, LLC

Signature

12/23/15
Date

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INVESTIGATOR PROTOCOL AGREEMENT SIGNATURE PAGE

Protocol Title: A Phase II, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multi-Center Study to Explore the Efficacy, Safety and Tolerability of VK5211 in Subjects with Acute Hip Fracture

Protocol Number: VK5211-201

By my signature, I confirm that my staff and I have carefully read and understand this protocol, protocol amendment, or amended protocol and agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by Viking Therapeutics, Inc.

I agree to conduct the study according to this protocol and the obligations and requirements of clinical Investigators and all other applicable requirements listed on form 1572 and in 21 CFR part 50, 54, 56, and 312 and all applicable local, state, and federal regulations and ICH guidelines. I will not initiate this study without the approval of an Institutional Review Board (IRB).

I understand that, should the decision be made by Viking Therapeutics, Inc. to terminate prematurely or suspend the study at any time for whatever reason, such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate immediately such decision in writing to Viking Therapeutics, Inc.

For protocol amendments, I agree not to implement the amendment without agreement from Viking Therapeutics, Inc. and prior submission to and written approval (where required) from the IRB, except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

Investigator's Signature Date

Investigator's Name

Address:

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Synopsis

Title	A Phase II, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multi-Center Study to Explore the Efficacy, Safety and Tolerability of VK5211 in Subjects with Acute Hip Fracture
Indication	Hip fracture
Clinical Phase	Phase IIa
Primary Objective	To determine the efficacy of VK5211 after 12 weeks of treatment based on mean placebo-corrected percentage change in total body less head (TBLH) lean body mass as assessed by whole body Dual Energy X-Ray Absorptiometry (DXA) scan.
Secondary and Exploratory Objectives	<u>Secondary</u> 1) To assess the safety and tolerability of VK5211 after 12 weeks of treatment by comparing overall adverse events, vital signs, 12-lead ECG data, physical examinations, and hematology/chemistry/urinalysis data to placebo. 2) To determine the efficacy of VK5211 after 12 weeks of treatment based on mean placebo-corrected change in: • Hip bone mineral density (BMD) as assessed by DXA • Total lean body mass • Appendicular lean body mass • Bone turnover markers (s-CTX and s-PINP) 3) To assess plasma concentration of VK5211 near T_{max} and at trough levels in relation to total lean body mass. <u>Exploratory</u> To determine the efficacy of VK5211 compared to placebo after 12 weeks of treatment based on: • Physical Performance Assessments o Six-Minute Walk Test (6MWT) and BORG Scale o Grip Strength o Short Physical Performance Battery (SPPB) • Patient Reported Outcomes o Physical activities of daily living (PADLs) and Instrumental activities of daily living (IADLs), pre- and post-fracture o Short Form-36 (SF-36)
Study Design	This is a randomized, double-blind, parallel group, placebo-controlled, multi-center study to investigate the safety, tolerability, and efficacy of VK5211 after 12 weeks of treatment. Males and females ≥65 years old who are ambulatory and recovering from a hip fracture will be eligible for participation 3-11 weeks post-injury. After completing all Screening requirements, subjects will be randomized to one of four treatment arms (VK5211 0.5 mg, 1.0 mg, 2.0 mg, or placebo) in a

	1:1:1:1 ratio and will receive their first dose of study treatment in the clinic. Baseline procedures will include: • Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate) • Hematology/Chemistry/Urinalysis • Bone Turnover Markers • Vitamin D • Thyroid Markers • Fasting Lipid Profile • Coagulation • Pituitary/Adrenal Hormone Blood Tests • Pancreatic Endocrine Markers • DXA Scan • 12-Lead Electrocardiogram (ECG) • 6MWT and BORG Scale, Grip Strength, and SPPB • Post-fracture PADLs/IADLs • SF-36 The first bottle of study treatment will be dispensed and subjects will be instructed to take one oral dose of the assigned treatment at approximately the same time every morning, 30 minutes prior to breakfast. They will receive a diary card to record their treatment administration and meal times for 3 days prior to Visit 2. Within 1 week of randomization, subjects will receive a phone call to review concomitant medications, discuss adverse events, and review compliance. Subjects will undergo safety and efficacy assessments as specified in the protocol on an approximately 4-week basis for a total treatment period of approximately 12 weeks. Following the 12-week treatment period, subjects will be followed for an additional 12-week period for assessment of safety and duration of drug effect. During the study safety will be assessed on an ongoing basis by adverse events, identification of dose-limiting toxicities (DLTs) (if any), plasma concentrations, general physical examinations, vital signs, clinical laboratory assessments in blood, urine, as well as other specialized testing as required. Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.03 [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf].
Total Sample Size	Approximately 120 subjects
Subject Selection Criteria	Recovering hip fracture patients ≥65 years old

Statistical Methods	All subjects who have taken a single dose of the study drug and provide follow-up information will be included in the safety population. All subjects who have taken a single dose of the study drug and have a valid pre-baseline and post-baseline efficacy assessment will be included in the Intent-to-Treat population. All subjects who have taken at least 80% of the expected number of doses and do not have a major protocol violation will be included in the Per Protocol population. Descriptive statistics and listings will be provided for all data.

Table of Contents

LIST OF IN-TEXT TABLES

List of Abbreviations and Definitions of Terms

6MWT	Six-Minute Walk Test
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARB	Angiotensin receptor blocker
BP	Blood pressure
bpm	Beats per minute
C_{max}	Maximum drug concentration
CRA	Clinical research associate
CRO	Contract research organization
CV	Coefficient of variation
DXA	Dual-energy x-ray absorptiometry scan
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FT	Free testosterone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HR	Heart rate
IADLs	Instrumental Activities of Daily Living
ICF	Informed consent form
ICH	International Council for Harmonization
IP	Investigational product
IRB	Institutional Review Board
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeters of mercury
MMSE	Mini-Mental State Exam

PADLs	Physical Activities of Daily Living
PE	Physical examination
PI	Principal Investigator
PSA	Prostate-specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
SAE	Serious adverse event
SBP	Systolic blood pressure
s-CTX	Serum C-terminal crosslinking telopeptide of type 1 collagen
SD	Standard deviation
SF-36	Short Form-36
SHBG	Sex hormone binding globulin
SOP	Standard operating procedure
s-PINP	Serum procollagen type 1 propeptide
SPPB	Short physical performance battery
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TT	Total testosterone
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

INTRODUCTION

More than 300,000 people in the U.S. experience hip fractures each year with the number expected to increase to 700,000 by 2050, driven by increased life expectancy and aging of the baby boom generation[1,2]. Surgical intervention is the cornerstone of hip fracture treatment. The short-term goal of surgery is to stabilize the hip fracture and allow for weight bearing and movement in order to prevent sequelae from prolonged bed rest and allow for fracture healing.

Despite surgical intervention, recovery after hip fracture is often incomplete and is associated with high morbidity and mortality rates in the elderly. Mortality risks are at their peak in the first three months following hip fracture, with patients demonstrating a five- to eight-fold increased risk of dying during this period[3]. Many patients never regain complete pre-fracture mobility and require long term assistance, which has a negative impact on their quality of life[4]. Furthermore, refracture and rehospitilization rates remain high, contributing to the increased pressure on health system resources[5].

The elderly population is often considered frail and undernourished[6,7], which may be due in part to an increased catabolic state[8]. An increased catabolic state leads to chronic muscle wasting and reduced muscle strength, often resulting in falls accompanied by impaired immunity and delayed wound healing. Since anabolic steroids have been shown to improve conditions associated with increased catabolic rates such as burns, chronic obstructive airway disease and acquired immune deficiency syndrome (AIDS), selective androgen receptor modulators (SARMS) could be similarly useful in hip fracture in the elderly[9]. SARMS may help to improve outcomes and recovery by promoting anabolic and bone strengthening activities, while at the same time avoiding the negative steroidal side effects including changes in voice, growth of facial hair in women, hair loss, acne, thromboembolic events and liver damage.

VK5211 is intended to produce the therapeutic benefits of testosterone in muscle and bone tissue with improved safety and tolerability and is the first SARM currently under investigation for the treatment of hip fracture. Based on the anabolic characteristics imparted by selective activation of the androgen receptor, we believe VK5211 may stimulate bone and muscle growth without the adverse bone remodeling properties of osteoporosis drugs such as bisphosphonates. VK5211 has already shown encouraging efficacy in a standard animal model of osteoporosis, demonstrating improved bone mineral content, density and strength. This may benefit patients following hip surgery, where loss of bone mineral density can exceed 12 times the background rate for patients with osteoporosis.

Two Phase I studies have been completed (VK5211-01 and 02) in healthy male volunteers to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of VK5211. In addition, a Phase I study to determine the PK and safety in subjects 65 years of age or older (VK5211-103) was recently completed and preliminary results are available. Phase I data in the younger males show that VK5211 rapidly stimulates the formation of lean body mass (LBM), an important property for the hip fracture recovery setting, where patients can lose up to 6% of lean body mass in the two months following injury.

In addition, VK5211was well-tolerated at doses well above those that will be tested in this study.

Preliminary safety results prior to data lock in study VK5211-103 reveal that VK5211 is well tolerated in male and female subjects 65 and older. Four subjects total (2 in the 1 mg cohort and 2 in the 3 mg cohort) reported adverse events. One subject in the 1 mg group experienced 2 separate, classic migraine headache episodes considered unrelated to the study drug, which resolved with medical treatment. The second subject suffered one episode of non-migraine headache, also resolved with treatment. In the 3 mg cohort, 1 subject experienced three separate mild AEs considered by the Investigator to be unrelated to the study drug (postprandial diarrhea, IV site pain, and mild headache). The second subject reported an AE of ankle swelling due to her antihypertensive medication (amlodipine). This case of ankle swelling was milder than her prior, pre-study episodes and resolved upon switching to a different antihypertensive medication.

Physical exam, vital signs and ECG values were all unremarkable. Laboratory evaluations revealed one subject in the 1 mg group who had minimally elevated ALT at day 9 (59 U/L (Normal range up to 55 U/L), while 5 subjects in the 3 mg dose group had asymptomatic AST or ALT values above the ULN. Four of the 5 subjects in cohort 3 had mild elevations ≤1.5X ULN at day 9. The fifth subject, while asymptomatic, had an AST elevation just under 5X ULN and an ALT elevation 7X ULN; bilirubin, alkaline phosphatase, and GGT levels did not change from baseline. Approximately two weeks later, the subject's AST/ALT had come down to 24 and 62 U/L, respectively. There were no other clinical or laboratory abnormalities of clinical significance reported from either dose cohort in study VK5211-103. Therefore, treatment with VK5211 has been safe and well tolerated in both young adults and subjects 65 years of age or older, and merits additional studies for indications such as acute hip fracture.

VK5211 has the potential to provide therapeutic benefits via once-daily oral dosing, an important advantage over injectable protein or bisphosphonate therapies.

1 ETHICS AND REGULATORY CONSIDERATIONS

1.1 Independent Institutional Review Board (IRB)

Before study initiation, the protocol and all amendments, consent form, subject recruitment materials and procedures (e.g., advertisements) and any other written information to be provided to subjects will be reviewed and approved by the relevant IRB.

The IRB will be provided with a copy of the Investigator Brochure information to be provided to subjects and any updates in accordance with local regulatory requirements. The IRB will be provided with reports, updates, and other information (e.g., Safety Updates, Amendments, and Administrative Letters) according to local regulatory requirements or Institution procedures.

1.2 Ethical Conduct of the Study

This document is a protocol for a human research study conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Council for Harmonization guidelines), applicable government regulations and Institutional Research Policies and Procedures.

The study will be conducted as described in the approved protocol, with amendments. All revisions to the protocol will be discussed with, and will be prepared by the Sponsor, Viking Therapeutics. The Investigator will not have authority to implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard to study subjects. Any significant deviation from the approved protocol will be documented in the Deviation Log.

Any deviation or change to the protocol required to eliminate an immediate hazard prior to obtaining IRB approval/favorable opinion, will be submitted as soon as possible to:

- IRB for review and approval/favorable opinion.
- Viking Therapeutics via appropriate designees.
- Regulatory Authorities, if required by local regulations.

Documentation of approval signed by the chairperson or designee of the IRB will be sent to Viking Therapeutics via appropriate designees.

If the revision is an Administrative Letter, Investigators will be required to inform their IRB.

If an Amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form will be revised and submitted to the IRB for review and approval/favorable opinion; (2) the revised form will be used to obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and (3) the new form will be used to obtain consent from any new subjects prior to enrollment.

1.3 Subject Information and Consent

The consent form will include all elements required by the International Council for Harmonization (ICH), good clinical practice (GCP) and applicable regulatory requirements and

adhered to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form will also incorporate or include as an attachment an authorization to use or release individual health information for research. This authorization will include a statement that protected health information may be shared with Viking Therapeutics and/or its agents, other researchers participating in this research, and regulatory authorities. Prior to the beginning of the study, the Investigator will obtain the IRB's written approval/favorable opinion of the written informed consent form and any other information to be provided to study subjects.

The informed consent form and any other information provided to subjects or the subject's legally acceptable representative will be revised whenever important new information becomes available that was relevant to the subject's consent, and receive IRB approval/favorable opinion prior to use. The Investigator, or a person designated by the Investigator, will fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication will be documented. Subjects will read and sign any and all revised informed consent forms.

During a subject's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the subject.

2 INVESTIGATIONAL PLAN

2.1 Overall Study Design and Plan: Description

This is a randomized, double-blind, parallel group, placebo-controlled, multi-center study to investigate the safety, tolerability, and efficacy of VK5211 after 12 weeks of treatment.

2.2 Screening

Screening will take place 3-11 weeks post-injury. After signing the informed consent form, inclusion/exclusion criteria, concomitant medications, and medical history will be reviewed and demographic information will be collected. Subject will have a physical examination, including height and weight. Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate) will be recorded. Samples will be collected for hematology/chemistry (with HbA1c)/urinalysis and prostate specific antigen (PSA, males only). A Mini Mental State Exam will be performed on all subjects to verify cognitive function. The 4-meter walk test will also be performed to verify ambulatory ability. A 12-lead ECG will be used to verify cardiac function. Pre-fracture physical and instrumental activities of daily living (PADLs/IADLs) will be conducted by subject interview. Baseline DXA scans will be scheduled at this time.

2.3 Randomization/Baseline

Approximately 1 week (±2 days) after Screening (4-12 weeks post-injury), subjects will be expected to arrive at the clinic following a minimum10-hour fast. They will be allowed to have a light snack after all bloodwork is complete.

Baseline procedures will include:

- Review concomitant medications
- Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate)
- Hematology/Chemistry/Urinalysis
- Bone Turnover Markers
- Vitamin D
- Thyroid Markers
- Fasting Lipid Profile
- Coagulation
- Pituitary/Adrenal Hormone Blood Tests
- Pancreatic Endocrine Markers
- Dual-Energy X-Ray Absorptiometry (DXA) Scans
- 12-Lead ECG at 2 hours post-dose
- Six-Minute Walk Test (6MWT) and BORG Scale, Grip Strength, and Short Physical Performance Battery (SPPB)
- Post-fracture PADLs/IADLs
- Short Form-36 (SF-36)

Subjects will be randomized to one of four treatment arms (VK5211 0.5 mg, 1.0 mg, 2.0 mg, or placebo) in a 1:1:1:1 ratio and will receive their first dose of study treatment in the clinic. Adverse events will be recorded. A bottle of study treatment (30 capsules) will be dispensed and subjects will be instructed to take one oral dose of the assigned treatment at approximately the same time every morning, 30 minutes prior to breakfast. Subjects will be informed that they may have more doses than they will need and must return any extra study treatment at Visit 2. They will receive a diary card to record their treatment administration and meal and snack times for 3 days prior to Visit 2.

2.4 Visit 1: Telephone Contact

Within 1 week of randomization, subjects will receive a telephone call to review concomitant medications, adverse events, and compliance. Subjects will be reminded to take their assigned study treatment at approximately the same time every morning, 30 minutes prior to breakfast.

2.5 Visit 2

Approximately 4 weeks (no more than 30 days) after randomization, subjects will report to the clinic following a minimum 10-hour fast at approximately 8 am (Visit 2). A pre-dose blood sample will be drawn for the fasting lipid profile. A pre-dose plasma concentration blood sample will be drawn, the subject will be provided with one dose of their assigned treatment, and a post-dose plasma concentration blood sample will be drawn at 2 hours (±10 min). They will have a physical examination, including weight, and vital signs will be recorded. Subjects will provide safety assessment samples for hematology/chemistry/urinalysis plus additional blood samples for bone turnover markers, pituitary/adrenal hormones, coagulation, and pancreatic endocrine markers. Following these blood tests, subjects will be allowed to have a light snack. They will provide data for Grip Strength, and SPPB. Post-fracture PADLs/IADLs will be conducted by subject interview. Following the interviews, they will perform the 6MWT and BORG Scale.

Concomitant medications, adverse events, compliance, and the diary card will be reviewed. The next bottle of study treatment (30 capsules) will be dispensed. Subjects will be reminded to take their assigned study treatment at approximately the same time every morning, 30 minutes prior to breakfast. Subjects will be informed that they may have more doses than they will need and must return any extra study treatment at Visit 3.

2.6 Visit 3

Approximately 8 weeks (no more than 60 days) after randomization, subjects will report to the clinic for Visit 3 and provide samples for plasma concentration, chemistry (GGT, ALT, AST, and total bilirubin), bone turnover markers and pancreatic endocrine markers. Vital signs will be measured. Subjects will provide data for Grip Strength, and SPPB. Post-fracture PADLs/IADLs will be conducted by subject interview. Following the interviews, they will perform the 6MWT and BORG Scale. Concomitant medications, adverse events, and compliance will be reviewed and the next bottle of study treatment (30 capsules) will be dispensed. Subjects will be informed that they may have more doses than they will need and must return any extra study treatment at Visit 4. They will receive a diary card to record their treatment administration and meal and snack times for 3 days prior to Visit 4. Subjects will be informed that they may have more doses than they will need and must return any extra study treatment at Visit 4. Visit 4 DXA scans should be scheduled at this time.

2.7 Visit 4

Approximately 12 weeks (no more than 90 days) after randomization, subjects will report to the clinic following a minimum 10-hour fast at approximately 8 am (Visit 4). A pre-dose blood sample will be drawn for the fasting lipid profile. A pre-dose plasma concentration blood sample will be drawn, the subject will be provided with one dose of their assigned treatment, and a post-dose plasma concentration blood sample will be drawn at 2 hours (±10 min). Diary card data, concomitant medications, compliance, and adverse events will be reviewed. They will have a physical examination, including weight, and vital signs will be measured. They will provide safety assessment samples for hematology/chemistry/urinalysis and additional blood samples for bone turnover markers, serum calcium, vitamin D, thyroid markers, pituitary/adrenal hormones, PSA (males only), coagulation, and pancreatic endocrine markers. Following these blood tests, subjects will be allowed to have a light snack. Subjects will provide data for Grip Strength, and SPPB. Post-fracture PADLs/IADLs and SF-36 will be conducted by subject interview. Following the interviews, they will perform the 6MWT and BORG Scale. ECG and DXA scans will be performed. Visit 5 DXA scans should be scheduled at this time.

2.8 Visit 5

Approximately 24 weeks after randomization, subjects will report to the clinic following a minimum 10-hour fast for a follow-up visit (Visit 5) to provide a blood sample for plasma concentration, chemistry (GGT, ALT, AST, and total bilirubin), bone turnover markers, fasting lipid profile, and coagulation. Concomitant medications and adverse events will be reviewed. They will have a physical examination, including weight, and vital signs will be measured. They will provide data for the Grip Strength, and SPPB. Post-fracture PADLs/IADLs and SF-36 will

be conducted by subject interview. Following the interviews, they will perform the 6MWT and BORG Scale. ECG and DXA scans will be performed. Subjects will exit the study.

2.9 Early Termination

In case of early termination, the events will be performed according to Table 1 and will be identical to Visit 4, excluding plasma concentration sample collection.

2.10 Schedule of Events

Table 1 below describes the schedule of events for all study visits.

Table 1. Schedule of Events for All Study Visits

Visit	Screening	Randomization /Baseline	Visit 1 TC	Visit 2	Visit 3	Visit 4	Visit 5	Early Term
Days	**-7 ± 2 days**	**0**	**7(-5/+2)**	**28(-5/+2)**	**56(-5/+2)**	**84(-5/+2)**	**168 ± 5**	
Informed Consent	X							
Medical History	X							
Demographics	X							
Inclusion/Exclusion Criteria	X							
Mini Mental State Exam	X							
4-Meter Walk Test	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Physical Exam[1]	X			X		X	X	X
Vital Signs	X	X		X	X	X	X	X
ECG[2]	X	X[2]				X[2]	X	X
Hematology/Chemistry/ Urinalysis[12,13]	X[12]	X		X	X[13]	X	X[13]	X
Lipid Profile		X		X		X	X	X
Coagulation		X		X		X	X	X
Thyroid Markers[3]		X				X		X
Vitamin D		X				X		X
Bone Turnover Markers[4]		X		X	X	X	X	X
Pituitary/Adrenal Hormone Blood Tests[5]		X		X		X		X
PSA (males)	X					X		X
Pancreatic Endocrine Markers[6]		X		X	X	X		X
DXA Scan		X				X	X	X
Physical Performance Assessments[7]		X		X	X	X	X	X
Patient Reported Outcomes[8]	X (pre-Fx. Only)	X		X	X	X	X	X
Plasma Concentration Blood Samples[9]				X[9]	X[9]	X[9]	X[9]	
Diary Card[10]		X		X	X	X		
IP Administration/ Dispensation/ Compliance[11]		X	X	X	X	X		X
Averse Events		X	X	X	X	X	X	X
Study Disposition							X	X

[1] Height and weight will be measured at Screening. Weight only at Visits 2, 4, and 5.
[2] At Randomization and at Visit 4, the ECG will occur at 2 hours post-dose.
[3]T3, T4, TSH
[4] s-CTX and s-PINP
[5] The hormones tested will include follicle stimulating hormone (FSH), luteinizing hormone (LH), sex-hormone binding globulin (SHBG), estradiol, cortisol, aldosterone, adrenocorticotropic hormone (ACTH) and total and free testosterone.
[6] Endocrine pancreatic markers include fasting insulin and fasting glucagon
[7] 6MWTand BORG Scale, Grip Strength, and SPPB.
[8] Pre-fracture PADLs/IADLs at Screening. SF-36 and post-fracture PADLs/IADLs at Randomization. Post-fracture PADLs/IADLs only at Visits 2 and 3. SF-36 and post-fracture PADLs/IADLs at Visits 4 and 5 and Early Termination.
[9]Samples will be drawn pre-dose and at 2 hours (±10 min) post-dose at Visits 2, 3, and 4. Visit 5 sample may be drawn along with the other blood work samples.
[10] Diary cards provided at Randomization and Visit 3, reviewed at Visits 2 and 4.
[11]IP administration and dispensation at Randomization. Compliance only at Visit 1 TC. Compliance, administration, and dispensation at Visit 2. Compliance and dispensation at Visit 3. Compliance and administration at Visit 4. Compliance only at Early Termination.
[12]HbA1c test will be performed at Screening only.
[13]Visits 3 and 5 will only include testing for GGT, ALT, AST, and total bilirubin.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to determine the efficacy of VK5211 after 12 weeks of treatment by mean placebo-corrected percentage change in total body less head (TBLH) lean body mass assessed by whole body DXA scan.

3.2 Secondary Objective(s)

The secondary objectives of this study are:

- To assess the safety and tolerability of VK5211 after 12 weeks of treatment by comparing overall adverse events, vital signs, 12-lead ECG data, physical examinations, and hematology/chemistry/urinalysis data to placebo.
- To determine the efficacy of VK5211 after 12 weeks of treatment by mean placebo-corrected change in:
  - Hip bone mineral density (BMD) assessed by DXA
  - Total lean body mass
  - Appendicular lean body mass
  - Bone turnover markers (s-CTX and s-PINP)
- To assess plasma concentration of VK5211 near T_{max} and at trough levels in relation to total lean body mass.

The exploratory objectives of this study are to determine the efficacy of VK5211 compared to placebo after 12 weeks of treatment by:

- Physical Performance Assessments
  - 6MWT and BORG Scale
  - Grip Strength
  - SPPB
- Patient Reported Outcomes
  - Pre- and Post-fracture PADLs/IADLs
  - SF-36

4 STUDY SUBJECT SELECTION

4.1 Inclusion Criteria

Each subject must meet the following criteria to be eligible for the study (subjects may be re-screened for failure of inclusion/exclusion criteria after consultation with medical monitor):

1. Males or females ≥65 years old who experienced a hip fracture (occurring 3-11 weeks prior) with no residual surgical issues will be eligible for participation.
2. Subjects must be willing and able to sign informed consent.
3. Blood pressure within the following parameters: systolic blood pressure (SBP) <180 mmHg *and* diastolic blood pressure (DBP) < 100 mmHg) with a heart rate of 45 to 90 bpm measured at Screening after resting for 5 minutes in the seated position.
4. MMSE score ≥ 20.
5. Ability to walk 4 meters at Screening with or without a cane or walker with a gait speed of ≤ 0.8 m/s.
6. Suitable for participation in the study in the opinion of the Investigator.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria must be excluded from the study:

1. Clinically significant new illness in the 1 month prior to Screening. (The qualifying hip fracture does not count as a significant illness).
2. Cognitive impairment as indicated by a score of < 20 on the MMSE performed at Screening or as determined by Investigator judgment if 20 or higher.
3. Pathological fracture (e.g. fracture due to Paget's disease of bone, malignancy, etc.). Fracture due to postmenopausal osteoporosis is not considered pathological for this trial.
4. Glycosylated hemoglobin (HbA1c) > 9.5 % at Screening.
5. Presence of hardware in the contralateral hip.
6. Previous participation in any clinical study with an investigational drug, biologic, or device within 4 weeks prior to Screening.
7. Previous participation in a VK5211 or LGD-4033 study.
8. Use of antibody-based therapy for bone disease within 6 months prior to Screening. Subjects taking antibody-based therapy may be weaned off and re-screened on a case-by-case basis pending evaluation by the Sponsor.
9. Use of the following medications within 30 days prior to Screening or during the study:
   - Hormone replacement therapy with estrogen agonists or SERMs (vaginal estrogens are permitted).
   - Teriperatide (Forteo) is excluded;[supplemental Vitamin D_3 and/or Calcium is permitted].
   - Initiation of ANY new bone active therapy after Screening for duration of the study and follow up period (examples include IV and oral bisphosphonates, Denosumab, Teriperatide, etc.)
10. History of severe allergies (i.e., anyone with a known history of anaphylaxis to medication[s] or allergens).

11. Subject who has donated any blood, or had significant blood loss not associated with the qualifying hip fracture within 56 days prior to dosing.
12. Subject who has donated plasma within 7 days prior to dosing.
13. History of regular smoking or tobacco use within 3 months prior to Screening.
14. Not suitable to participate in the study in the opinion of the Investigator including an existing physical or mental condition that may prevent compliance with the protocol.
15. Not suitable to participate in the study in the opinion of the Investigator on the basis of clinically significant laboratory values.
16. ECG will be performed at Screening. Subjects with QTcF interval >450 msec (or >500 msec in the presence of a bundle branch block or paced ventricular rhythm) or any other exclusionary cardiac conditions noted previously on the locally read ECG are excluded from study participation. Other abnormal findings on the ECG should be carefully considered and any subject excluded who, in the judgment of the PI, may not safely complete treatment in this study.
17. History of active or uncontrolled heart failure or hypertension within 3 months of Screening.
18. Symptoms of acute or unstable coronary artery disease within 6 months of Screening.
19. History of cerebrovascular disease within 1 year of Screening.
20. History of epilepsy or any other seizure disorder within 1 year of Screening.
21. History of unexplained or untreated syncope in the past 12 months.
22. History of organ transplantation.
23. Positive history of human immunodeficiency virus, or acute/active hepatitis B, or hepatitis C.
24. Malignancy within 5 years of Screening (with the exception of previously treated basal cell carcinoma and squamous cell skin carcinoma in-situ).
25. History (within 2 years prior to Screening) of alcohol or drug/solvent abuse.
26. Documented sensitivity to any of the ingredients in the Investigational Product (IP) formulation.

4.3 Removal of Subjects from Therapy or Assessment

Subjects are free to withdraw consent and discontinue participation in the study at any time, without prejudice to further treatment. Subjects who discontinue prior to day 28 will be replaced.

A subject's participation in the study may be discontinued at any time at the discretion of the investigator. The following are reasons that may lead to a subject's discontinuation:

1. Subject develops intolerable adverse effects.
2. Subjects who experience a >60 msec prolongation of QTc interval or absolute QTc >500 msec (or >550 msec in the presence of a bundle branch block or paced ventricular rhythm) will be discontinued from treatment and followed by ECG until the QTc returns to baseline levels. Other abnormal findings on the ECG should be carefully considered and any subject excluded who, in the judgment of the PI, may not safely complete treatment in this study will be terminated from participation.
3. The subject is grossly non-compliant defined as:
   a. Uncooperative/noncompliant and will not adhere to study responsibilities, including failure to appear at two consecutive visits.

   b. Taking prohibited medications as described in Section 5.7.1, pending evaluation by the Sponsor.
4. The subject's health would be jeopardized by continued participation.
5. In the opinion of the Investigator, it is in the best interest to discontinue subject from study.
6. The subject wishes to withdraw for any reason.
7. The Sponsor elects to end the study, or any portion thereof, for any reason.
8. Any other safety results or adverse experiences that, in the opinion of the investigator, raise concerns about the safety or tolerability of VK5211.

Although a subject will not be obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subject's rights. All subjects who are randomized and treated (i.e., received any amount of study drug) will be included in the safety analyses. Thus, every effort will be made to contact any subject who fails to attend any follow-up appointments/contacts, in order to ensure that he/she is in satisfactory health.

If a subject withdraws from the study as a result of meeting discontinuation criteria after the start of study drug administration, all post-treatment evaluations must be completed.

5 STUDY TREATMENT

5.1 Identity of Investigational Product

Viking Therapeutics will provide a supply of VK5211 in 0.5 mg, 1.0 mg, and 2.0 mg capsules plus matching placebo.

5.2 Treatment Quantity, Schedule and Form of Administration

Subjects will be provided with 1 bottle of VK5211 or placebo containing 30 capsules at Randomization. The clinical site will dispense one bottle at Randomization, Visit 2, and Visit 3. At each Visit, the previous bottle will be returned by the Subject and either re-dispensed to the subject or retained at the site until further notice from the Sponsor.

Subjects will be provided with a diary card at Randomization and Visit 3 and instructed to record times of dosing administration and meals and snacks beginning three days prior to Visits 2 and 4. The Investigator or designee will record this information on the eCRF.

5.3 Dose Justification

Dose selection for this Phase IIa efficacy, safety and tolerability study in subjects recovering from acute hip fracture is intended to establish the optimal dose for further development. Doses were selected based on study design and expected efficacy, safety, and tolerability.

In a 21-day Phase I study of VK5211 a trend toward increased lean body mass, as measured by Dual Energy X-ray Absorptiometry (DXA), was observed and was considered statistically significant at 1 mg VK5211, with no apparent change in fat body mass. Pharmacodynamic activity was also observed with dose-dependent changes for various hormones and lipids tested.

Dose-dependent decreases from baseline were noted for total testosterone and SHBG, while decreases from baseline for free testosterone were only observed at 1 mg of VK5211. Upon discontinuation of VK5211, serum total testosterone, free testosterone, and SHBG levels returned to (and were not significantly different than) baseline levels by Day 56. No apparent changes were noted for the FSH or LH. Dose-dependent changes were noted for HDL in the 0.3 mg and 1 mg groups, which also affected the total cholesterol to HDL ratio. No apparent changes were observed for the other lipid parameters tested: LDL, total cholesterol, and triglycerides. Therefore, testing a dose just above 1 mg (i.e. 2 mg) in this study will yield additional information on dose range effects. The placebo arm is included to fully assess safety and efficacy and to comply with Food and Drug Administration (FDA) guidance for New Drug Application (NDA) filing. Summarized below is the rationale for the doses selected in this study: 0.5 mg, 1 mg, and 2 mg/day of VK5211 capsules.

A total of 124 healthy male subjects have been enrolled across two completed Phase I clinical studies (48 subjects in Study V5211-01 [single dose study] and 76 subjects in Study V5211-02 [multi-dose study]). VK5211, administered orally in capsules, was safe and well tolerated by healthy male subjects up to the highest single dose tested (22 mg), and at daily doses of 0.1 mg, 0.3 mg, and 1 mg over a period of 21 days. No deaths or withdrawals due to adverse events (AEs) were reported. No subjects who received VK5211 had a serious adverse event (SAE); 1 subject who received placebo in Study V5211-02 had a SAE of Grade 3 cellulitis, which was considered unrelated to treatment. Of the 79 subjects who received at least one dose of VK5211 in the two Phase I studies, 40 subjects exhibited treatment-emergent adverse events (TEAEs). The most common TEAEs reported by two or more healthy male subjects were headache, procedural pain (only in subjects receiving muscle biopsies), dry mouth, and upper respiratory tract infection. Twelve subjects had TEAEs classified as study-drug related. The only treatment-related AEs occurring in more than one individual were dry mouth, acne, and increased LDL (2 subjects each). All TEAEs were mild or moderate in severity, and there were no premature study discontinuations due to an AE. All events were either transient or lasted for a few days and resolved before study termination. There was no dose-related trend in AEs. The changes from baseline in clinical laboratory parameters, vital signs, and ECG values were not graded as clinically important other than as mentioned above, and physical examination findings in all study subjects were not considered clinically significant.

The doses of 0.5 mg, 1 mg, and 2 mg/day of VK5211 over the 12-week study period in this Phase IIa study are likely to be well-tolerated based on the previous human data described above. These doses are expected to produce significant, clinically meaningful, and dose-dependent increases in lean body mass. These doses are also expected to enable an estimate of the minimal effective dose and possibly the dose needed to produce the maximal effect.

5.4 Labeling Information

Study subjects will receive an ID number to mask their identity.

Investigational products (IP) will be supplied to the study site in bottles containing 30 capsules. A single panel label on each container of IP will contain: protocol number, IP name, amount, randomization number, and instructions for use and storage (including temperature range). The following warning will also be included on the label “Caution: New Drug – Limited by Federal (or United States) law to investigational use.”

The Investigator agrees to neither dispense the study drug from, nor store it at any site other than the site listed on Form FDA 1572 or Investigator's Agreement. The Investigator agrees that the study drug will be dispensed by the Investigator or Sub-Investigator named on Form FDA 1572 or Investigator's Agreement, or qualified designees. The Investigator, Sub-Investigators, or qualified designees also agree that the trial drug will be dispensed only to study subjects who have provided written informed consent and have met all entry criteria. Clinical supplies may not be used for any purpose other than that stated in the protocol.

An adequate quantity of the study drug will be provided to replace units damaged in shipment/handling, to supply replacement subjects meeting the entry criteria.

5.5 Storage, Issue and Retention of Supplies

Viking Therapeutics, Inc. will provide all study treatment. Study treatment must be kept in an appropriate, secure area. All drug supplies are to be shipped under ambient conditions and stored at room temperature (between 15 - 25ºC or 59 - 77ºF), while at the clinical site. At the subject's home, the study treatment will be stored at ambient temperature. Excessive humidity should be avoided. Deviations from the established temperature, as well as the occurrence of excessive humidity, should be documented, and the sponsor should be notified.

The study treatment as supplied is considered study medication, which must be accounted for on the eCRF and in the paper drug accountability log at the time the medication is dispensed to the subject. Any unused portion should be returned to the clinic at each Visit or at the Early Termination Visit and should be recorded on the eCRF and in the paper drug accountability log.

The Principal Investigator will maintain an accurate record of the receipt of all study treatment as shipped by Sherpa Clinical Packaging on behalf of Viking Therapeutics, Inc., including the date received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation. This inventory record must be available for inspection at any time. Copies of this record will be provided to Viking Therapeutics, Inc. at the conclusion of the study.

Clinical supplies are to be used only in accordance with this protocol and under the supervision of the Principal Investigator.

After the study is completed, the Principal Investigator must account for all study treatment used, unused and partially used. After reconciliation, study treatment (used, unused, partially used) from each study site will be destructed on site per site standard operating procedures. If a site has no specified procedure for the destruction of study treatment, it must be returned to Sherpa Clinical Packaging for possible analysis and final destruction.

5.6 Treatment and Protocol Compliance

5.6.1 Treatment and Protocol Compliance

At Screening, subjects who have been enrolled in the study as defined by signing the informed consent form will be assigned a subject number. The subject number will be a 5 digit number which will be assigned consecutively at the time the subject is screened (i.e. 2 digit site number plus 3 digit number for each subject screened, first subject screened will be 01-001, second

subject screened will be 02-002, etc…). The subject number will be used to identify the subject throughout the study.

Subjects who are randomized will receive a randomization number. The randomization number will be a 4 digit number that corresponds to the randomization schedule. The order in which treatments are received will be according to the randomization schedule.

Enrolled subjects who are not randomized, for whatever reason, will be discontinued from the study. Subjects who are randomized, but did not complete the study will also be discontinued from the study. Discontinued subjects will be included in the safety population or intent-to-treat population according to guidelines described in Section 9.2.

5.6.2 Maintenance of Randomization Codes and Unblinding Procedures

A programmer not directly involved with the study will generate the randomization code. A sealed copy of the randomization scheme will be retained at the study site from the onset of the study and should be available to US FDA Investigators at the time of site inspection to allow for verification of the treatment identity for each subject, if requested. The randomization schedule will be available to the statistician after database lock.

Unblinding the study without the permission of Viking Therapeutics, Inc. is explicitly forbidden, except in the event of a **medical emergency** where the identity of the study treatment and dose must be known in order to properly treat the subject. Under these circumstances, the Investigator must contact the safety monitor or authorized designee for permission to unblind (See Section 10.4.2). The safety monitor or designee will verify the need and agree to unblind, retrieve the treatment code from the IWRS system, and provide the treatment information to the Investigator.

If the blind is broken, the safety monitor or authorized designee must document the date, time, and reason. A written report should be sent to Viking Therapeutics, Inc. within 1 working day.

Viking Therapeutics, Inc. may unblind the treatment assignment for any subject with an expedited SAE report. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report identifying the subject's treatment assignment may be sent to clinical investigators in accordance with local regulations and/or the policies of Viking Therapeutics, Inc.

5.7 Concomitant Therapy

5.7.1 Allowable Medications and Therapies

As described in the inclusion/exclusion criteria, subjects will be permitted to stay on their stable dose(s) of blood pressure medication, diabetes medications (excluding insulin), and lipid-lowering medications. Medications such as antibody-based therapy (denosumab), parathyroid hormone, systemic estrogens or estrogen receptor modulators (SERMS) will not be permitted during the 3 month treatment period and 3 month follow up period. Bisphosphonates taken at the time of Screening may be continued unchanged throughout the 3 month treatment period and 3 month follow-up period. Hormonal therapy is not permitted during the trial. If a subject begins taken any of these medications, the subject may be discontinued from the study pending individual evaluation by the Sponsor. Vitamin D_3 and/or calcium supplements are permitted during the study. Other chronic medications will be permitted based on Investigator judgment and after consultation with the Sponsor's medical monitor.

5.7.2 Food and Fluid Intake Restrictions

Consumption of foods and beverages containing the substances listed below will be prohibited as indicated. Exceptions may be permitted upon the joint agreement of the Sponsor and the Investigator provided the safety of the subject and integrity of the study are not compromised.

- Caffeine/xanthines: Prohibited 4 hours prior to daily dosing

For Visits 2 and 4, subjects will be provided with a diary card and instructed to record times of meal consumption beginning three days prior to these visits and during these visits. The Investigator will record this information on the eCRF.

5.7.3 Lifestyle Restrictions

Consumption of tobacco products will be prohibited during the study. Subjects who have any history of regular tobacco product use more recently than 3 months prior to Screening will not be allowed in the study.

6 STUDY PROCEDURES AND ASSESSMENTS

6.1 Informed Consent

According to the ICH guideline for GCP (E6) and all institutional local, state, and federal laws, the Investigator will obtain and document an ICF for each subject screened for this study. All subjects will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures. The subject's medical record should contain written documentation indicating that informed consent was obtained. The ICF must be reviewed and approved by the Investigator's designated IRB and by Viking Therapeutics, Inc. clinical staff. The ICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

6.2 Medical History

At Screening, a complete medical history and social history, including smoking, caffeine and alcohol use, will be collected by subject interview. Concomitant medications, recent blood donations, illnesses, and participation in other investigational drug studies will also be recorded.

6.3 Physical Examination

A physical examination including weight will be performed at Screening, Visit 2, Visit 4, Visit 5, and in case of early withdrawal. Height will be measured at Screening only.

6.4 Vital Signs

Vital signs will be recorded at every clinic visit. Vital signs including seated blood pressure (two blood pressure readings separated by 2 minutes), heart rate (measured after the first blood pressure reading), will be measured after the subject has been seated for at least 5 minutes. The recorded value will be the mean of two measurements. Vitals signs will be measured prior to any blood draw that occurs at the same time point.

6.5 Electrocardiography (ECG)

6.5.1 ECG Acquisition

An ECG will be performed at Screening, Randomization (at 2 hours post-dose), Visit 4, and Visit 5. The 12-lead ECG equipment will be set to 25mm/sec and 10mm/mV. The operator will enter selected subject demographic information prior to obtaining the ECG. The following subject information will be entered into the machine:

- Subject initials (example: XYZ or X-Z).
- Subject number.
- Subject date of birth (mm/dd/yyyy).
- Study day and time.

ECGs will be recorded with subjects in the recumbent position and resting. Subjects will have been in this resting position for 5 minutes prior to ECG recording and performed prior to any blood draw that occurs at the same time point.

In case of baseline tremor, measures will be taken to eliminate this as it may interfere significantly with the quality of the interpretation. Prior to electrode placement, the 10 anatomical sites will be prepared to allow for proper skin/electrode interface.

6.6 Mini Mental State Exam (MMSE)

The MMSE will be performed at Screening to evaluate cognitive function. A description and copy of the exam are provided in Appendix 15.1.

6.7 Four-Meter Walk Test

The 4-meter walk test will be performed at Screening to evaluate the subject's ability to ambulate. The subject will be instructed to walk a continuous, straight four meters without turns. Use of a cane or walker is permitted. The subject must be walking with a gait speed of <0.8 m/s.

6.8 Physical Performance Assessments

All physical performance assessments will be done at the Randomization visit and at Visits 2, 3, 4, and 5 as shown in Table 1. These assessments will also be done in case of early withdrawal.

6.8.1 Six-Minute Walk Test (6MWT) and BORG Scale

The 6MWT will be used to assess functional cardiovascular status. The BORG Scale will also be administered. This test may be performed as part of the physical examination. Instructions are provided in Appendix 15.2.

6.8.2 Grip Strength

Grip strength is used to provide a generalized assessment of upper body strength. Instructions for use of the Dynamometer are provided in Appendix 15.3.

6.8.3 Short Physical Performance Battery (SPPB)

The SPPB test is a group of assessments that examines walk speed, chair stand, and balance. Scores range from 0 to 12 and instructions are provided in Appendix 15.4.

6.9 Patient Reported Outcomes

6.9.1 Short From-36 (SF-36)

The SF-36 questionnaire will be conducted by subject interview at Randomization, Visit 4, Visit 5, and in case of early withdrawal as shown in Table 1. A sample questionnaire is provided in Appendix 15.5.

6.9.2 Physical and Instrumental Activities of Daily Living (PADLs/IADLs)

PADLs/IADLs will be conducted by subject interview at Screening, Randomization, Visits, 2, 3, 4, and 5 and in case of early withdrawal as shown in Table 1. At Screening, only the pre-fracture PADLs/IADLs will be conducted by subject interview. At all other visits, only the post-fracture PADLs/IADLs will be conducted. The pre-fracture PADLs/IADLs questionnaire is provided in Appendix 15.6; the post-fracture PADLs/IADLs questionnaire is provided in Appendix 15.7.

6.10 DXA Scans

DXA scans will be performed at Randomization and at Visits 4 and 5, or in case of early withdrawal as shown in Table 1. Instructions for DXA scans are provided in the study reference manual.

6.11 Clinical Laboratory Tests

All details regarding clinical laboratory sample collection, preparation, and shipment will be included in the laboratory manual provided by the central laboratory and the Viking pharmacokinetics manual provided by Viking Therapeutics, Inc.

In the event of abnormal clinical laboratory values, the Investigator will make a judgment whether or not the abnormality is clinically significant.

6.11.1 Laboratory Parameters

Clinical laboratory tests will include the following:

Serum Chemistry

- Sodium
- Potassium
- Chloride
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Gamma-glutamyl transferase (GGT)
- Total bilirubin (TBIL)
- Alkaline phosphatase (ALP)
- Albumin
- Total Protein (TP)

- Blood urea nitrogen (BUN)
- Creatinine
- Glucose
- Calcium
- Phosphate
- HbA1c (Screening only)

Hematology

- Hemoglobin
- Platelet count

- Red blood cell count
- White blood cell count with differential

Additional tests

- Vitamin D
- T3, T4, and TSH
- s-CTX and s-PINP

These tests will be performed according to the schedule of events (Table 1).

6.11.2 Urinalysis

Urinalysis parameters for clinical laboratory tests include the following:

- appearance
- bilirubin
- color
- glucose
- ketones
- leukocyte esterase
- occult blood
- pH
- protein
- specific gravity
- urobilinogen

6.11.2.1 Special Laboratory Tests for Hormone Levels, Hematology, Lipids, and Kidney/Pancreatic Function

Pituitary/Adrenal Hormone Blood Tests

- FSH
- LH
- SHBG
- FT
- TT
- Estradiol
- Adrenocorticotropic hormone (ACTH)
- Cortisol
- Aldosterone

Male Hormone

- Prostate-specific antigen (PSA)

Fasting Lipid Profile

- Total Cholesterol
- LDL
- HDL
- Triglycerides
- Cholesterol/HDL ratio (calculated)
- Non-HDL Cholesterol (calculated)

Pancreatic Endocrine Markers

- Fasting insulin

Fasting glucagon

Coagulation

- Prothrombin time (PT)
- Partial thromboplastin time (PTT)

6.11.3 These tests will be performed according to the schedule of events (Table 1).Sample Collection, Storage and Shipping

Blood samples for hematology and serum chemistry will be collected according to the laboratory manual provided by the central laboratory and according to the schedule of events (Table 1).

6.12 Plasma Concentration Sample Collection

Blood samples to determine plasma study drug concentration will be collected at Visits 2, 3, 4 and 5 as shown in Table 1.

Pre-dose samples will be collected on the appropriate days at 0 to 20 min pre-dose (Visits 2, 3, and 4). A single post-dose sample will be collected thereafter at 2 hours (± 10 min) post-dose (Visits 2, 3, and 4), plus one additional sample at Visit 5.

At each collection, 5 mL of blood will be collected into a Vacutainer tube containing lithium heparin (green top) and immediately placed in an ice bath. Within 30 minutes of collection, the plasma fraction will be separated by centrifugation at 2,500 rpm (1,000 x g) for 15 minutes at 4ºC. The plasma fraction will be separated into equal aliquots and transferred into 2 labeled 5 mL polypropylene tubes and frozen at approximately -20°C or -70°C.

Blood volume collected for these samples will be approximately 20 mL total per subject.

Plasma concentration samples should be shipped on dry ice via overnight delivery to MicroConstants for analysis. Samples will ship only on a Monday, Tuesday or Wednesday to minimize the possibility of the samples being in transit over a weekend. Duplicate plasma concentration samples will ship after MicroConstants confirms receipt of the initial samples.

6.13 Concomitant Medication Assessments

All medications or treatments study subjects are taking or have taken during the 30 days prior to treatment will be recorded in the subject's record and the eCRF. Any bisphosphonate medication taken during the 5 years prior to treatment will also be recorded in the subject's record and the eCRF. All treatments administered to subjects following the first dose of the study drug will be recorded in the subject's record and the eCRF. Medications administered should be recorded according to the generic name when possible. Concomitant medications should be limited to those that are medically necessary. Any concomitant medication used should have an indication recorded and this indication must be represented as either an adverse event, for the management of a pre-existing condition, or for prophylaxis.

Dosage increases for any concomitant medication should be noted and the reason for the dosage increase recorded as an adverse event (assumes worsening condition). The side effects of concomitant medications will be recorded as adverse experiences.

Any subject whose condition becomes disqualifying during the course of the study may be treated for that condition. If condition is suspected during screening the subject should not be enrolled. Treatment of the condition should be instituted according to the Investigator's/attending physician's judgment.

Drugs that have no treatment intent but rather are part of supportive routine care such as local anesthetics, intravenous solutions to maintain fluid balance and keep access open, medications used for prophylaxis, and narcotics for postsurgical pain must also be recorded in the eCRF.

7 STUDY ACTIVITIES

7.1 Screening Visit (Day -7± 2)

At the initial Screening, potential subjects will be given a detailed presentation describing the nature, purpose, risks, and requirements of the study and will also receive detailed written information.

They will have adequate opportunity to ask the appropriate person of the clinical staff (i.e., Principal Investigator or designee) presenting the study about any aspect of the study. Once the subject is satisfied that he/she is willing to participate in the study, he/she will be asked to sign the study ICF. The ICF will include all the elements as outlined in Section 4.8.10 of the ICH guidelines for GCP (E6). The clinical personnel obtaining written consent from the subject will also sign the form to confirm consent has been obtained.

Once signed, the Investigator will retain the original for the subject's study records and provide the subject with a signed copy. The Investigator will verify that informed consent has been obtained from each subject prior to admission into the study and prior to the subject undergoing any study-related procedures.

Within 3-11 weeks post-fracture, all screening activities subsequent to obtaining informed consent will be conducted and consist of the following:

- Satisfaction of inclusion/exclusion criteria (Section 4)
- Completion of medical and social history including tobacco, alcohol, and caffeine use
- Concomitant medications assessment
- Collection of demographic data (sex, age, race/ethnicity)
- Mini Mental State Exam (MMSE)
- Physical examination, including height and weight
- 4-Meter Walk Test
- Vital signs (SBP, DPB, HR)
- ECG
- Clinical laboratory tests including hematology, chemistry (with HbA1c) and urinalysis (Section 6.6)
- Prostate-specific Antigen (PSA) test, males only
- Pre-fracture PADLs/IADLs
- Schedule the Baseline DXA scan.

Subjects who fulfill all inclusion and exclusion criteria will be randomized within 9 days of

Screening.

7.2 Screening Failures

A screening failure is defined as a subject who has signed the ICF, does not meet all the entry criteria outlined in Section 4 of this protocol and has not been randomized or received study treatment. The Investigator (or designee) will describe the reason for the screening failure in the EDC system.

7.3 Randomization/Baseline (Day 0)

Randomization will occur approximately one week after Screening. The following activities will be performed according to the schedule of events in Table 1:

- Record concomitant medications
- Record adverse events
- Vital signs (SBP, DBP, HR)
- Hematology/Chemistry/Urinalysis
- Bone Turnover Markers
- Vitamin D
- Thyroid Markers Pituitary/Adrenal Hormone Blood Tests
- Pancreatic Endocrine Markers
- Fasting Lipid Profile
- Coagulation
- A light snack is permitted after bloodwork has been completed.
- DXA Scan
- ECG at 2 hours post-dose
- Grip Strength and SPPB (to be performed before the PADLs/IADLs and SF-36)
- Post-fracture PADLs/IADLs
- SF-36
- 6MWT and BORG Scale (to be performed after the PADLs/IADLs and SF-36)
- Study drug administration; dispense 4-week supply of study drug and provide dosing instructions
- Provide diary card to record treatment administration and meal and snack times for 3 days prior to Visit 2

7.4 Visit 1 Telephone Contact (Day 7 -5/+2)

At Visit 1, the following will take place:

- Record concomitant medications
- Record adverse events
- Review study treatment compliance

7.5 Visit 2 (Day 28 -5/+2)

At Visit 2, the following will take place:

- Record concomitant medications

- Physical examination, including weight
- Vital signs (SBP, DBP, HR)
- Plasma concentration sample collection (pre-dose and 2 hours ± 10 min post-dose)
- Hematology/Chemistry/Urinalysis
- Bone Turnover Markers
- Pituitary/Adrenal Hormone Blood Tests
- Pancreatic Endocrine Markers
- Fasting Lipid Profile
- Coagulation
- A Light snack is permitted after bloodwork has been completed.
- Grip Strength and SPPB (to be performed before the PADLs/IADLs)
- Post-fracture PADLs/IADLs
- 6MWT and BORG Scale (to be performed after the PADLs/IADLs)
- Record adverse events
- Review diary card
- Review study treatment compliance; administer and dispense/re-dispense study treatment

7.6 Visit 3 (Day 56 -5/+2)

At Visit 3, the following will take place:

- Record concomitant medications
- Vital signs (SBP, DBP, HR)
- Plasma concentration sample collection (pre-dose and 2 hours ± 10 min post-dose)
- GGT, ALT, AST, and total bilirubin
- Bone Turnover Markers
- Pancreatic Endocrine Markers
- Grip Strength and SPPB (to be performed before the PADLs/IADLs)
- Post-fracture PADLs/IADLs
- 6MWT and BORG Scale(to be performed after the PADLs/IADLs)
- Record adverse events
- Review study treatment compliance; dispense/re-dispense study treatment
- Provide diary card to record treatment administration and meal and snack times for 3 days prior to Visit 4
- Schedule the Visit 4 DXA scan.

7.7 Visit 4 (Day 84 -5/+2)

At Visit 4, the following will take place:

- Record concomitant medications
- Physical examination, including weight
- Vital signs (SBP, DBP, HR)
- Plasma concentration sample collection (pre-dose and 2 hours ± 10 min post-dose)

- ECG at 2 hours post-dose
- Hematology/Chemistry/Urinalysis
- Thyroid Markers
- Vitamin D
- Bone Turnover Markers
- Pituitary/Adrenal Hormone Blood Tests
- Pancreatic Endocrine Markers
- Fasting Lipid Profile
- Coagulation
- PSA (males only)
- A light snack is permitted after bloodwork has been completed.
- DXA Scan
- Grip Strength and SPPB (to be performed before the PADLs/IADLs and SF-36)
- Post-fracture PADLs/IADLs
- SF-36
- 6MWT and BORG Scale(to be performed after the PADLs/IADLs and SF-36)
- Record adverse events
- Review diary card
- Review study treatment compliance and administer study treatment
- Schedule the Visit 5 DXA scan.

In case of early withdrawal, all Visit 4 events should be performed, excluding plasma drug concentration assessments and study drug dispensation.

7.8 Visit 5 Follow- Up (Day 168±5)

At Visit 5, the following will take place:

- Record concomitant medications
- Physical examination, including weight
- Vital signs (SBP, DBP, HR)
- Plasma concentration sample collection
- GGT, ALT, AST, and total bilirubin
- Bone Turnover Markers
- Fasting Lipid Profile
- Coagulation
- 12-lead ECG
- DXA Scan
- Grip Strength and SPPB (to be performed before the PADLs/IADLs and SF-36)
- Post-fracture PADLs/IADLs
- SF-36
- 6MWT and BORG Scale (to be performed after the PADLs/IADLs and SF-36)
- Record adverse events

8 DATA MANAGEMENT

8.1 Data Collection

All data (ECGs, clinical laboratory data, and all other study-related data) will be collected according to the CRO's SOPs.

8.2 Database Management and Quality Control

Data items from the eCRFs are entered into the study database. Subsequently, Data Management staff, using both electronic and manual checks, systematically checks the data. Obvious errors (self-evident corrections) will be corrected and documented by Integrium personnel. Other errors or omissions will result in queries, which will be sent electronically to the investigational site.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and adverse events will be coded using the most recent Medical dictionary for regulatory activities (MedDRA) terminology.

Clinical laboratory samples will be processed by ACM Global Central Laboratory at 160 Elmgrove Park, Rochester, NY, 14624, and the results will be sent electronically to Integrium. For plasma concentration samples, MicroConstants, Inc., 9050 Camino Santa Fe, San Diego, CA 92121, will determine the drug concentration at both time points and the information will be submitted electronically to Integrium. Both clinical laboratory and plasma concentration results are imported into the database.

8.3 Quality Assurance and Database Lock

A 100% critical variable review of all key safety and efficacy data in the database will be performed. Following this review, a data quality control audit equal to the square root plus 1 of the total population will be performed.

A random sample equal to the square root plus 1 of the total population will be sampled for a quality assurance audit prior to database lock.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Sponsor, Integrium and the study biostatistician.

9 STATISTICAL METHODS

9.1 Justification of Sample Size

Based on the observed change in total lean body mass information from previous studies (as percentage change in total lean body mass information is not available), it seems reasonable to estimate the placebo-adjusted difference in total lean body mass for the 0.5 mg group to be 0.5 kg and 1.0 kg for the 1 mg group. For the purpose of power calculations, the 2 mg group is extrapolated to show a 1.5 kg adjusted difference. The estimate of standard deviation, based on information from the previous study, is estimated to be 1.3. A sample size of 30 subjects per treatment group yields 84% power to detect a

difference between the 1 mg treatment group and placebo and 99% power to detect a difference between the 2 mg treatment group and placebo.

Even though the sample size estimate is based on the observed change in total lean body mass, we believe that the resulting calculations are reasonable for the analysis of percentage change in body less head lean body mass.

9.2 Definition of Populations

All subjects who have taken a single dose of the study drug and provide follow-up information will be included in the safety population.

All subjects who have taken a single dose of the study drug and have a valid pre-baseline and post-baseline efficacy assessment will be included in the Intent-to-Treat population.

All subjects who have taken at least 80% of the expected number of doses and do not have a major protocol violation will be included in the Per Protocol population.

9.3 Efficacy Analysis

9.3.1 DXA Scan Measurements

The total body less head and total lean body mass, hip bone mineral density, total body weight and fat mass, appendicular lean body mass and bone turnover markers will be analyzed using an Analysis of Covariance model with baseline value as a covariate and treatment as a primary factor.

Observed values, percentage change and absolute change from baseline and placebo adjusted change from baseline will be summarized using mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum. A 95% confidence interval on the placebo adjusted change from baseline will also be presented.

9.3.2 Physical Performance Assessments

The 6MWT total distance walked will be analyzed using an Analysis of Covariance model with baseline value as a covariate and treatment as a primary factor. Observed values, change from baseline and placebo adjusted change from baseline will be summarized using mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum.

Grip strength will be analyzed using an Analysis of Covariance model with baseline value as a covariate and treatment as a primary factor. Observed values, change from baseline and placebo adjusted change from baseline will be summarized using mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum.

SPPB score will be summarized using frequency counts. Observed values and change from baseline will be summarized. A Kruskal-Wallis test (ANOVA on ranks) will be used to test for differences between treatment groups.

9.3.3 Patient Reported Outcomes

The SF-36 individual subscales (Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE) and Mental

Health (MH)) and summary measures (Physical Health and Mental Health) will be analyzed using an Analysis of Covariance model with baseline value as a covariate and treatment as a primary factor. Observed values, change from baseline and placebo adjusted change from baseline will be summarized using mean, standard deviation, median, minimum and maximum.

The PADLs/IADLs will be analyzed as follows:

- Change in number of subjects entirely dependent in performing each activity of daily living from screening at each post-screening visit will be analyzed using the Cochran-Mantel-Haenszel Test.
- Difference in number of subjects entirely dependent in performing each activity of daily living at each visit between treatment groups will be compared using the Cochran-Mantel-Haenszel Test.
- Each activity of daily living for each visit collected will be summarized using mean, standard deviation, median, minimum and maximum.
- Significant change from screening for each activity of daily living will be analyzed using the Wilcoxon signed-rank test.
- Differences between treatment groups for each activity of daily living will be analyzed using the Kruskal-Wallis test on the change from screening value.

9.4 Plasma Concentrations Analysis

Pre-dose and single post-dose plasma concentrations at Visits 2 and 4 will be summarized using mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum.

Correlations between T_{max} and trough plasma concentrations and total lean body mass (observed and change from baseline) will be derived and presented in a graphical layout.

9.5 Safety Evaluation

All safety variables (including adverse experiences, vital signs measurements, clinical laboratory results, ECG results, and other safety variables) will be listed by subject and domain. The incidence of all AEs, treatment-emergent adverse experiences, and treatment-related adverse experiences will be tabulated by MedDRA® preferred term, system organ class, dose, and treatment group. All laboratory results, vital sign measurements, and other safety variables will be summarized using appropriate descriptive statistics. The incidence of treatment emergent abnormalities will be summarized by dose.

9.5.1 Adverse Events

Adverse events (AE) will be coded using the most current version of MedDRA and tabulated, including categorical information of interest such as onset and resolution times, time of onset relative to dose, severity at onset, causal relationship to study medication, and action taken. AEs will be regarded as ‘pretreatment’ if they occur between Screening and the time of administration of the first dose of VK5211 and will be recorded as medical history.

Treatment-emergent adverse events (TEAEs) are defined as any AE that started after the first dose of study medication or started prior to the first dose but increased in severity or frequency after dosing. The incidence of TEAEs will be presented by system organ class and preferred term. Adverse events will also be summarized by severity and relationship to the study drug. The incidence of AEs leading to withdrawal from the study will be presented.

Listings of any serious adverse events (SAEs), deaths, and AEs or abnormal laboratory values leading to discontinuation of a subject from the study will be presented.

9.5.2 Laboratory Evaluations

Individual laboratory values will be listed by visit and summarized using descriptive statistics. Individual change from baseline in laboratory values will be calculated and summarized descriptively. Shift tables from baseline to final visit will also be produced for the laboratory assessments based on the categories of Low, Normal, and High. A clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or sponsor.

9.5.3 Vital Signs

Individual vital sign measurements (systolic/diastolic BP and heart rate) will be listed by measurement time and summarized using descriptive statistics. Individual change from baseline in vital sign measurements will be calculated and summarized descriptively. A clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or sponsor.

9.5.4 Physical Examination and ECG

Physical examination results and EGC results will be summarized for each visit at which they are performed. Any clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or sponsor. Individual ECG values will be listed by visit and summarized using descriptive statistics. Intervals to be provided for each ECG are: RR, PR, QRS, QT, and QTcF.

9.5.5 Concomitant Medications

Prior and concomitant medications will be identified using the most current version of the WHO Drug dictionary. The incidence of prior and concomitant medications will be summarized.

9.6 Handling of Missing, Unused, or Spurious Data

Descriptive statistics and listings will be provided for all data. No substitution of missing data will be used in any calculations. Data points that appear to be spurious will be investigated and will not be excluded from the listings. Influential cases will be handled in an appropriate statistical manner.

10 ADVERSE EVENTS AND SAFETY REPORTING

10.1 Safety Assessments

Safety will be assessed on an ongoing basis by adverse events, identification of dose-limiting toxicities (DLTs), (if any), general physical examinations, vital signs, clinical laboratory assessments in blood and urine according to the Common Terminology Criteria for Adverse Events (CTCAE)

version 4.03 [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf].

Clinical safety data will be reviewed by the medical monitor on an ongoing basis. Safety data will undergo formal review by an independent Data Monitoring Committee (DMC) who will meet on a regular basis and ad hoc as needed, will receive unblinded data results, and will make recommendations on continuation of the study.

10.2 Definition of Adverse Event

An adverse event (AE) is any unfavorable or unintended sign, symptom or disease temporally associated with the use of the study drug whether or not considered related to the study drug. Adverse events may include:

- Objective signs observed by the Principal Investigator or study personnel.
- Subjective or objective signs/symptoms.
- Concomitant disease or accidents.
- Clinically relevant adverse changes in laboratory parameters observed in a subject in the course of a clinical study.
- Pre-existing conditions that worsen in severity or frequency or have new signs/symptoms associated with them.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency
- Extravasation
- Exposure in utero

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Other findings related to abnormal clinical investigations not regarded as clinically significant by the Investigator are not considered AEs.

10.3 Definition of a Serious Adverse Event

The Principal Investigator or other study personnel must immediately (within 24 hours) inform the Sponsor/CRO of all serious adverse events (SAEs) that occur in study subjects.

A SAE is an AE that:

- Results in death.
- Is life threatening.
- Requires in hospitalization, or prolongation of existing hospitalization.
- Results in persistent disability/incapacity.
- Is a congenital anomaly/birth defect.
- Any other important medical event. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An unexpected adverse reaction is any adverse reaction that is not consistent with current investigational product information (e.g. as described in the Investigator's Brochure or other labeling. A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious adverse reaction that may or may not be dose related and that is unexpected.

Adverse events reported from clinical trials associated with hospitalization, or prolongation of hospitalization, are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (*e.g.*, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

10.3.1 Hospitalization

Hospitalization does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (*e.g.*, caregiver relief)
- Skilled nursing facilities
- Nursing homes

- Same day surgeries (as outpatient/same day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (*e.g.*, for work-up of persistent pre-treatment lab abnormality)
- Social admission (e.g., subject has no place to sleep)
- Administrative admission (e.g., for yearly physical exam)
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol)
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery)
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

10.4 Eliciting and Reporting of Adverse Events

During the study period all AEs reported by the subject, observed or otherwise identified by the Principal Investigator, or other study personnel will be documented. Subjects will be queried concerning the occurrence of AEs throughout the study.

10.4.1 Adverse Events

All AEs that are observed by the Investigator, his/her medical collaborators, or those reported by the subject will be recorded in compliance with the requirements of 21 CFR 312.32. All AEs must be recorded on the appropriate AE reporting page of the subject's eCRF/Source Documents.

For each AE, the seriousness, severity, and classification of causal relationship to IP will be assessed including all actions taken with regard to the IP, and any other treatment measures for the AE. Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE if it occurs or is detected during the study period. Planned surgical measures and the conditions leading to these measures are not AEs if the condition(s) was (were) known before the study treatment. In the latter case, the condition should be reported as medical history. If an outcome for an AE is not available at the time of the initial report, follow-up will proceed until an outcome is known or followed up to 30 days after the final visit.

Medical conditions existing at Screening should be recorded as medical history. New or worsening pre-existing medical conditions or diseases are considered AEs if they arise or worsen after the Screening visit.

10.4.2 Serious Adverse Events

The Sponsor will adhere to all SAE FDA regulatory reporting requirements as per 21 CFR 312.32.

The Principal Investigator or other study personnel must immediately (within 24 hours of becoming aware of the event) inform the Sponsor or their designated representative (CRO) of any AE considered serious or otherwise medically significant (i.e. SAEs). This notification of SAEs can be via facsimile or email transmission of a written SAE reporting form (SAERF) signed by the Principal Investigator. To the best of the Investigator's ability, the supplied SAERF must be completed in its entirety or at a minimum must include the subject's demographics, relevant medical history, the diagnosis and description of the SAE, concomitant medications, and the Principal Investigator's assessment as to whether the SAE was or was not related to the use of the study medication. The initial SAERF and any subsequent follow-up SAERFs submitted to provide more accurate, corrected or new information must be signed by the Investigator. The Investigator and Site Personnel must make every reasonable effort to obtain, from other institutions if necessary, all supporting medical case records as needed to comply with expedited investigational new drug (IND) safety reporting.

If the SAE involves expedited IND safety reporting (as determined by the Sponsor or designee), all supporting medical records must be submitted to the Sponsor or designee within 4 calendar days for death or life threatening events, and 10 calendar days for all other events. In cases where medical records and supporting documentation are unobtainable, the Investigator must generate a narrative of the event utilizing, when necessary, interviews with the subject, their family members and care givers as appropriate. The Principal Investigator must also promptly inform the governing IRB of the SAE in accordance with the governing IRB's requirements. The DMC will be notified by the Sponsor or Sponsor's authorized designee. Ultimately, the final SAE diagnosis recorded on the final serious adverse event reporting form (SAERF) must reconcile with the subject's AE log in the study's database.

Any SAE that occurred within 30 days after the final visit will be followed and reported as above.

The CRO contact information for SAERF and supporting medical records submission is as follows:

Carmen Margaritescu, MD
Safety Office, Integrium, LLC
Office: 714-210-6665
Cellular: 714-328-7083
Fax: 714-210-7089
Email: safety@integrium.com

10.5 Causality Assessment of Adverse Events

For all AEs, the Principal Investigator will provide an assessment of causal relationship to the IP. The causality assessment must be recorded on the appropriate AE reporting page of the subject's eCRF/Source Documents. Causal relationship will be classified according to the following criteria:

- **UNRELATED**: The event is definitely not associated with the study medication.
- **POSSIBLE:**
    - The event follows a reasonable temporal sequence from drug administration.
    - The event could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.

- **PROBABLE:**
  - The event follows a reasonable temporal sequence from drug administration.
  - The event abates upon discontinuation of the drug.
  - The event cannot by reasonably explained by the subject's clinical condition or other therapy.
- **DEFINITE:**
  - The event follows a reasonable temporal sequence from drug administration.
  - The event abates upon discontinuation of the drug.
  - The event cannot by reasonably explained by the subject's clinical condition or other therapy.
  - The event occurs immediately following study drug administration, improves on stopping the study drug OR reappears on re-exposure.

10.6 Adverse Event Severity Assessment

The severity of each adverse event will be determined from the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

Severity Assessment of Adverse Events

Grade 1: Mild asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above in Section 10.2.

10.6.1 Assessment of Adverse Event Outcome

Outcome of AEs will be defined according to ICH Topic E2B, ICH Guideline.

- **Recovered/Resolved:** The subject has recovered fully from the adverse event without any remaining effects or impairment.
- **Recovered/Resolved with Sequelae**: The subject has recovered, but with an after effect possibly due to disease or treatment.
- **Not Recovered/Not Resolved:** The condition is still present.
- **Fatal.**

- **Unknown**: The primary outcome is not known at the time of the initial report.

10.7 Clinical Findings

Any significant clinical findings will be followed until the condition returns to pre-study status, stabilized, or can be explained as not being IP related. This also applies to all AEs and SAEs that continue at the final visit. Any AE that occurred prior to the final visit will be followed up to 30 days after the final visit.

11 AMENDMENTS/MODIFICATIONS OF THIS PROTOCOL

As the study progresses it may become necessary to change or modify parts of the protocol. No protocol changes may be implemented without prior approval from Viking Therapeutics, Inc. and the governing IRB. Where a modification of the protocol is performed to eliminate or reduce the risk to the subject, it may be implemented before review and approval. However, Viking Therapeutics, Inc. and the IRB must be informed in writing of such a desire for safety necessitated modifications and approval obtained within reasonable time limits.

12 INVESTIGATOR OBLIGATIONS

12.1 Regulatory Documentation

Prior to the start of the study, the following documents must be prepared:

- A completed and signed Form FDA 1572. If during the course of the study any changes occur that are not reflected on the 1572, a new 1572 form must be completed and returned to Sponsor/CRO for submission to the FDA.
- Current signed curriculum vitae and medical licenses (within 2 years) for the Principal Investigator and all Sub-Investigators listed on the 1572.
- A copy of the original approval for conducting the study by the IRB. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IRB policy.
- A copy of the IRB approved informed consent form.
- IRB member list and DHHS General Assurance Number (if IRB has an Assurance number).
- Signed Financial Disclosure Form for all personnel listed on the 1572 with a statement of non-voting by study staff.
- The final page of this protocol signed and dated by the Principal Investigator.

Documents will be collected by the CRO and will be forwarded to:

Sponsor Contact: Marianne Mancini
Viking Therapeutics, Inc.
12340 El Camino Real, Suite 250
San Diego, CA 92130

12.2 Protection of Human Subjects

Upon identification of a subject, the study will be explained in detail, the consent form reviewed, questions answered and the consent form signed. Protocol procedures will then begin to be scheduled.

Potential Risks:

- This study requires blood drawing. Some of the risks of blood drawing include, bleeding at the puncture site, bruising and pain. These risks occur in a very small portion of the population.

12.2.1 Institutional Review Board

This protocol and relevant supporting data are to be submitted to the appropriate IRB for review and approval before the study can be initiated. Amendments to the protocol will also be submitted to the IRB prior to implementation of the change. Viking Therapeutics, Inc. must receive a letter documenting the IRB approval prior to initiation of the study. The PI is also responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The IRB must be informed at the time of completion of the study and should be provided with a summary of the results of the study by the PI. The PI must notify the IRB in writing of any SAE or any unexpected AE according to ICH guidelines.

12.2.2 Subject Informed Consent

The Principal Investigator must comply with informed consent regulations (U.S. 21CFR Part 50) and relevant state regulations (i.e., Experimental Subject's Bill of Rights for California patients). The study will be explained to each prospective subject and written informed consent must be obtained before he or she participates in any study related procedures. Copies of the signed and dated informed consent must be given to the subject and placed in the Principal Investigator's study files.

12.3 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. This is detailed in the written information provided to the subject. An agreement for disclosure of any such information will be obtained in writing and is included in both copies of the ICF signed by the subject. The study data shall not be disclosed to a third party without the written consent of the sponsor.

12.4 Case Report Forms

All data relating to the study will be recorded on the electronic CRFs (eCRFs) to be provided by the EDC vendor. The eCRFs are to be completed at the time of the subject's visit with the exception of results of tests performed outside the Principal Investigator's office. The Principal Investigator or documented Sub-Investigator must see the subject at every clinic visit and verify that all data entries in the eCRFs are accurate and correct by signing the subject's eCRF investigator signature screen.

12.5 Source Documentation

Source documents may include a subject's medical record, hospital charts, clinic charts, the Principal Investigator study files, as well as the results of diagnostic tests, e.g., liver function tests and ECG.

12.6 Retention of Records

The PI has the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by Viking Therapeutics, Inc., the IRB and regulatory authorities (i.e., FDA or international regulatory authorities) at any time and should consist of the following elements:

> Subject files, containing the supporting source documentation from the medical record including laboratory data and the ICF; Regulatory files, containing the protocol with all amendments and Investigator signature pages, copies of all other regulatory documentation,

and all correspondence between the site and the IRB and Viking Therapeutics, Inc.; and Drug accountability files, including a complete account of the receipt and disposition of the study medication (test article).

Records are to be available for 2 years after marketing application approval, or if the application is not approved or never submitted, 2 years after the last shipment and delivery of the material and the appropriate competent regulatory authorities are notified. Viking Therapeutics, Inc. will provide written notification when it is appropriate for the Investigator to discard the study-specific documents referenced above.

12.7 Study Summary

A Principal Investigator summary of the study will be provided to Viking Therapeutics, Inc. and the governing IRB shortly after completion of the study.

13 STUDY ADMINISTRATION

13.1 Clinical Monitoring

In cases where the PI/Sub-Investigator and coordinator did not attend the Investigator's Meeting, a representative of Viking Therapeutics, Inc. or their designee will meet with the Principal Investigator and site staff to review study procedures and eCRF completion prior to screening the first subject. After enrollment of the first subject, the Principal Investigator will permit Viking Therapeutics, Inc. or their designee to monitor the progress of the study on site periodically. The Principal Investigator will make available the eCRFs as well as the subject's medical records, signed consent forms and the subject's hospital medical records (if necessary). The Principal Investigator or designee will review the eCRFs, provide missing or corrected data, and e-sign the appropriate eCRF page(s).

13.2 On-Site Audits

The FDA may request access to all study records for inspection and copying. A representative of Viking, Therapeutics, Inc. also may use similar auditing procedures. The clinical Principal Investigator must agree to permit the FDA, the governing IRB, Viking Therapeutics, Inc., and Integrium access to all study records and original subject records for auditing purposes and provide support for these actions.

13.3 Data Quality Assurance

In order to ensure accurate, complete and legible eCRFs:

eCRFs are provided for each subject. All forms must be filled out as instructed by appropriate personnel who have undergone eCRF training. Data will be entered into the eCRF as information becomes available on a visit-by-visit basis. All data recorded on the eCRFs should be supported by source documentation. Only in those incidences where data are recorded solely in the eCRF will the eCRF act as source and additional supporting source documentation will not be required. The study completion information page of the eCRF must be electronically signed and dated by an Investigator listed on the 1572.

All eCRF corrections must be made by the PI or other study site personnel. The PI or Sub-Investigator must authorize changes to the recorded safety and efficacy data, and this authorization must be documented in the source documents. The name of anyone making corrections must appear on either the FDA 1572 form or the PI's statement. Each error must be corrected separately.

Documentation of procedures and visits will also be maintained in source documents and signed by the Investigator or Sub-Investigator.

A subject's name must not appear on documents transmitted to the Sponsor in order to maintain confidentiality.

13.4 Publication Policy

Viking Therapeutics, Inc. shall retain ownership of all case report forms, data analyses, and reports that result from this study.

All information obtained as a result of the study will be regarded as confidential, until appropriate analysis and review by Viking Therapeutics, Inc. and the Investigator are completed. The results of the study may be published or presented by the Investigator after the review by, and in consultation and agreement with, Viking Therapeutics, Inc. and such that confidential or proprietary information is not disclosed.

Prior to publication or presentation, a copy of the final text should be forwarded by the Investigator to Viking Therapeutics, Inc. for comment. Such comments will ensure that the scientific content of the proposed publications and/or presentations and the data and material referring to Viking Therapeutics, Inc. products and activities receive fair, accurate, and reasonable presentation.

13.5 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information provided by Viking Therapeutics, Inc. and Integrium in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by the designated CRO (protocols, investigators' brochures, eCRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by Viking Therapeutics, Inc. and Integrium to the Investigator may not be disclosed to others without direct written authorization from Viking Therapeutics, Inc., except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

14 REFERENCES

1. D'Adamo CR, Hawkes WG, Miller RR, Jones M. Short-term changes in body composition after surgical repair of hip fracture. Age and Aging 2014; 43: 275 – 280.
2. Butler M, Forte M, Kane RL, Joglekar S, Duval SJ, Swiontkowski M., Wilt T. Treatment of Common Hip Fractures. Evidence Report/Technology Assessment No. 184 (Prepared by the Minnesota Evidence-based Practice Center under Contract No. HHSA 290 2007 10064 1.) AHRQ Publication No. 09-E013. Rockville, MD. Agency for Healthcare Research and Quality. August 2009.
3. Haentjens P, Magaziner J, Colón-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, et al. Meta-analysis: excess mortality after hip fracture among older women and men. Annals of Internal Medicine 2010;152(6):380–90.
4. Adachi JD, Loannidis G, Berger C, Joseph L, Papaioannou A, Pickard L, et al. The influence of osteoporotic fractures on health-related quality of life in community-dwelling men and women across Canada. Osteoporosis International 2001; 12(11):903–8.
5. Braithwaite RS, Col NF, Wong JB. Estimating hip fracture morbidity, mortality and costs. Journal of American Geriatrics Society 2003;51(3):364–70.
6. Bachrach-Lindström M, Johansson T, Unosson M, Ek AC, Wahlström O. Nutritional status and functional capacity after femoral neck fractures: a prospective randomized one-year follow-up study. Aging 2000;12(5):366–74.
7. Lumbers M, New SA, Gibson S, Murphy MC. Nutritional status in elderly female hip fracture patients: comparison with an age-matched home living group attending day centres. British Journal of Nutrition 2001;85(6):733–40.
8. Patterson BM, Cornell CN, Carbone B, Levine B, Chapman D. Protein depletion and metabolic stress in elderly patients who have a fracture of the hip. Journal of Bone and Joint Surgery - American Volume 1992;74(2):251–60.
9. Berger JR, Pall L, Hall CD, Simpson DM, Berry PS, Dudley R. Oxandrolone in AIDS-wasting myopathy. AIDS 1996; 10(14):1657–62.

15 APPENDIX

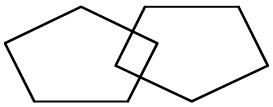
15.1 Mini Mental State Exam

The Mini Mental State Examination (MMSE) is a tool that can be used to systematically and thoroughly assess mental status. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment; a score of ≥ 20 is required for inclusion. The MMSE takes only 5-10 minutes to administer. A copy of the exam is shown below.

Mini-Mental State Examination (MMSE)

Patient's Name:_____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 

30		TOTAL

Interpretation of the MMSE:

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

Source:

- Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." *J Psychiatr Res* 1975;12:189-198.

15.2 Six-Minute Walk Test (6MWT)

The 6MWT will be standardized according to the American Thoracic Society March 2002 guidelines* using a 30 m (100 ft) hallway or corridor.

Safety Issues

1. Perform testing in a location where a rapid, appropriate response to an emergency is possible, including ready access to a crash cart.

2. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support. Advanced cardiac life support is desirable. Training, experience and certification in related health fields, (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) is also desirable.
3. Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
4. If a subject is on chronic oxygen therapy, oxygen should be given at its standard rate or as directed by a physician. Oxygen should be delivered in the same way in all subsequent serial tests. If the flow must be increased during subsequent visits due to worsening gas exchange, it should be noted on the worksheet or source document. The type of oxygen delivery device (e.g., hand-carried liquid oxygen or pushed or pulled oxygen tank delivery, pulsed or continuous) should also be noted in the records. Note that a technician walking behind the subject with the oxygen source is not recommended for the 6MWT. Measurements of pulse and oxygen saturation should be made after waiting at least 10 minutes after any change in oxygen delivery.
5. Reasons for immediately stopping a 6MWT include chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis or pale or ashen appearance. Technicians should be trained to recognize these problems and the appropriate responses.

Testing Lane

- The following criteria should be used for the location of the 6MWT and setup of the testing lane:
- Indoors along a flat, straight, enclosed corridor with a hard surface that is seldom traveled.
- The walking course must be 30 m (100 ft) in length. A shorter corridor requires subjects to take more time to reverse directions more often, reducing the total distance walked during testing.
- The length of the course should be marked every 3 m.
- The turnaround points should be marked with a cone, such as an orange traffic cone.
- A starting line, which marks the beginning and end of each 60-meter lap, should be marked on the floor using brightly colored tape.
- Use of a treadmill or a rolling distance measuring wheel for a continuous testing lane is not permitted.

Equipment Needed

1. Countdown time or stopwatch
2. Mechanical lap counter

3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard

Equipment Recommended

1. A source of oxygen
2. Sphygmomanometer
3. Telephone
4. Automated electronic defibrillator

Subject Preparation

The subject should be instructed to wear comfortable clothing and appropriate shoes for walking. Subjects should use their usual walking aids during the test (e.g., cane, walker, etc.). Usual medical regimen should be continued. A light meal is acceptable before early morning or early afternoon tests. Subjects should not have exercised vigorously within 2 hours of the beginning of the 6MWT.

Testing Protocol and Distance Measurements

1. Repeat 6MWT testing during the course of the study should be performed about the same time of day to minimize intra-day variability.
2. Do not perform a "warm-up" period.
3. The subject should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet or source document of the test.
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation, following manufacturer's instructions to maximize the signal and minimize motion artifact. Make sure the readings are stable before recording. Do not use pulse oximeter during the 6MWT.
5. Have the subject stand and rate his/her baseline dyspnea and overall fatigue using the Borg scale.
6. Set the lap counter to zero and the time to 6 minutes. Assemble all necessary equipment and move to the starting point.
7. Instruct the subject as follows:

   The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

   You will be walking back and forth around the cones. You should pivot briskly and around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation.

   Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

   Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

   Start now or whenever you are ready.

8. Position the subject at the starting line. You should also stand near the starting line during the test. Ideally, if the subject's steadiness of gait permits, do not walk with the subject. However, if the subject's gait is unsteady, staff should walk behind and to the side of the subject throughout the test, ready to catch the subject should they lose balance, but without pacing the subject. Ideally, the test should be performed in the same manner each time, with or without walking accompaniment. As soon as the subject starts to walk, start the timer.
9. Do not talk to anyone during the testing, use a cell phone, or become distracted in any way—focus entirely on the subject. Use an even tone of voice when using the standard phrases of encouragement below. Watch the patient. Do not get distracted and lose count of the laps. Each time the subject returns to the starting line, click the lap counter once or mark the lap on a worksheet. Let the subject see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

   After the **first minute**, tell the subject the following in even tones:

   You are doing well. You have 5 minutes to go.

   When the timer shows **4 minutes remaining**, tell the subject the following:

   Keep up the good work. You have 4 minutes to go.

   When the timer shows **3 minutes remaining**, tell the subject the following:

   You are doing well. You are halfway done.

   When the timer shows **2 minutes remaining**, tell the subject the following:

   You have only 2 minutes left.

   When the timer shows only **1 minute remaining**, tell the subject:

   You are doing well. You have only 1 minute to go.
   Do not use other words of encouragement or body language to speed up.
   If the subject stops walking during the test and needs a rest, say this:

   You can lean against the wall if you would like; then continue walking whenever you feel able.

   Do not stop the timer. If the subject stops before the 6 minutes are up and refuses to continue or you decide he/she should not continue, move the chair over for the subject to sit on, discontinue the test, and note on the worksheet or source document the distance, the time stopped and the reason for stopping prematurely.

   When the timer is **15 seconds from completion**, say this:

   In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you.

   When the **timer rings**, say this:

   Stop!

   Walk over to the subject and take the chair if he/she looks exhausted. Mark the spot where the subject stopped by placing a bean bag or piece of tape on the floor.

10. Post-test: Record the post-walk Borg dyspnea and fatigue levels and ask this:

What, if anything, kept you from walking farther?

11. If using a pulse oximeter, measure the oxygen saturation and pulse rate.
12. Record the number of laps from the counter or tick marks on the worksheet.
13. Record the distance covered in the final partial lap. Calculate the total distance walked, round to the nearest meter and record it on the worksheet or source document.
14. Congratulate the subject on good effort and offer a drink of water.

Practice Test

A practice test is not needed in most clinical settings but should be considered. If a practice test is done, wait for least 1 hour before the second test and report the highest distance walked in the 6MWT as the subject's baseline.

Study Staff Training

Study staff performing the 6MWT should be trained using this standard protocol and then supervised for several tests before performing them alone. Preferably the same staff member should perform all 6MWT; if not feasible, the same staff member should perform serial testing on the same subject.

Encouragement

Only the standardized phrases for encouragement in this protocol must be used during the test.

The BORG Scale:

At the beginning of the 6MWT, show the scale (printed on heavy paper in 20-point type size) to the subject and ask him/her to rate the following:

Please grade your level of shortness of breath using this scale.

Then ask:

Please grade your level of fatigue using this scale.

At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

The Borg Scale

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

15.3 Grip Strength

Hand grip strength is a commonly used measure of upper body skeletal muscle function and has been widely used as a general indicator of frailty with predictive validity for both mortality and functional limitation. Other than possible temporary discomfort during the test itself, there are no known risks for the participant. If the participant reports current flare-up of pain in the wrist or hand, or has undergone fusion, arthroplasty, tendon repair, synovectomy, or other related surgery of the hand or wrist in the past 3 months, the affected side should not be tested.

All staff performing the grip strength measurements on participants must be certified. Certification must be renewed annually. The dynamometer should be calibrated monthly. If the device is dropped or mishandled, the calibration should be checked. This is done by slowly lifting 20 kilograms strapped to the handle. The dial reading should be within 2 kilograms of the referenced weight.

15.3.1 Procedure

1. This test should be done with the participant in a seated position.
2. Determine whether the participant is right- or left-handed. The test should be completed in the dominant hand unless the participant is unable as described above.
3. Set the dynamometer handgrip at position two. Adjust it for a smaller or larger hand when necessary. Check that arrow is set at ZERO.
4. The dynamometer is fairly heavy, so caution the participant when handing out the instrument. Allow one practice try to familiarize participant with the feel of the instrument. Ensure that the bars are the proper distance apart for a comfortable grip.
5. The participant's arm should be resting on the table with the elbow bent.
6. Complete two measurements.
    a. For each measurement, instruct the participant to squeeze as hard as they can. This is accomplished by instructing the participant prior to beginning the test and then stating loudly during the test, "Squeeze, squeeze, squeeze!"
    b. Allow 10 seconds between each measurement.
    c. Record each value to the nearest 2 kilograms, e.g. 40 (kg). If < 10 kg, right justify and zero fill, e.g. 8 (kg) = 08.
    d. After each reading, reset the arrow to ZERO.
7. Discontinue a measurement with anyone complaining of pain, then code 'unable' noting reason why unable.

15.4 Short Physical Performance Battery

The short physical performance battery (SPPB) is a group of measures that combines the results of the gait speed, chair stand, and balance tests. It has been used as a predictive tool for possible disability and can aid in the monitoring of function in older people. The scores range from 0 (worst performance) to 12 (best performance). The SPPB has been shown to have predictive validity showing a gradient of risk for mortality, nursing home admission, and disability.

15.4.1 Required Equipment

The following equipment is required for the SPPB: stopwatch, masking tape, chain with fine links measuring just over 4 meters (approximately) in length, and a straight-backed chair with a hard seat. If this type of chair is not available, a chair with a softer seat or a chair with arms may be substituted. Do not use a folding chair, a soft chair, a deep chair, or a chair on wheels.

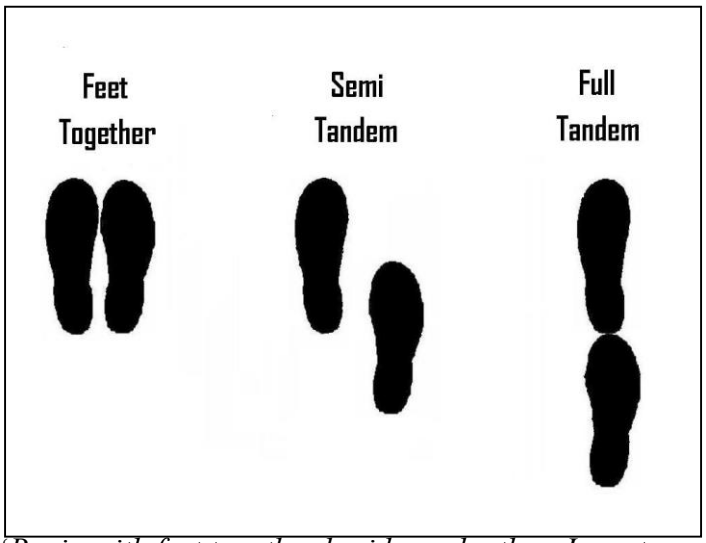
15.4.2 Procedures

Assess the safety and suitability of the participant to perform the tests. If you feel they are too unsteady or weak please do not perform the SPPB measures.

15.4.2.1 Balance Testing

The tests of balance provide an assessment of the participant's ability to hold three basic standing positions with the eyes open. No equipment other than a stopwatch is needed. The three positions are side-by-side stand, semi-tandem stand, and full tandem stand (or heel-to-toe) and are performed in this order. Participants taking this test must be able to stand unassisted without using a cane or a walker. Don't assume that a participant who arrives for testing using a cane or walker can't stand unassisted. Ask them if they can stand without the device and are willing to try the test. If they say yes, you can assist them to assume the correct position for testing. Each test is timed and the participant is allowed only one chance to maintain each position.

1. Explain "*We will now look at your standing balance. We want to know if you can stand unsupported for 10 seconds with your feet in a certain position*".
    a. Demonstrate the positions shown below (feet together, semi tandem, full tandem).



    b. Explain "*Begin with feet together beside each other. I want you to try to stand with your feet together, side by side, for about 10 seconds. Please watch while I*

demonstrate. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop".

c. Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and let's go of your arm. The test is stopped when the participant moves their feet, grasps the interviewer for support, or when 10 seconds has elapsed.
d. Record time on Case Report Form
e. If they are able to complete 10 seconds, progress to semi-tandem stand.

2. Repeat in semi tandem stand (heel of one foot placed next to and touching the big toe of the other foot).
    a. Explain "*Now I want you to try to stand with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop*".
    b. Demonstrate.
    c. Begin timing when participant has feet in position and let's go of your arm. The test is stopped when the participant moves their feet, grasps the interviewer for support, or when 10 seconds has elapsed.
    d. Record time on Case Report Form
    e. If they are able to complete 10 seconds, progress to tandem stand.
3. Tandem Stand (feet directly in front of each other)
    a. Explain **"***Now I want you to try to stand with the heel of one foot in front of and touching the toes of the other foot for 10 seconds. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop*".
    b. Demonstrate.
    c. Begin timing when participant has feet in position and let's go of your arm. The test is stopped when the participant moves their feet, grasps the interviewer for support, or when 10 seconds has elapsed.
    d. Record time on Case Report Form

15.4.2.2 4-Meter Walk

1. The subject will be instructed to walk a continuous, straight four meters without turns. Mark out the distance with a tape measure. Place a chair at the other end if you think the participant might require it.
2. Explain:
    a. **"***Now I am going to observe how you normally walk. If you use a cane or other walking aid and you feel you need it to walk a short distance, then you may use it. This is our walking course. I want you to walk to the other end of the course at your usual speed, just as if you were walking down the street to go to the store."*
    b. Demonstrate the walk.
    c. *"Walk all the way past the other end of the tape before you stop. I will walk with you. Do you feel this would be safe?"*
    d. Have the participant stand with both feet touching the starting line.

e. *"When I want you to start, I will say: "Ready, begin.""* When the participant acknowledges this instruction say: "*Ready, begin.*"
f. Press the start/stop button to start the stopwatch when the participant's foot starts to move across the starting line. Walk behind and to the side of the participant.
g. Stop timing when one of the participant's feet is completely across the end line.

1. Complete scoring on Case Report Form.
2. After a short break, repeat the walk and record the time.

15.4.2.3 Chair Stands

In this test, participants are first instructed to fold their arms across their chest and to try to stand up one time from an armless chair placed against a wall. To perform this test you will need a stopwatch and a straight-backed chair with a hard seat.

If the participant is successful rising from the chair once, they are then asked to stand up and sit down 5 times as quickly as possible. Timing begins as soon as the command to stand is given and continues until the participant straightens at the end of the fifth stand. When learning to do this, it is useful for two or more people to time the test so that the times can be compared for precision. For efficiency, it is valuable to have two chairs available so that the examiner can do the demonstration while the participant sits in the other chair and watches. If only one chair is available then the participant will have to get up to watch the demonstrations.

To ensure safety, the examiner should stand in front of the participant and be prepared to catch them if they fall forward. However, do not stand so close that the participant feels hemmed in and slows their pace during the chair stands.

1. Explain "*I want to see how long it takes you to stand up and sit down **as quickly as possible** 5 times without stopping. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. Please watch while I demonstrate. I'll be timing you with a stopwatch*"
2. Demonstrate to the patient**.**
3. Ask the participant if they are ready. If so, begin timing as soon as they bend forward at the hips.
4. Count out loud the number of sits the participant has performed.
5. Stop the stop watch when they have sat down having completed the 5th stand. Also stop if the participant starts to use their arms, or after 1 minute they have not completed the test. Stop if the participant cannot complete 5 rises, and if you are concerned about the participant's safety. Record the number of seconds and the presence of imbalance. Then complete scoring according to outcome measure template.

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

(SF-36v2® Health Survey Standard, United States (English))

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

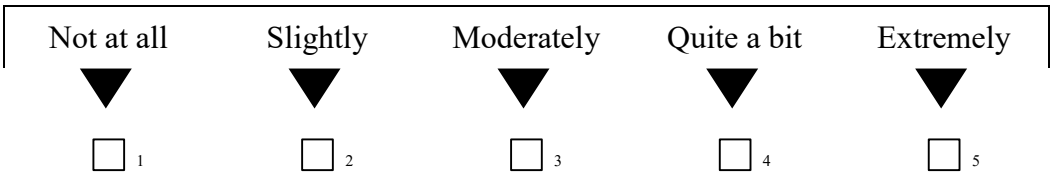
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

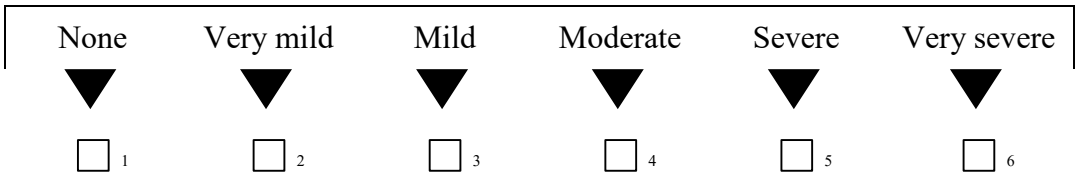
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

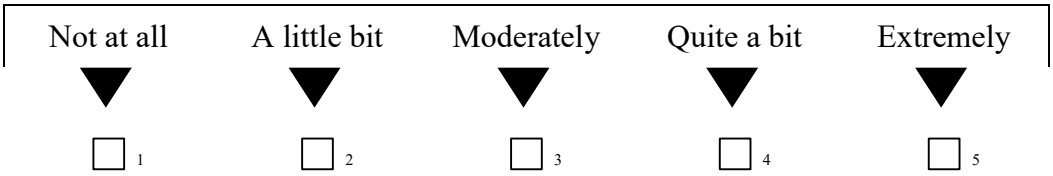
6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?



8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

15.6 Self-Reported Physical and Instrumental Activities of Daily Living

PRE-FRACTURE

INTRODUCTION

Thank you for participating in our study. I am going to be asking you questions that are written down for me in this booklet. For some of the questions, I will read you a list of response choices. For these questions, listen to the choices as I read them then choose the one that is closest to your situation. For other questions, I will not read a list, but I will ask you for either a yes or no, a number, or an answer of your own. I will let you know what kind of response I'd like as we are going along. Do you have any questions before we begin?

The intent of these questions is to ascertain whether the device connotes an increase in dependence. These items measure whether the participant required assistance to perform each of the activities listed below. Treat each item as one entity; if the participant needed help for **any** part of the item (e.g., *needs* help getting in bed but *does not need* help to get out of bed), code as Assistance Used.

When asking the question, emphasize **on average** and that we are referring to any period of time within the specified time frame.

We want to know if they used some device or equipment or the help of another person to do the activity. It is particularly important that the participant keep in mind our broad definition of “equipment assistance”.

As incorporated in the instructions, the following examples are provided to the participant: using a walker, cane, or furniture for walking; using dressing sticks or shoe horns to get dressed; using raised toilet seats, bathseats, and grab bars in the toilet or tub; and using long-handled reachers. Please make sure that the participant keeps these examples in mind as s/he responds. Additional types of equipment include a seat raiser, blocks under chair legs, button hooks, and adaptive clothing. Decisions about whether other items constitute equipment will be more difficult to make.

If a response seems in opposition to a response provided elsewhere (e.g., reports using no help to get on and off the toilet, but previously reported using grab bars for the toilet seat), **clarify and correct the discrepancy with the participant.**

If the participant has not performed an activity, determine if it was not performed due to health reasons or non-health reasons. You may need to ask whether s/he found it too difficult or unsafe to perform the activity (Did Not Perform: Health), or whether s/he did not have the opportunity or preferred not to do the activity (Did Not Perform: Non-health).

Pre-Fracture Physical Activities of Daily Living (PADLs)

[all 16 items]

In this group of questions, I am interested in whether you had help in performing each of these activities.

By “help” I mean whether you used some device or equipment or the help of another person, to do the activity. Let me first give you some examples of what I mean when I ask whether you used equipment.

- To get dressed, some people use special dressing sticks or shoe horns.
- In the bathroom, raised toilet seats, bath seats, and grab bars in the toilet or tub are sometimes used.
- To reach things, you might use long-handled reachers.

Basically, I am interested in whether "in the week prior to your fracture" you used any devices or help from another person to perform these activities.

In the **ONE WEEK** before your fracture, ON AVERAGE, did you use help to

	No Help 0	Used Equip 1	Used Human Assist 2	Used Equip & Human Assist 3	Didn’t perform: Health 4	Didn’t perform: Non-health 5	Don’t Know 7	Refused 8
a. Walk 10 feet or across a room								
If 1 or 3 selected indicate type of equipment **1=Cane(s)** **2=Walker** **3=Wheelchair** **4=Crutches** **5=Other**				☐				
b. Walk one block on a level sidewalk								
If 1 or 3 selected indicate type of equipment **1=Cane(s)** **2=Walker** **3=Wheelchair** **4=Crutches** **5=Other**				☐				
c. Climb 5 stairs								
d. Get into car								
e. Get in and out of bed								
f. Rise from an armless chair								

g. Put on a shirt/blouse								
h. Button a shirt/blouse								
i. Put on pants								
j. Put on socks, shoes on both feet								
k. Get in/out of bath or shower								
l. Wash all parts of body								
m. Get on/off the toilet								
n. Feed yourself after food is readied								
o. Groom yourself (brush hair and teeth)								
p. Reach for an item on the ground from sitting position								

Pre-Fracture Lower Extremity Physical Activities of Daily Living (LPADLs)

[only 12 items]

In this group of questions, I am interested in whether you had help in performing each of these activities.

By “help” I mean whether you used some device or equipment or the help of another person, to do the activity. Let me first give you some examples of what I mean when I ask whether you used equipment.

- To get dressed, some people use special dressing sticks or shoe horns.
- In the bathroom, raised toilet seats, bath seats, and grab bars in the toilet or tub are sometimes used.
- To reach things, you might use long-handled reachers.

Basically, I am interested in whether "in the week prior to your fracture" you used any devices or help from another person to perform these activities.

In the **ONE WEEK** before your fracture, ON AVERAGE, did you use help to

	No Help 0	Used Equip 1	Used Human Assist 2	Used Equip & Human Assist 3	Didn't perform: Health 4	Didn't perform: Non-health 5	Don't Know 7	Refused 8
a. Walk 10 feet or across a room								
If 1 or 3 selected indicate type of equipment **1=Cane(s)** **2=Walker** **3=Wheelchair** **4=Crutches** **5=Other**	☐							
b. Walk one block on a level sidewalk								
If 1 or 3 selected indicate type of equipment **1=Cane(s)** **2=Walker** **3=Wheelchair** **4=Crutches** **5=Other**	☐							
c. Climb 5 stairs								
d. Get into car								
e. Get in and out of bed								
f. Rise from an armless chair								
g. Put on pants								
h. Put on socks, shoes on both feet								
i. Get in/out of bath or shower								
j. Wash all parts of body								
k. Get on/off the toilet								
l. Reach for an item on the ground from sitting position								

Pre-Fracture Instrumental Activities of Daily Living (IADLs)

I have a few more questions about common activities of daily life.

I would like to know if you did these activities during the TWO WEEKS before you broke your hip. For each activity, I'd like you to select the statement which best describes the amount of assistance you required to do each activity.

Q1. During the TWO WEEKS before you broke your hip how did you USUALLY get to places out of walking distance? Did you:

☐	**1=Travel alone on buses, taxis, or drive your own car**	**Go to Q2**
☐	2=Have someone to help you or go with you when traveling	Go to Q2
☐	3=Did not perform: health reason	Go to Q2
☐	4=Did not perform: non-health reason	Go to Q1a

Q1a. If you did not travel, could you travel:

☐	**1=Independently**
☐	2=With Assistance
☐	3=Would not be able to at all

Q2. During the TWO WEEKS before you broke your hip, assuming you had transportation, how did you usually go shopping for groceries or clothes, Did you:

☐	**1=Take Care of all your shopping needs yourself**	**Go to Q3**
☐	2= Have someone to go with you on all shopping trips	Go to Q3
☐	3=Did not perform: health reason	Go to Q3
☐	4=Did not perform: non-health Reason	Go to Q2a

Q2a. If you did not shop, could you shop:

☐	**1=Independently**
☐	2=With Assistance
☐	3=Would not be able to at all

Q3. During the TWO WEEKS before you broke your hip how did you usually prepare your meals? Did you:

☐	**1=Plan and cook meals fully yourself**	**Go to Q4**
☐	2=Prepare some things, but were unable to cook full meals yourself	Go to Q4
☐	3=Did not perform: health reason	Go to Q4

☐	4=Did not perform: non-health Reason	Go to Q3a

Q3a. If you did not prepare meals, could you prepare meals:

☐	**1=Independently**
☐	2=With Assistance
☐	3=Would not be able to at all

Q4. During the TWO WEEKS before you broke your hip how did you usually do your house cleaning? Did you:

☐	**1=Do heavy work, such as scrubbing floors, by yourself**	**Go to Q**
☐	2=Do light housecleaning, but had help with heavy work	Go to Q
☐	3=Did not perform: health reason	Go to Q
☐	4=Did not perform: non-health Reason	Go to Q4a

Q4a. If you did not house clean, could you clean:

☐	**1=Independently**
☐	2=With Assistance
☐	3=Would not be able to at all

15.7 Self-Reported Physical and Instrumental Activities of Daily Living

POST-FRACTURE

INTRODUCTION

Thank you for participating in our study. I am going to be asking you questions that are written down for me in this booklet. For some of the questions, I will read you a list of response choices. For these questions, listen to the choices as I read them then choose the one that is closest to your situation. For other questions, I will not read a list, but I will ask you for either a yes or no, a number, or an answer of your own. I will let you know what kind of response I'd like as we are going along. Do you have any questions before we begin?

The intent of these questions is to ascertain whether the device connotes an increase in dependence. These items measure whether the participant required assistance to perform each of the activities listed below. Treat each item as one entity; if the participant needed help for **any** part of the item (e.g., *needs* help getting in bed but *does not need* help to get out of bed), code as Assistance Used.

When asking the question, emphasize **on average** and that we are referring to any period of time within the specified time frame.

We want to know if they used some device or equipment or the help of another person to do the activity. It is particularly important that the participant keep in mind our broad definition of "equipment assistance".

As incorporated in the instructions, the following examples are provided to the participant: using a walker, cane, or furniture for walking; using dressing sticks or shoe horns to get dressed; using raised toilet seats, bathseats, and grab bars in the toilet or tub; and using long-handled reachers. Please make sure that the participant keeps these examples in mind as s/he responds. Additional types of equipment include a seat raiser, blocks under chair legs, button hooks, and adaptive clothing. Decisions about whether other items constitute equipment will be more difficult to make.

If a response seems in opposition to a response provided elsewhere (e.g., reports using no help to get on and off the toilet, but previously reported using grab bars for the toilet seat), **clarify and correct the discrepancy with the participant.**

If the participant has not performed an activity, determine if it was not performed due to health reasons or non-health reasons. You may need to ask whether s/he found it too difficult or unsafe to perform the activity (Did Not Perform: Health), or whether s/he did not have the opportunity or preferred not to do the activity (Did Not Perform: Non-health).

Post-Fracture Physical Activities of Daily Living (PADLs)

[all 16 items]

In this group of questions, I am interested in whether you had help in performing each of these activities.

By “help” I mean whether you used some device or equipment or the help of another person, to do the activity. Let me first give you some examples of what I mean when I ask whether you used equipment.

- To get dressed, some people use special dressing sticks or shoe horns.
- In the bathroom, raised toilet seats, bath seats, and grab bars in the toilet or tub are sometimes used.
- To reach things, you might use long-handled reachers.

Basically, I am interested in whether "in the past week" you used any devices or help from another person to perform these activities.

In the PAST WEEK, ON AVERAGE, did you use help to….

	No Help 0	Used Equip 1	Used Human Assist 2	Used Equip & Human Assist 3	Didn’t perform: Health 4	Didn’t perform: Non-health 5	Don’t Know 7	Refused 8
q. Walk 10 feet or across a room								
If 1 or 3 selected indicate type of equipment **1=Cane(s)** **2=Walker** **3=Wheelchair** **4=Crutches** **5=Other**				☐				
r. Walk one block on a level sidewalk								
If 1 or 3 selected indicate type of equipment **1=Cane(s)** **2=Walker** **3=Wheelchair** **4=Crutches** **5=Other**				☐				
s. Climb 5 stairs								
t. Get into car								
u. Get in and out of bed								
v. Rise from an armless chair								
w. Put on a shirt/blouse								

x. Button a shirt/blouse								
y. Put on pants								
z. Put on socks, shoes on both feet								
aa. Get in/out of bath or shower								
bb. Wash all parts of body								
cc. Get on/off the toilet								
dd. Feed yourself after food is readied								
ee. Groom yourself (brush hair and teeth)								
ff. Reach for an item on the ground from sitting position								

Post-Fracture Lower Extremity Physical Activities of Daily Living (LPADLs)

[only 12 items]

In this group of questions, I am interested in whether you had help in performing each of these activities.

By “help” I mean whether you used some device or equipment or the help of another person, to do the activity. Let me first give you some examples of what I mean when I ask whether you used equipment.

- To get dressed, some people use special dressing sticks or shoe horns.
- In the bathroom, raised toilet seats, bath seats, and grab bars in the toilet or tub are sometimes used.
- To reach things, you might use long-handled reachers.

Basically, I am interested in whether "in the past week" you used any devices or help from another person to perform these activities.

In the **PAST WEEK**, ON AVERAGE, did you use help to….

	No Help	Used Equip	Used Human Assist	Used Equip & Human Assist	Didn’t perform: Health	Didn’t perform: Non-health	Don’t Know	Refused
	0	1	2	3	4	5	7	8

m. Walk 10 feet or across a room								
If 1 or 3 selected indicate type of equipment **1=Cane(s)** **2=Walker** **3=Wheelchair** **4=Crutches** **5=Other**	☐							
n. Walk one block on a level sidewalk								
If 1 or 3 selected indicate type of equipment **1=Cane(s)** **2=Walker** **3=Wheelchair** **4=Crutches** **5=Other**	☐							
o. Climb 5 stairs								
p. Get into car								
q. Get in and out of bed								
r. Rise from an armless chair								
s. Put on pants								
t. Put on socks, shoes on both feet								
u. Get in/out of bath or shower								
v. Wash all parts of body								
w. Get on/off the toilet								
x. Reach for an item on the ground from sitting position								

Post-Fracture Instrumental Activities of Daily Living (IADLs)

I have a few more questions about common activities of daily life.

I would like to know if you did these activities during the PAST TWO WEEKS. For each activity, I'd like you to select the statement which best describes the amount of assistance you required to do each activity.

Q1. During the TWO WEEKS how did you usually get to places out of walking distance? Did you:

☐	**1=Travel alone on buses, taxis, or drive your own car**	**Go to Q2**
☐	2=Have someone to help you or go with you when traveling	Go to Q2
☐	3=Did not perform: health reason	Go to Q2
☐	4=Did not perform: non-health reason	Go to Q1a

Q1a. If you did not travel, could you travel:

☐	**1=Independently**
☐	2=With Assistance
☐	3=Would not be able to at all

Q2. During the PAST TWO WEEKS, assuming you had transportation, how did you usually go shopping for groceries or clothes? Did you:

☐	**1=Take Care of all your shopping needs yourself**	**Go to Q3**
☐	2= Have someone to go with you on all shopping trips	Go to Q3
☐	3=Did not perform: health reason	Go to Q3
☐	4=Did not perform: non-health Reason	Go to Q2a

Q2a. If you did not shop, could you shop:

☐	**1=Independently**
☐	2=With Assistance
☐	3=Would not be able to at all

Q3. During the PAST TWO WEEKS how did you usually prepare your meals? Did you:

☐	**1=Plan and cook meals fully yourself**	**Go to Q4**
☐	2=Prepare some things, but were unable to cook full meals yourself	Go to Q4
☐	3=Did not perform: health reason	Go to Q4
☐	4=Did not perform: non-health Reason	Go to Q3a

Q3a. If you did not prepare meals, could you prepare meals:

☐	**1=Independently**
☐	2=With Assistance
☐	3=Would not be able to at all

Q4. During the PAST TWO WEEKS how did you usually do your house cleaning? Did you:

☐	**1=Do heavy work, such as scrubbing floors, by yourself**	**Go to Q**
☐	2=Do light housecleaning, but had help with heavy work	Go to Q
☐	3=Did not perform: health reason	Go to Q
☐	4=Did not perform: non-health Reason	Go to Q4a

Q4a. If you did not house clean, could you clean:

☐	**1=Independently**
☐	2=With Assistance
☐	3=Would not be able to at all