

An Open-Label Phase 2 Study of Abaloparatide to Mitigate Distal Femoral Bone Loss Following Total Knee Arthroplasty

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Abaloparatide-SC

Clinical Study Protocol # 14788 (HSC #2019-0685)

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Following Total Knee Arthroplasty**

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

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COMPLIANCE STATEMENT

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812):

In addition, we agree to the following:

- To conduct this study in accordance with the design and provisions of this protocol.
- To await Institutional Review Board (IRB) approval for the protocol and informed consent (IC) before initiating enrollment into the study.
- To ensure that requirements for obtaining IC are met and to obtain IC from patients before their enrollment into the study.
- To collect and record data as required by this protocol into the case report form (CRF).
- To maintain the confidentiality of all information received or developed in connection with this protocol.
- To conduct this study in accordance with the International Conference on Harmonisation (ICH), the Declaration of Helsinki, and applicable regulatory requirements.

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Date

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LIST OF ABBREVIATIONS

<u>Abbreviation</u>	<u>Term</u>
25(OH)D	25-hydroxyvitamin D
AAHKS	American Association of Hip and Knee Surgeons
ABL	Abaloparatide
AOA	American Orthopaedic Association
ASBMR	American Society for Bone and Mineral Research
AE	Adverse event
BIS	Bioelectrical Impedance Spectroscopy
BMD	Bone mineral density
CRF	Case report form
DXA	Dual energy X-ray absorptiometry
GCP	Good clinical practice
HPLC	High Performance Liquid Chromatography
IC	Informed consent
ICH	International Conference on Harmonization
IFU	Instruction for Use
IOF	International Osteoporosis Foundation
ISCD	International Society for Clinical Densitometry
IQR	Interquartile Range
IRB	Institutional review board
KOOS JR	Knee injury & Osteoarthritis Outcome Score
LOCF	Last Observation Carried Forward
OCRCP	UW Osteoporosis Clinical Research Program
PI	Principal Investigator
PRO	Patient Reported Outcomes
PTH	Parathyroid Hormone
ROIs	Regions of Interest
TBS	Trabecular Bone Score
TJA	Total Joint Arthroplasty
TKA	Total Knee Arthroplasty
THA	Total Hip Arthroplasty
TRIP	Texture Research Investigation Platform
UW	University of Wisconsin
VR-12	Veterans RAND 12 Question Health Survey
VFA	Vertebral Fracture Assessment

1.0 STUDY RATIONALE

Total knee arthroplasty (TKA) is commonly performed to improve mobility and quality of life in older adults. It is estimated that 15% of Americans age 70+ have had a TKA¹ and that ~3.5 million procedures will be performed annually by 2030.^{2, 3} Importantly, 60-80% of patients undergoing TKA have low bone mineral density (BMD).^{4, 5} Consistent with this, in our prior work low BMD was present in 119/200 (59.5%) of individuals undergoing total joint replacement at the University of Wisconsin. An important and currently underappreciated consequence of TKA is femoral bone loss, which makes the individual susceptible to periprosthetic fracture. Such fractures are not rare, occurring in up to ~5.5% of TKA patients, are challenging to repair and have devastating consequences.⁶⁻⁹ Indeed, it is reasonable to consider distal femoral periprosthetic fractures as comparable to classic osteoporosis-related hip fractures as their personal and societal consequences are strikingly similar. Specifically, periprosthetic fractures are associated with functional decline, major healthcare cost, frequent hospital readmission (> 20% within 3 months) and > 20% one year mortality.¹⁰⁻¹³ Given the aging of our population coupled with long-term survival post TKA, the numbers of older individuals with total joint replacements (and subsequent periprosthetic fractures) will increase over the foreseeable future. Specifically, in 2010, 4.3 Million people in the USA are living with TKA and each year 700,000 TKAs are performed; a number projected to triple by 2030.¹ As such, efforts to reduce periprosthetic fracture risk are essential.

TKA leads to bone loss;¹⁴⁻¹⁸ potential mechanisms for this include stress shielding, immobilization, quadriceps muscle loss and inflammatory changes following operative trauma.¹⁹⁻²¹ This decline in BMD is substantial; in our group's recent meta-analysis of 14 studies (see appended submitted manuscript), Prince, et. al., find an average distal femur BMD decline of ~16% following TKA. While absence of standard dual-energy absorptiometry (DXA) protocols and regions of interest (ROIs) compromise existing reports, these studies consistently find distal femur BMD decline to occur rapidly, mostly within 6 months, and is not restored up to 7 years later. To address the issue of DXA distal femur non-standardization, we have performed pilot work using existing DXA software and identified distal femur ROIs at which BMD can be measured with excellent precision (see appended manuscripts; Thomas, et. al., and Blaty, et. al.);^{22, 23} these regions will be utilized in this proposed study. In addition to this approach, we will also explore the clinical utility of PA and lateral knee DXA scans to evaluate bone mass change after time using existing techniques.²⁴⁻²⁶

Importantly, existing data finds that bone loss after TKA can be mitigated by pharmacologic treatment (bisphosphonates or teriparatide [TPD]).²⁷ For example, Suzuki, et. al.,²⁶ studied 17 osteoporotic women with osteoarthritis undergoing TKA and compared 12 months of TPD treatment to untreated controls. They found that the treated group had stability or a slight BMD increase while the controls experienced the expected bone loss (~9-11%). Thus, the TPD to control BMD difference after 12 months of treatment (depending on the ROI) was 8-18%. Kobayashi, et. al.,²⁸ reported a three-armed RCT comparing TPD to alendronate or placebo in patients with total hip arthroplasty; both treated groups maintained BMD while the placebo group sustained a 15% loss.

In addition to increasing periprosthetic fracture risk, inadequate bone stock is associated with subsidence around arthroplasty implants. Thus, in addition to reducing periprosthetic fracture risk, interventions to improve BMD may lead to better and more durable results after total joint arthroplasty. Consistent with this, a meta-analysis finds bisphosphonate treatment following total hip and TKA reduces revision surgery by over 50%.²⁹ To our knowledge, no similar data with bone anabolic agents exists. While beyond the scope of this proposed study, it is

plausible that bone anabolic therapy would not only reduce periprosthetic fracture risk, but also periprosthetic subsidence.

Finally, it is well accepted that falls increase fracture risk and that the age-related physical function impairment and muscle mass decline, i.e., sarcopenia, contributes to falls.³⁰⁻³² As patients may experience leg muscle loss and physical function impairment after TKA³³⁻³⁵ it is reasonable to expect this contributes to fracture risk after surgery. Consequently, we propose to collect pilot data evaluating body composition by total body DXA and bioelectric impedance spectroscopy (BIS) to evaluate change in lean mass with TKA.^{36, 37}

2.0 STUDY OBJECTIVE

Based on the above, it is clear that bone anabolic agents are of interest in orthopedic surgical patients. A recent review on non-classical use of anabolic agents concluded *“Based on a large array of literature, patients with osteoporosis require bone interventions.... Would benefit from an anabolic agent over the use of anti-resorptive agent”* and *“additional studies are needed to substantiate the role of other anabolic agents such as abaloparatide...”*³⁸ **To this end, we hypothesize that treating osteoporotic patients with ABL prior to and after TKA will significantly reduce the amount of bone loss, as measured by BMD at the 25% distal femur ROI, 15 months post TKA.** To assess the effect of ABL, we will compare the bone loss seen in this study to the 0.16 g/cm² average BMD lost in untreated osteoporotic patients at 12 and 24 months following TKA reported in Prince et.al.³⁹

2.1 Primary Study Endpoints

Specific Aim 1: To estimate the amount of distal femur bone loss in ABL treated osteoporotic patients 15 months post TKA and to compare the bone loss to the bone loss seen in untreated osteoporotic patients 12 months following TKA as reported by the meta-analysis of Prince et.al.³⁹ The limitation of this design is the comparison to a historic control rather than a control arm in this study. The reason this design was chosen is because it would be unethical to not offer treatment to newly diagnosed osteoporotic patients. Therefore, randomization to a control arm is not possible. Furthermore, based on our recent clinical experience we believe the rate of patient choice to refuse treatment will be quite low making recruitment of a non-randomized osteoporotic control arm futile. This reflects a dramatic change in osteoporosis care within orthopedic surgical practice at UW within the past year. Lastly, it is well documented that bone loss will occur in this patient population following TKA as seen in the multiple studies summarized in the Prince article.

Specific Aim 2: To estimate the amount of distal femur bone loss in untreated osteopenic patients 15 months post TKA.

The hypothesis for this aim is that TKA will significantly reduce BMD from baseline to 15 months post surgery in osteopenic patients. To assess this we will conduct a single arm pre-post observational study.

This design was chosen because data in the literature is sparse for BMD levels pre and post TKA in an osteopenic population. Collection of these data could demonstrate significant reduction in BMD following TKA which would lead to the justification of a future prospective study comparing a bone loss mitigating treatment to no treatment (current standard of care) in osteopenic TKA patients.

Specific Aim 3: To compare the amount of bone loss in ABL treated osteoporotic patients to untreated osteopenic patients 15 months following TKA.

The hypothesis for this aim is that the percent decrease from baseline in BMD at 15 months post TKA will be greater in the untreated osteopenic group compared to the treated osteoporotic group.

It is understood these groups differ at baseline in BMD, but the belief is that after TKA the osteopenic group will become similar to the treated osteoporotic group. This is an exploratory analysis, and as such we may be under-powered to detect a significant effect. If trends in the differences are seen, and osteopenic patients are becoming osteoporotic after TKA, this would further bolster the need for future treatment studies in the osteopenic population.

2.2 Secondary Endpoints/Secondary aims:

- Distal femoral BMD change at the 15% and 60% ROIs
- Femur cortical thickness change at the 15%, 25% and 60% femur ROIs
- Trabecular bone score (TBS) assessment by Texture Research Investigation Platform (TRIP) software change at the 15%, 25% and 60% femur ROIs
- Patient reported outcomes; KOOS JR (knee function score), VR-12 (Veterans RAND 12 Item Health Survey) and Forgotten Joint Survey
- Precision of custom knee regions of interest
- Body composition and lean mass change
- TKA complications, e.g., revision surgery, fracture, etc

3.0 PRELIMINARY DATA

3.1 Meta-analysis of BMD loss after TKA (See Prince, et. al.)³⁹

This meta-analysis of 14 studies that quantified distal femur BMD change after primary TKA. In the distal femoral supracondylar region, mean BMD losses of 0.09 [0.05,0.13], 0.14 [0.08,0.20], 0.16 [0.10,0.23], and 0.16 [0.12,0.20] g/cm² were reported 3, 6, 12, and 24 months respectively following TKA. This corresponds to a 9.3%, 13.2%, 15.8%, and 15.4% BMD loss at these time points. In summary, there is a rapid and significant ~15% decrease in BMD in the first 6 months after TKA that is sustained to 24 months. Better understanding regarding how pre-/perioperative bone health optimization may affect BMD loss and the subsequent periprosthetic fracture risk of is essential.

3.2 Distal femoral BMD and cortical thickness after TKA compared to the contralateral (non-operated) side (See Thomas et. al, and Blaty, et. al.^{22, 23})

We initially performed measurements in 1 cm ROI increments to define BMD change throughout the femur (Thomas, et. al.). Based upon that data, we developed and evaluated a standardized technique to measure BMD and cortical thickness utilizing existing atypical femur fracture DXA software. We then compared distal femoral BMD and cortical thickness on the TKA side to the contralateral non-operative leg (Blaty, et. al.).²³ Thirty adults (15 M/15 F) age 59-80 years with well-functioning unilateral, primary TKA 2-5 years after surgery had femoral DXA scans performed. BMD and cortical thickness were measured at ROIs located at 15%, 25%, and 60% of the femur length measured from the distal notch. Femur BMD and cortical thickness were compared between limbs (TKA vs. non-operated side) by paired t-test.

BMD was 9.7%, 9.6%, and 3.2% lower ($p < 0.0001$) in the operated femur at the 15%, 25%, and 60% ROI respectively. Evaluation of this cohort by BMD status (normal, osteopenia, osteoporosis) finds distal femur BMD at the 25% ROI to be 12% lower in those with osteopenia and 10.3% lower in those with osteoporosis. Cortical width was lower by 22% ($p < 0.05$) at the 25% ROI on the TKA side but not at the 15 or 60% ROI, likely due to current software limitations. Importantly, at these distal femur ROIs, BMD reproducibility was excellent, despite

manual analysis, ranging from 0.85-1.3% at these custom sites. Based upon this work, distal femur BMD can be reproducibly measured using DXA and is ~10% lower on the TKA leg. Similarly, medial and lateral cortices are thinner at the 25% ROI. These bone changes likely increase periprosthetic fracture risk. TBS values at these ROIs are currently being obtained by colleagues at Medi-Maps (developers of TBS) using the recently released TRIP software.

3.3 Preoperative bone health status prior to arthroplasty (See Bernatz, et. al. #1)⁴⁰

We hypothesized that preoperative osteoporosis is under-recognized and undertreated in the total joint arthroplasty (TJA) population. The purpose of this study was to determine preoperative osteoporosis prevalence prior to TJA and rates of pharmacologic osteoporosis treatment in the TJA population.

This was a retrospective case series of 200 consecutive adults (106F, 94M) age 48-92 years who underwent elective TJA (100 TKA, 100 THA) at the University of Wisconsin. Charts were reviewed to determine preoperative osteoporosis risk factors, prior osteoporosis screening and previous osteoporosis pharmacotherapy. Fracture risk was estimated using FRAX and NOF criteria for screening and treatment were applied to all patients.

119 of these 200 patients (59.5%) met criteria for osteoporosis screening, but only 21 (17.6 percent) had DXA performed in the two years prior to surgery. Forty-nine patients (24.5%) met NOF criteria for pharmacologic treatment but only 11 of these 49 received a prescription for pharmacotherapy within six months of surgery. Given that an estimated 1 million TKAs will be performed annually by 2020, if these results are generalizable it is likely that ~250,000 TKA patients are candidates for pharmacologic treatment. Thus, the majority of patients undergoing elective TJA met criteria for osteoporosis screening, however only a small percentage were. One quarter of these patients met criteria to receive pharmacotherapy but few are prescribed treatment. This lack of preoperative osteoporosis screening and treatment likely contributes to periprosthetic fracture risk.

3.4 Osteoporosis prevalence in well-functioning TKA patients 2-5 years after surgery (See Bernatz, et. al., #2)⁴¹

This study reports osteoporosis prevalence in a healthy cohort of patients with well-functioning TKA. We hypothesize that osteoporosis is under-recognized in this population.

This was a cross-sectional study of 30 adults (15 M/15 F) age 59-80 years selected to have no known bone health issues. Routine clinical DXA and custom distal femur scans were performed 2-5 years (mean 3.2 ± 0.8) after primary unilateral TKA. DXA examination included lumbar spine, hip and radius BMD, trabecular bone score and vertebral fracture assessment. These data, plus, clinical risk factors, were used to estimate fracture risk via FRAX and the WHO skeletal status classification (normal, osteopenic, osteoporotic) was determined. The NOF criteria for treatment were applied.

Six of these 30 patients (20%) had osteoporosis (lowest BMD T-score ≤ -2.5), 18 (60%) were osteopenic and 20% had normal BMD. Five patients with normal or osteopenic BMD had occult vertebral fractures on vertebral fracture assessment (VFA). Based on NOF guidelines, eleven (37%) patients met criteria for pharmacologic treatment.

The prevalence of unappreciated osteoporosis (37%) requiring treatment after TKA in this series of patients who were specifically excluded for known bone disease is substantial and may contribute to periprosthetic fracture risk. These data support the further study of postoperative osteoporosis and consideration of DXA testing after TKA.

4.0 STUDY DESIGN/METHODS

4.1 Patient cohort

Patients age ≥ 55 years and meeting entry criteria when the decision is made to proceed with TKA will be offered the option of study participation. Those consenting will receive a screening DXA (lumbar spine, bilateral femur/hip and VFA to determine eligibility. The inclusion/exclusion criteria (see below) are modeled after prior ABL clinical trials.

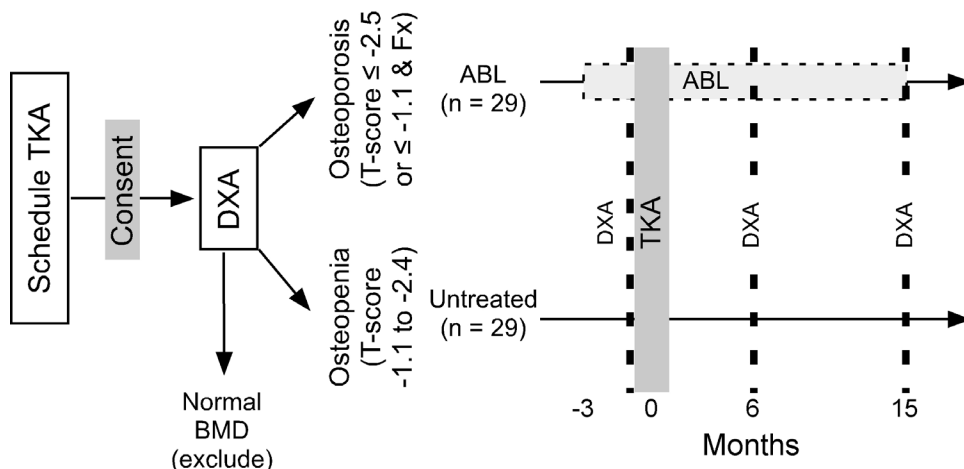
4.2 Participant recruitment and study design

Study participants will be recruited from the UW Total Joint Program at the American Center. Patients expressing interest in study participation at the time of TKA scheduling will subsequently be contacted by a University of Wisconsin Osteoporosis Clinical Research Program (OCRP) study coordinator. Those expressing study interest will be scheduled at the OCRP where, following informed consent, medical history, collection of FRAX risk factors and a screening DXA of the lumbar spine, bilateral femurs/hips and VFA will be performed.

The overall study design is noted in Figure 1. Briefly, study eligibility will be determined by DXA. Those with osteoporosis who elect ABL will make up the treatment group ($n = 29$). An equal number ($n = 29$) will be recruited into the untreated group, i.e., those with osteopenia and no prior fragility fracture.

At screening, all participants will have a physical examination and blood collected for a metabolic panel, 25(OH)D and parathyroid hormone (PTH) measurement with additional sample to bank for potential future testing related to bone metabolism. Additionally, calcium and PRO questionnaires will be collected consisting of the KOOS JR, VR-12, and Forgotten Joint Survey. Subjects will be advised on how to achieve a daily calcium intake of 1,000-1,200 mg through food plus supplements, if needed, and up to 4000 IU of vitamin D₃ daily (as noted below; section 5.1). Subsequently, for those meeting all inclusion/exclusion criteria, ABL will be initiated in the treatment group approximately 3 months (depending on the surgery schedule) prior to their TKA and serum calcium will be assessed after one month of dosing. Subsequently, all subjects will have lumbar spine and bilateral femur DXA repeated within two weeks prior to TKA (± 7 days from the month -0.25 study visit) and again 6 and 15 months post TKA. At these same visits, PRO questionnaires will be administered and blood will be collected for serum banking.

Figure 1: Study Design Schematic



4.3 Inclusion Criteria

1. Post-menopausal women and men age ≥ 55 years and scheduled to undergo primary TKA at the University of Wisconsin Total Joint Program.
2. Osteoporosis, i.e., BMD T-score (using female reference data) ≤ -2.5 at the lumbar spine, femoral neck OR total hip or ≤ -1.1 with VFA confirmed vertebral fracture or history of low-trauma nonvertebral fracture in the past 5 years OR osteopenia, BMD T-score (using female reference data) -1.1 to -2.4 at the lumbar spine, femoral neck or total hip and no prior low-trauma fracture.
3. Serum calcium (albumin-corrected), serum creatinine and PTH values all within the normal range and $25(\text{OH})\text{D} > 10 \text{ ng/mL}$.
4. Willing to supplement with daily calcium and/or vitamin D_3 at protocol specified doses.
5. Able to provide written informed consent.

4.4 Exclusion Criteria

1. Unevaluable distal femur BMD due to hardware or other artifacts.
2. History of bone disorders (e.g., Paget's disease) other than osteoporosis.
3. History of prior external beam or implant radiation therapy involving the skeleton other than radioiodine.
4. History of chronic or recurrent renal, hepatic, pulmonary, allergic, cardiovascular, gastrointestinal, endocrine, central nervous system, hematologic or metabolic diseases, or immunologic, emotional and/or psychiatric disturbances that, in opinion of the principal investigator, would compromise study data validity.
5. History of Cushing's disease, growth hormone deficiency or excess, hyperthyroidism, hypo- or hyperparathyroidism or malabsorptive syndromes within the past year.
6. History of significantly impaired renal function (serum creatinine $> 2.0 \text{ mg/dL}$. If the serum creatinine is > 1.5 and $\leq 2.0 \text{ mg/dL}$, the calculated creatinine clearance (Cockcroft-Gault) must be $\geq 37 \text{ mL/min}$).
7. History of nephrolithiasis or urolithiasis within the past five years.
8. History of cancer in prior 5 years (basal cell or squamous skin cancer is permissible).
9. History of osteosarcoma at any time.
10. Patients known to be positive for Hepatitis B, Hepatitis C, HIV-1 or HIV-2.
11. Known hypersensitivity to any of the test materials or related compounds.
12. Prior treatment with PTH- or PTHrP-derived drugs, (ABL, teriparatide or PTH (1-84)).
13. Prior treatment with IV bisphosphonates at any time or oral bisphosphonates within the past three years. Patients who had received a short course of oral bisphosphonate therapy (3 months or less) may be enrolled as long as the treatment occurred 6 or more months prior to enrollment.
14. Treatment with fluoride or strontium in the past five years or prior treatment with bone-acting investigational agents at any time.
15. Treatment with calcitonin the past 6 months or denosumab in the past 18 months.
16. Treatment with anticonvulsants affecting vitamin D metabolism (phenobarbital, phenytoin, carbamazepine or primidone) or chronic heparin within the prior 6 months.
17. Treatment with anabolic steroids or calcineurin inhibitors (cyclosporin, tacrolimus)
18. Daily treatment with oral, intranasal or inhaled glucocorticoids in the prior 12 months.
19. Exposure to any investigational drug within 12 months.
20. Consumption of > 2 alcoholic drinks per day or use of illegal drugs within 12 months of screening.
21. Not suitable for study participation due to other reasons at the investigators discretion.

5.0 VISIT SUMMARIES

Table 1: Assessment/Procedure Schedule

	Screen	Treatment Initiation ^{5,6}	Treatment Follow-up ⁶	Pre-Surgery	Visit 1 Follow-up	Visit 2 Follow-up
Time	Month -3.5	Month -3	Month -2	Month -0.25	Month 6	Month 15
Window			± 5 days	± 7 days	± 7 days	± 7 days
Informed Consent	X					
Medical History	X					
Confirm Eligibility	X ¹					
Vitals	X ²					
DXA ³	X			X	X	X
VFA	X	X ⁷	X ⁷	X ⁷	X ⁷	X ⁷
Body Composition ⁴	X			X	X	X
Physical Exam	X	X ⁷	X ⁷	X ⁷	X ⁷	X ⁷
Clinical Falls/Fracture Assessment		X	X	X	X	X
Comprehensive Metabolic Panel	X					
Parathyroid Hormone	X					
Total 25(OH)D	X					
Blood collection	X			X	X	X
Serum Calcium			X			
PRO & Diet questionnaires ⁸	X			X	X	X
ABL Administration Training	X ⁵	X				
Dispense calcium/vitamin D ⁹	X			X	X	
Dispense abaloparatide ¹⁰		X		X	X	

¹To be completed after laboratory results are available.

²To include blood pressure, pulse, height and weight

³To include lumbar spine, femur (hip and distal), forearm (PA & lateral knee performed on eligible subjects)

⁴To include total body DXA scan and Bioimpedance spectroscopy

⁵This can be an in-person, video or phone visit per subject preference

⁶Activity only completed by subjects taking abaloparatide

⁷Symptom driven evaluation, performed as appropriate

⁸Questionnaires include KOOS JR, VR-12, and Forgotten Joint Survey; Diet only performed at screening; Forgotten Joint only performed after surgery

⁹Dispensed to all subjects as determined at screening and/or pre-surgery per protocol

¹⁰Dispensed only to subjects in the treatment arm, some subsequent dispensing will occur via UPS every 3 months

5.1 Screening

Interested subjects will provide written informed consent and self-reported medical history to confirm study eligibility. Those meeting eligibility criteria will have DXA scans (lumbar spine, bilateral femur/hip, forearm and VFA) performed. Those with normal bone density based on a female normative database (i.e., T-scores ≥ 1.0) at the femoral neck, total proximal femur and lumbar spine (with vertebral exclusion per ISCD recommendations), will be excluded from further participation. Remaining potential subjects will receive PA and lateral knee DXA, body composition measurement by DXA and BIS, a physical exam with vitals (blood pressure, pulse, height and weight), complete a dietary calcium assessment and PRO questionnaires to include KOOS JR, VR-12 and Forgotten Joint Survey. Additionally, they will have blood collected to measure a comprehensive metabolic panel, PTH and total 25(OH)D. Samples will

also be collected for potential future testing related to bone metabolism related to this protocol. Those with abnormal calcium, creatinine, albumin, PTH or 25(OH)D < 10 ng/mL will be excluded from the study. DXA results performed within the prior 6 months on the research scanner are acceptable for the screening visit. Laboratory values and PRO questionnaires collected as part of a UWHealth evaluation in the 6 months prior to the screening visit can be utilized as screening data. Additionally, physical exam may be delayed to the initiation visit for the treatment group or pre-surgery visit for osteopenic group.

Subjects meeting the entry criteria based on osteoporosis diagnosis (T-score \leq -2.5 or -1.1 with prevalent vertebral fracture or recent low trauma clinical fracture) will discuss ABL treatment and those electing to participate will receive training on how to administer the medicine using the Radius ABL Instructions for Use (IFU) manual. Subjects declining treatment will be excluded from the study. Subjects in the osteopenia group will have a lowest BMD T-score of -1.1 to -2.4 at the lumbar spine, femoral neck or total proximal femur and a negative fragility fracture history.

All subjects meeting screening criteria will receive recommendations regarding daily calcium and vitamin D₃ optimization/supplementation during the study. Participants consuming less than 1000-1200 mg of calcium daily will be advised to take a supplement. If serum 25(OH)D is \geq 30 ng/mL no change in vitamin D supplementation will be initiated. For those whose 25(OH)D is 10.1-20.0 ng/mL, 4000 IU of daily vitamin D₃ will be provided, those between 20.1-30.0 ng/mL will receive 2000 IU daily. Supplementation will be provided as needed up to 500 mg of calcium and 4000 IU D₃.

5.2 ABL initiation

After screening labs have been reviewed and eligibility is confirmed, subjects in the treatment group will start daily ABL. As noted above, this will be initiated 12 weeks before scheduled TKA. If ABL is started greater than 12 weeks after screening, all DXA scans should be repeated at the treatment initiation visit. ABL will be administered daily for 18 months via self subcutaneous injection of 80 mcg. Each pen may be used for 30 days, as most pen volume exceeds this need, pens will be labeled with a start date. Research staff will call subjects each month and remind them to change out pens. A 3-month supply of ABL, vitamin D and calcium if needed, will be dispensed to subjects via mail or in person. For those having preparation mailed, the study coordinator will call to confirm package receipt, review dosing instructions and discuss adverse events. Those preferring live interaction will be offered video (e.g., facetime) or in person visits to pick-up supplies, review ABL dosing and meet with the study coordinator. A blood collection visit to measure serum calcium will be scheduled 4 weeks \pm 5 days after initiating ABL.

5.3 Treatment Follow-up

Only subjects in the treatment group will return to the OCRP for total calcium measurement. For any pre-dose serum calcium value that is >10.5 mg/dL, the hypercalcemia will be confirmed by prompt retesting. If a participants' pre-dose serum calcium is >10.5 mg/dL on repeat testing, calcium and vitamin D supplementation will be withheld and the serum calcium repeated 1-2 weeks later. If serum calcium is \leq 10.5 mg/dL, supplementation will not be restarted and ABL treatment continued. If hypercalcemia (> 10.5 mg/dL) persists the ABL dose will be reduced to 40 mcg. In this situation, a fasting serum calcium will be repeated in 1-2 weeks. If hypercalcemia (>10.5 mg/dL) persists despite dose reduction treatment will be discontinued and study participation terminated. Finally, subjects will be questioned regarding adverse events, falls and fractures; a physical exam or VFA may be performed if indicated per an investigator.

5.4 Pre-TKA Study Visit

All subjects will have TKA surgery approximately 3 months after their screening DXA visit, depending on the surgery schedule. The osteopenic group must have screening data at least 4 weeks prior to but not more than 6 months before this visit. The osteoporotic group must have received at least 8 weeks of ABL prior to this visit. Such variability is acceptable as this reflects clinical care and the primary comparison is BMD change from immediately prior to surgery to 15 months after TKA. As the usual wait time for surgery scheduling in our facility is ~2 months, this should not present a major impediment to study recruitment. The week prior to their scheduled TKA surgery all subjects will return to the OCRP and have repeat lumbar spine, bilateral femur/hip (including distal femur), forearm, PA & bilateral knee and total body DXA measurement, BIS, blood collection and adverse event assessment. Calcium and vitamin D₃ will be dispensed as appropriate. Additionally, subjects will be questioned regarding adverse events, falls and fractures; a physical exam or VFA may be performed if indicated per an investigator. If surgery is delayed for any reason, the study physician will determine if study continuation is appropriate and adjust the study visit timeline as necessary, this may include repeating laboratory tests and/or DXA exams.

5.5 6-month

All subjects will return to the OCRP for DXA (lumbar spine, bilateral femur/hip (including distal femur), forearm, total body, PA & lateral knee), BIS measurement and blood collection. Subjects will be questioned regarding adverse events, falls and fractures and PRO questionnaires will be completed; a physical exam or VFA may be performed if indicated per an investigator. Calcium and vitamin D will be dispensed as needed.

5.6. 15-month

All subjects will return to the OCRP for DXA (lumbar spine, bilateral femur/hip (including distal femur), forearm, PA & lateral knee and total body), BIS measurement and blood collection. Subjects will be questioned regarding adverse events, falls and fractures and PRO questionnaires will be completed; a physical exam or VFA may be performed if indicated per an investigator.

5.7 DXA Knee Precision

As PA and lateral knee bone density measurement is a new method, some assessment of technique reproducibility is indicated. The field standard is to acquire replicate scans by the same technologist in 30 subjects with repositioning in between. This will be acquired in 30 subjects volunteering for these additional scans at either the 6 or 15 month visit. A subject cannot volunteer to have this procedure twice, and one technologist will be identified to perform all scans.

5.8 Study participant recruitment and retention

Subjects will be recruited through the UW Total Joint Program and referred to the study at the time of their TKA consultation visit. Clinic staff will notify patients of the study and give them contact information to the OCRP study staff. Preliminary eligibility will be assessed via phone, and a screening visit scheduled as appropriate. To engage the untreated osteopenic group, we propose to share their 15-month post TKA BMD data.

5.9 Subject Discontinuation or Early Termination

Subjects will be informed that they have the right to withdraw from study participation at any time for any reason without prejudice to their medical care. The Investigator must withdraw subjects for the following reasons:

- Hypercalcemia (two consecutive measurements of > 10.5 mg/dL) that persists despite ABL dose reduction.
- Severe hypersensitivity to abaloparatide
- Inability to complete study procedures
- Lost to follow-up

The Investigator may withdraw subjects for any of the following reasons:

- Serious adverse events
- Non-compliance or protocol violations
- Incident vertebral or non-vertebral fragility fracture
- Other situations that may harm subjects or compromise study integrity

All subjects withdrawn prior to completing the study should be encouraged to have study procedures scheduled for the Month 15 visit as deemed appropriate by the PI. Subjects who discontinue or are withdrawn from the study will not be replaced.

6.0 STUDY PROCEDURES

6.1 DXA and BIS performance

Lumbar spine, bilateral femur/hip, forearm, total body and VFA DXA will be performed in the routine clinical manner per ISCD best practice recommendations using a Lunar iDXA (GE Healthcare). Prior to DXA, height will be measured with a wall-mounted stadiometer and weight with a calibrated analogue scale. Distal femur measurements will be obtained as described in prior work by Blaty et. al.²³ Briefly, the AFF feature of the Lunar enCORE software will be used to acquire a full femur DXA scan that starts at the proximal end of the tibia and continues beyond the greater trochanter. The DXA software is used to measure femur length and distances at 15%, 25% and 60% are calculated. Marker lines are then drawn 1 cm beyond each calculated distance and the top of a 2 cm ROI is placed at this point, thereby centering the ROI around 15%, 25% and 60% regions on the femur. Additionally, cortical width measurements of a 0.25mm cross-section will be extracted at each of these 3 defined points to evaluate changes in cortical thickness. Standard clinical DXA results will be shared with participants at screening, 15-month and early termination visits. Correspondence with primary health care providers and/or UW Total Joint Program staff will occur per subject preference. Additionally, PA & lateral bilateral knee scans will be acquired to determine utility of this technology in pre-surgical bone health assessment and post-surgical evaluation of skeletal change. Specific acquisition and analysis approaches will be determined based on available literature²⁴⁻²⁶

Bioimpedance spectroscopy (BIS) will be performed using the ImpediMed Imp SFB7 Body Composition Analyzer to assess body composition, as described in prior studies.⁴² This is a commercially available FDA approved device to measure body composition used in research, typically not in a clinical application. Briefly, subjects will lay on their back and adhesive tabs (leads) are placed on their hands and feet to connect cables leading to the BIS instrument, which will deliver small constant current, typically 200 uA RMS, with in the frequency range of 4 kHz to 1000 kHz sequentially, between two current electrodes spanning the body. Various leads placement combinations will generate fat free body composition measurements of the whole body and segmented arms and legs.

6.2 Calcium/vitamin D

Calcium citrate, 500mg, will be provided to those needing supplementation to meet the 1000-1200 mg daily intake recommendation. Additionally, vitamin D₃ (cholecalciferol) 2000 IU will

be provided as needed per protocol section 5.1. Subjects will be allowed to supply their own supplements as long as they adhere to protocol dosing regimens.

6.3 ABL training

Study staff will train subjects in the treatment arm to administer ABL at the screening visit using the Radius ABL IFU, which will be given to subjects for reference. Study staff will review training at the time dosing starts either via tele/video communication or in person.

6.4 Laboratory

A comprehensive metabolic panel, calcium and PTH will be measured at the UW Clinical Laboratories per their standard clinical approach. Vitamin D research best practices require 25(OH)D measurements be performed using chromatography-based methodologies, consequently, 25(OH)D will be measured in the clinical laboratory using high performance liquid chromatography (HPLC).

7.0 DATA INTEGRITY

The OCRP research staff will ensure that appropriate approvals and documentation are in place per Federal and local requirements, including posting on clinicaltrials.gov. Additionally, they will design data collection tools, collect, clean and prepare all data for analysis by the statistician. In brief, data will be dually entered into Excel files, thus validating all entries. Ideally, dual-entry will be performed by different individuals; should it be necessary to have the same individual enter data, at least seven days will transpire between data entry cycles. Entry will then be compared and any discrepancy between entries will be corrected and validated.

8.0 POWER CALCULATION AND DATA ANALYSIS PLAN

Specific Aim 1: Sample size justification: Based on previously collected data by this study team, we assume that the osteoporotic patients will have an average (SD) BMD prior to surgery of 1.15 g/cm² (0.2). We hypothesize that on average there will be minimal (< 0.02 g/cm²) bone loss at the 15 month follow-up. With a SD of 0.2, if we have follow-up data on at least 21 osteoporotic patients, we will have 86% power with a two-sided one-sample t-test to conclude that ABL effectively reduces bone loss less than 0.16g/cm². To account for up to 26.5% attrition previously reported in the pivotal ABL study,⁴³ we will enroll and treat 29 osteoporotic patients under going TKA.

Specific Aim 2: Sample size justification: If we assume that there will be a medium to large (Cohen's D = 0.65) effect in the paired differences of BMD from baseline to 15 months post TKA in an osteopenic population, then we will need to recruit 21 patients to have 80% power to detect this effect size. To account for up to 26.5% attrition we will enroll and follow 29 osteopenic patients under going TKA.

Baseline demographic and characteristic variables will be summarized with mean (SD), median (IQR), or N (%) based on the statistical distribution of the variable. The primary comparison will be on the change in distal femoral BMD at 25% ROI of the surgical leg from 3 months pre-TKA to 15 months post-TKA. We will test for a significant difference in the osteoporotic population versus a null hypothesis of -0.16g/cm² with a two-sided one-sample t-test. Similarly, we will test for a significant change in BMD in the osteopenic population versus a null hypothesis of 0g/cm² with a one-sample t-test. Exploratory analyses will compare the change in BMD over time between osteoporotic patients treated with ALB and untreated osteopenic patients with repeated measures ANOVA while controlling for age, sex, and BMI as covariates and treating patient as a random effect. Changes over time in secondary variables

will be estimated by paired differences and tested for significant changes from baseline with paired t-tests. All tests will be conducted at a 5% significance level.

If a subject drops out or is lost to follow-up prior to data collection at time of surgery, they will be completely removed from the study and a new participant will take their place. If a subject drops out or is loss to follow-up after surgery, they will remain in the study and we will implement various data imputation methods like last observation carried forward (LOCF) and linear prediction imputation.

8.1 Study timeline

This study is planned to span 3 years (Table 1). The first month will be spent finalizing the protocol, designing recruitment material and establishing resources in the UW system. Months 2-3 will be dedicated to obtaining IRB approval and ensuring the project is compliant with other regulatory requirements. Study tools, materials and recruitment pathways will also be finalized during this time, with the anticipation that subject recruitment will begin in month 4. Our goal is to enroll 5-6 subjects per month and complete study enrollment in 12 months. This has our final visits occurring in year 3, around 33 months. In year 3, study staff will dedicate time to conducting final visits, cleaning data and performing final analyses. It is planned that preliminary data will be used to submit abstracts to key meetings in the bone fields (Orthopedics and Medicine) including AAHKS, AOA, ASBMR, ISCD and perhaps IOF. Final manuscripts will be submitted for publication in year 3.

Table 2: Study Timeline

	Year 1												Year 2												Year 3											
Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Finalize Protocol																																				
Regulatory																																				
Study Prep																																				
Recruitment																																				
Conduct																																				
Data Clean																																				
Analysis																																				
Publication																																				

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