PROTOCOL OP0002 AMENDMENT 3

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ROMOSOZUMAB TREATMENT IN POSTMENOPAUSAL CHINESE WOMEN WITH OSTEOPOROSIS

PHASE 3

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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AE	adverse event
AFF	atypical femoral fracture
ALN	alendronate
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BMD	bone mineral density
BP	blood pressure
BSAP	bone-specific alkaline phosphatase
BTM	bone turnover marker
BW	body weight
CDE	Center of Drug Evaluation
CDMS	clinical data management system
CI	confidence interval
COVID-19	coronavirus disease 2019
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
CSR	Clinical Study Report
CV	cardiovascular
DMC	Data Monitoring Committee
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report form
EOS	End-of-Study
ES	Enrolled Set
ET	Early Termination
FAS	Full Analysis Set
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
HDL	high density lipoprotein
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IMP	investigational medicinal product
iPTH	intact parathyroid hormone
IRB	Institutional Review Board
IRT	interactive response technology
iv	intravenous(ly)
L	lumbar
LDL	low density lipoprotein
LLOQ	lower limit of quantification
LS	least squares
MedDRA®	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NHANES	National Health and Nutritional Examination Survey
OC	osteocalcin
OH	hydroxy
OL	open-label
ONJ	osteonecrosis of the jaw
P1NP	procollagen type 1 N-telopeptide
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamic Per-Protocol Set
PFS	prefilled syringe(s)
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per-Protocol Set
po	orally

PPS	Per-Protocol Set
PS	Patient Safety
PT	preferred term
PTH	parathyroid hormone
QM	every month
QW	every week
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
sCTX	serum type I collagen C-telopeptide
SD	standard deviation
SERM	selective estrogen receptor modulator
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SQ0, SQ1, SQ2, SQ3	visual semiquantitative grading scale for vertebral fractures on lateral spine x-rays: SQ0=no fracture; SQ1=mild fracture; SQ2=moderate fracture; SQ3=severe fracture (Genant et al, 1993)
SS	Safety Set
T4	thyroxine
TEAE	treatment-emergent adverse event
TMF	trial master file
TPTD	teriparatide
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WHO	World Health Organization

1 SUMMARY

OP0002 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study followed by an Open-Label (OL) Treatment Period to evaluate the efficacy, safety and tolerability of romosozumab treatment in postmenopausal Chinese women with osteoporosis across approximately 30 study sites in mainland China.

The study consists of 4 study periods: a Screening Period (Day -35 to Day -1); a 6-month Double-Blind, Placebo-Controlled Period; a 6-month OL Treatment Period; and a 3-month Follow-Up Period.

Overall, approximately 300 postmenopausal Chinese women with osteoporosis are expected to be randomized in the study to meet the study objectives. Subject eligibility will be confirmed during the Screening Period.

Eligible subjects will be randomized, stratified by age, in a 2:1 ratio to receive romosozumab 210mg subcutaneously (sc) every month (QM) or matched placebo sc QM in a blinded manner for 6 months. From Screening until the End-of-Study (EOS) Visit, subjects will be required to take daily calcium and vitamin D supplementation.

Upon completion of the 6-month Double-Blind, Placebo-Controlled Period, all subjects will enter the OL Treatment Period and receive romosozumab 210mg sc QM for 6 months in an OL fashion. During this period, all subjects will receive active treatment (romosozumab) allowing for the collection of efficacy and safety data for an additional 6 months (a total of 12 months for subjects initially randomized to romosozumab and 6 months for those initially randomized to placebo).

Subjects can decide to discontinue investigational medicinal product (IMP) but continue participation in the study. However, subjects who withdraw early from the study should complete the Early Termination (ET) Visit. Subjects who withdraw from the study will not be replaced.

After completing the OL Treatment Period, subjects will be followed up for an additional 3 months and will complete the EOS Visit (Month 15). Subject participation in the study is concluded after the EOS Visit. Subjects who test positive for neutralizing antibodies to romosozumab at the EOS Visit or ET Visit will be asked to return for additional follow-up testing for up to 1 year after final administration of investigational medicinal product (IMP).

No interim analysis is planned for the study. An independent Data Monitoring Committee (DMC) will be formed to monitor the safety of subjects during the study.

The 6-month analysis of efficacy and safety will be performed using the data obtained from the 6-month Double-Blind, Placebo-Controlled Period. The primary variable of the 6-month analysis is the evaluation of the effect of romosozumab treatment compared with placebo on the percent change in bone mineral density (BMD) at the lumbar spine, as assessed by dual-energy x-ray absorptiometry (DXA). In addition, analyses of secondary efficacy variables include evaluation of the effect of romosozumab treatment compared with placebo on the percent change in BMD at the total hip and femoral neck. The pharmacokinetic (PK) variable (serum concentrations of romosozumab), pharmacodynamic (PD) variables (bone turnover markers [BTMs]), and safety variables will be assessed.

The final analysis will be performed after all subjects have the opportunity to complete the Month 15 Visit. The remaining efficacy, PD, and safety analyses for Month 12 and the safety analyses for the overall study period, ie, the period from the start of double-blind treatment to the Month 15 Visit for each subject, will be evaluated. The serum concentrations of romosozumab after 12 months of treatment (continuing 6 months of romosozumab in subjects who are initially randomized to 6 months of romosozumab treatment) and 6 months of treatment (in subjects who are randomized to placebo for 6 months and transition to romosozumab for 6 months) will be assessed.

2 INTRODUCTION

2.1 Background of product

Romosozumab is a humanized immunoglobulin G (IgG) monoclonal antibody that binds to and inhibits sclerostin (Poole et al, 2005; van Bezooijen et al, 2004; Winkler et al, 2003; Balemans et al, 2001; Brunkow et al, 2001). Romosozumab has a dual effect on bone, increasing bone formation and decreasing bone resorption (McClung et al, 2014; Ominsky et al, 2014; Padhi et al, 2011), leading to rapid and substantial gains in BMD, improved bone structure and strength, and fracture risk reduction.

2.2 Global clinical development program

A comprehensive clinical program has been developed globally for romosozumab and comprises of approximately 14,000 subjects across 19 clinical studies conducted in North America, Europe, Asia (including Hong Kong, Taiwan, Korea, and Japan), and other regions and included healthy subjects, postmenopausal women with osteoporosis or low BMD, and men with osteoporosis.

Population PK/PD analyses were performed, including development of a population PK model, a dose-response model (which described the relationship between dose and BMD gains at both lumbar spine and total hip), and a concentration-response model (which described the relationship between romosozumab concentrations, BTMs [procollagen type 1 N-telopeptide (P1NP) and serum type I collagen C-telopeptide (sCTX)], and BMD gains at the lumbar spine).

The PK profile of romosozumab is typical for an IgG monoclonal antibody, showing nonlinear PK at low doses due to target-mediated drug disposition. Dose-proportional increases in exposure are observed for doses of 140mg and higher. The PK is linear over time. No dose adjustments are required on the basis of patient characteristics. Population PK analysis identified weight, age, gender, race (Japanese vs non-Japanese), and estimated glomerular filtration rate as having an impact on PK, with the effect of body weight (BW) having the greatest impact (decreasing BW resulting in increased exposure). However, PK/PD modelling demonstrated BW had minimal impact on BMD gain at 12 months (±15% compared to a typical subject).

Two studies conducted in postmenopausal Japanese women, a single-dose Phase 1 study (20090378) and a Phase 2 efficacy and safety study (20101291), showed similarity in dose response in the Japanese population versus the global population of postmenopausal women.

Based on the Phase 2 dose-ranging study results (20060326), 2 global Phase 3 fracture studies (20070337 [FRAME], and 20110142 [ARCH]) were conducted in postmenopausal women with osteoporosis using 210-mg QM dosing for 12 months followed by antiresorptive therapy to demonstrate reduction of fracture risk.

A 12-month romosozumab treatment duration in the global Phase 3 studies was supported by the following considerations:

- Substantial increases in BMD were observed during 12 months of romosozumab administration in the Phase 2 dose-ranging study. At 12 months, the 210-mg QM dosing regimen resulted in a BMD increase from baseline of 11.3% at the lumbar spine and 4.1% at the total hip. The BMD increases were greater with the romosozumab dose of 210mg QM compared with alendronate (ALN), teriparatide (TPTD), and placebo.
- Increases in bone formation as assessed with bone formation markers were not apparent beyond 12 months in the Phase 2 dose-ranging study. For the romosozumab 210-mg QM dosing regimen, the median P1NP was 10.2% below baseline 1 week after the Month 12 dose; in contrast to an increase of 82.7% above baseline 1 week after the Day 1 dose.
- Based on Month 18 data available for the 210-mg QM treatment group in the Phase 2 dose-ranging study, beyond Month 12, the BMD appeared to increase more gradually, likely primarily due to the antiresorptive effect and due to attenuation of the bone-forming effect as mentioned above.

The 210-mg romosozumab QM dosing regimen was selected for the global Phase 3 program based on the following data:

- In the Phase 2 dose-ranging study, the romosozumab 210-mg QM dosing regimen resulted in a greater increase in BMD at the lumbar spine and total hip at 12 months compared with other romosozumab dosing groups.
- The romosozumab 210-mg QM dosing regimen resulted in the largest and most prolonged increase in markers of bone formation, including bone-specific alkaline phosphatase (BSAP), P1NP, and osteocalcin (OC) in the Phase 2 dose-ranging study. Median P1NP and OC levels remained above baseline up to Months 6 and 9, respectively, and median BSAP levels remained above baseline up to Month 12. In comparison, the 140-mg QM dosing regimen increased markers of bone formation for 3 to 6 months.
- The incidence of adverse events (AEs) in the Phase 2 dose-ranging study was not dose related, and the incidence of neutralizing antibodies against romosozumab was low (2%) and similar across QM doses. Thus, the safety profile of the 210-mg QM dosing regimen does not appear to be appreciably different from that of lower doses.

The sequential treatment of romosozumab followed by an antiresorptive was selected for the Phase 3 program based on the following findings:

- The Phase 2 findings provided early evidence that 12 months of romosozumab treatment at a dose of 210mg QM may lay the foundation of increased bone mass that translated into significant antifracture efficacy.
- Because the BMD gains are reversible when treatment is discontinued, follow-on with an antiresorptive is recommended to preserve this benefit. This established the concept of the sequential therapy of romosozumab for 12 months followed by an antiresorptive therapy, which was used for the design of the Phase 3 studies.

The ability of romosozumab to reduce the risk of fracture in postmenopausal women with osteoporosis has been demonstrated in the 2 pivotal Phase 3 fracture studies:

20070337

This Phase 3, multicenter, parallel-group study in women with postmenopausal osteoporosis was designed to evaluate if romosozumab treatment for 12 months compared with placebo was effective in reducing the incidence of new vertebral fractures, and if romosozumab treatment for 12 months followed by denosumab treatment for 12 months was effective in reducing the incidence of new vertebral fractures compared with 12 months of placebo followed by denosumab treatment for 12 months. The study met the coprimary endpoints by reducing the incidence of new vertebral fracture through Months 12 and 24 in postmenopausal women with osteoporosis treated with romosozumab. Subjects receiving sc injections of romosozumab 210mg QM had a statistically significant 73% reduction in the relative risk of a vertebral fracture through 12 months compared with those receiving placebo ($p < 0.001$). The effect size persisted after both groups were transitioned to denosumab through the second year of treatment. Specifically, through Month 24, romosozumab followed by denosumab reduced the relative risk of new vertebral fracture by a statistically significant 75% compared with placebo followed by denosumab ($p < 0.001$).

20110142

In this Phase 3, multicenter, randomized, double-blind, ALN-controlled study, 4093 postmenopausal women with osteoporosis were randomized in a 1:1 ratio to receive either romosozumab 210mg sc QM (2046 subjects) or ALN 70mg orally (po) every week (QW) (2047 subjects) for 12 months. After the initial 12-month study period, all subjects received ALN while remaining blinded to their initial treatment assignment. The Primary Analysis was performed when clinical fracture events (comprising of nonvertebral fracture or clinical vertebral fracture) were confirmed for at least 330 subjects and all subjects had the opportunity to complete the Month 24 study visit.

The results at the time of the Primary Analysis (median observation time 33 months) demonstrated that treatment with romosozumab for 12 months followed by ALN significantly reduced the incidence of new vertebral fractures through 24 months (coprimary endpoint), clinical fractures (coprimary endpoint), and nonvertebral fractures (key secondary endpoint) in postmenopausal women with osteoporosis at high risk for fracture compared with ALN alone. At 24 months, subjects in the romosozumab treatment group had a statistically significant 50% reduction in the relative risk of a new vertebral (spine) fracture compared with those receiving ALN alone. At the time of the Primary Analysis, subjects in the romosozumab treatment group had a 27% reduction in the relative risk of clinical fracture and a 19% reduction in nonvertebral fractures, compared with those receiving ALN alone. A nominally significant reduction in hip fractures was also observed in subjects in the romosozumab treatment group.

Subject incidence of AEs and serious adverse events (SAEs) were generally well balanced between treatment groups in each study. In the 2 Phase 3 studies (20070337 and 20110142), the number of positively-adjudicated events of atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ) was low. In 20110142, a numerical imbalance in the positively-adjudicated cardiovascular (CV) SAEs was observed between the romosozumab and ALN groups at 12 months. This imbalance was observed specifically for serious cardiac ischemic and

cerebrovascular events, with a higher incidence in the romosozumab group compared with the ALN group (romosozumab: 0.8% for both events; ALN: 0.3% for both events). These findings were not observed at 12 months in the larger, placebo-controlled study in postmenopausal women with osteoporosis (20070337). A causal relationship between romosozumab and CV SAEs has not been established.

Across the studies, the benefit-risk profile of romosozumab is considered favorable. Treatment with romosozumab has demonstrated fracture risk reduction within 12 months, ongoing fracture risk reduction maintained with follow-on antiresorptive therapy, and robust improvement in BMD at the spine and the hip (including in subjects previously treated with antiresorptive therapy).

Further information on the studies mentioned above can be found in Section 5.4.

Refer to the Investigator's Brochure (IB) for more detailed information on romosozumab (eg, pharmacology, quality, nonclinical data, clinical data, and Reference Safety Information).

2.3 Osteoporosis

2.3.1 Prevalence of osteoporosis

Osteoporosis is a condition caused by an imbalance of osteoblast and osteoclast activity resulting in progressive loss of bone density and strength, which can lead to fragility fractures and result in patient burden and increased mortality (Cummings and Melton, 2002; NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001).

The lifetime risk of osteoporotic fracture overall is 40% to 42% among women in Western Europe and Australia, and approximately 50% among white women aged 50 years and older in the US (National Osteoporosis Foundation, 2014; Office of the Surgeon General, 2004). Estimates from the USA, Europe, Australia, Canada, and Japan suggest that across these countries approximately 44 million women aged 50 years or older have postmenopausal osteoporosis (Wade et al, 2014; Hernlund et al, 2013) and approximately 4.5 million suffer osteoporotic fractures annually (Hernlund et al, 2013; Wade et al, 2012; Burge et al, 2007). The number of osteoporosis-related fractures is projected to increase substantially as the world's population ages. While osteoporosis and osteoporotic fractures are most commonly associated with postmenopausal women, these are also observed in men.

2.3.2 Burden of the disease

Osteoporosis and resulting fragility fractures are a costly burden to patients, payers, and society. In particular, fractures lead to significant impairment in mobility, which can have a long-lasting impact on social and physical functioning. In addition, fractures and associated functional losses lead to high levels of disability resulting in increased use of long-term institutional care and rehabilitation services.

In postmenopausal women and in men, fragility fractures confer ongoing pain and discomfort, which impact physical function, emotional status, self-care, and usual activities, resulting in long-term health-related quality of life reductions similar to those seen with chronic diseases such as diabetes, arthritis, and lung disease. Moreover, fragility fractures, particularly those of the hip or spine, are associated with increased mortality, which may persist for several years.

This mortality risk increases even further with the occurrence of a second fracture (Bliuc et al, 2009; Johnell et al, 2004).

Prior fracture is among the strongest risk factors for subsequent fracture. Hip fractures result in a 2.5-fold increased risk of subsequent fractures, and vertebral fractures result in a 5-fold increased risk for subsequent vertebral fracture and a 2- to 3-fold increased risk for fractures at other sites (National Osteoporosis Foundation, 2014; van Helden et al, 2006; Colón-Emeric et al, 2003). The incidence of a new vertebral fracture in the year after a previous fracture is about 19% (Lindsay et al, 2001). Van Geel and colleagues, in a population-based study of 4140 postmenopausal women, found the risk of subsequent clinical fracture (which encompasses nonvertebral fractures and symptomatic vertebral fractures) was about double the risk of a first fracture (van Geel et al, 2009). Of all subsequent fractures, 23% occurred within 1 year after the first fracture and 54% occurred within 5 years.

2.3.3 Prevalence of osteoporosis in China

Although limited, epidemiology data on osteoporosis are available for China as shown in Table 2–1.

Table 2–1: Epidemiology data on osteoporosis in China

	Total population			50 years and older		
	General	Male	Female	General	Male	Female
2006 survey[a]	NA	4.2%	12.8%	15.7%	8.8%	30.8%
2009 review[b]	13%	NA	NA	NA	22.4%	40.1%
2016 meta-analysis[c]	NA	15.33%	25.41%	34.65%	NA	NA

NA=not applicable
[a] China Health Promotion Foundation. White Paper, 2008
[b] Wang et al, 2009
[c] Chen et al, 2016

The prevalence rate of osteoporosis in China has increased in past decades. A 2016 meta-analysis showed that the prevalence rate in 2003 to 2008, 2009 to 2011, 2012 to 2015 was 14.94%, 23.65%, and 27.96%, respectively. Similar to the global population, in China the prevalence rates of osteoporosis increased with age. In the 2016 meta-analysis, the prevalence rate by age group (40 to 50, 50 to 60, 60 to 70, 70 to 80, and 80+ years) was 8.88%, 19.57%, 35.1%, 43.48%, and 56.10%, respectively (Chen et al, 2016). This indicates that aging is one of the main risk factors of osteoporosis. China has a population of 1.4 billion, which is about 18.9% of the world population. The population aged over 60 years had increased from 130 million (10.97%) at the end of the twentieth century to 210 million (15.5%) in 2015 (Osteoporosis and Bone Mineral Research Society of the Chinese Medical Association, 2017; Lin et al, 2015). The National Statistics Bureau data stated that in China in 2016 around 418 million inhabitants were over 50 years of age, of whom, 150 million had osteoporosis. Due to the aging population in China, osteoporosis will gradually become a major public health problem.

Osteoporotic fracture, one of the most severe complications of osteoporosis, is prevalent among the elderly population with osteoporosis. This is considered to be a fracture from low-energy

trauma that is defined as a fall from a standing height or less, or a trauma that would not give rise to fracture in a healthy individual. A cross-sectional and population-based study conducted in Shanghai showed that the prevalence of osteoporotic fractures in the elderly was 15.9% in females and 14.3% in males. A large national study in Beijing found that the prevalence of fractures in the elderly was 26.6% (Lin et al, 2015).

Hip fracture can lead to devastating consequences, causing both significant morbidity and excess mortality. The average annual number of hip fractures in people older than 50 years, according to the Beijing Ministry of Health, increased from 479 to 2423 in women and from 441 to 1586 in men between 1990 and 2004. Meanwhile, from 2002 to 2006, the rates of hip fractures for those aged 50 years or older increased by 58% in women and 49% in men. Similar trends can also be seen in other areas of China including Taiwan, Chongqing, and Hefei. A patient who has survived a hip fracture usually exhibits decreased mobility, impaired quality of life, more dependence on family, and increased demand for medical caregivers and social services, as well as a substantial physical, mental, and financial burden. The rate of disability is up to 50% and the mortality is as high as 15% to 33% in the first year after the hip fracture. Worse still, about 28% of females and 37.5% of males who suffer a hip fracture die by the second year. Similar to other countries, among all types of osteoporotic fractures, the cost of hip fractures is the highest (Lin et al, 2015).

Despite being the most common complication of osteoporosis, accounting for almost 50% of all osteoporotic fractures, vertebral fractures have received less attention compared to hip fractures. The prevalence of vertebral fracture is increasing in association with aging. The prevalence of vertebral fractures is lower than 20% for people aged 50 to 69 years in Beijing, Chengdu, and Shanghai, and for people aged 70 to 79 years is 19%, 25.1%, and 25.42%, respectively. However, for people over 80 years of age, the prevalence of vertebral fractures is above 36% in all 3 cities (Lin et al, 2015).

In China in 2015, 2.69 million major osteoporotic fractures (vertebral, hip, wrist fractures) occurred and cost 72 billion RMB, with estimates of osteoporotic fractures reaching 4.83 million in 2035 and 5.99 million in 2050. Meanwhile, the cost in 2035 and 2050 is estimated to be $19.92 billion and $25.43 billion, respectively (Si et al, 2015). Overall, beyond the burden to the patients and families, osteoporosis and associated fractures represents also a high financial burden to society.

2.3.4 Current treatments for osteoporosis and their limitations

Despite there being a broad range of available therapies, there is an existing unmet medical need in osteoporosis, especially for patients who are at increased risk of fractures. The efficacy of antiresorptive therapies for the treatment of osteoporosis has been well documented. And yet, for patients with osteoporosis at increased risk of fracture, notably in those who have had a recent fracture, the time to onset of effect with current therapies may leave certain groups of patients insufficiently protected early in treatment. For some antiresorptive therapies (ALN, ibandronate, and bazedoxifene), studies have shown that it takes 3 years or longer to demonstrate a significant reduction in the risk of vertebral, nonvertebral, or clinical fracture. Given that patients with osteoporosis are most likely to suffer subsequent fractures in the 2-year period immediately following their previous (or first) fracture, there is an immediate need for treatments that lead to clinically meaningful improvements in BMD within this 2-year period.

In addition to efficacy concerns, nitrogen-containing bisphosphonates such as ALN, risedronate, and ibandronate have been associated with gastrointestinal side effects. Alendronate and oral ibandronate are contraindicated in patients with disorders involving delayed passage through the esophagus, such as esophageal stricture and achalasia (Boniva® package insert, 2016; Bonviva Summary of Product Characteristics [SmPC]; Fosamax® package insert, 2015; Fosavance SmPC). Furthermore, drugs of this class have to be administered with an adequate volume of water at the time of awakening every morning when taken po, and patients receiving this therapy are not permitted to lie down, to ingest anything else but water, nor to take other oral medication for at least 30 minutes after each dose. Because of these limitations, there are patients who cannot begin or continue to use this class of drugs or who cannot comply with the instructions for dosing, despite an increased risk of fracture.

Although other antiresorptive therapies such as risedronate, raloxifene, and denosumab demonstrated significant reductions of 60% to 68% in the risk of vertebral fractures in their respective pivotal clinical studies within 1 year (Cummings et al, 2009; Maricic et al, 2002; Harris et al, 1999), bone-forming therapies can provide larger improvements in bone structure and strength; however, only 1 class of bone-forming therapies is available – parathyroid hormone (PTH) analogs.

The PTH fragment, TPTD, is the only widely available bone-forming agent. Teriparatide has some limitations, such as the need for daily injections, a relatively small BMD increase at the hip (2.6% total hip in 19 months and even more limited in patients previously exposed to a bisphosphonate [Miller et al, 2008; Neer et al, 2001]), and a special warning of potential risk of osteosarcoma, limiting the treatment duration to 24 months in a lifetime. For TPTD, the time to onset of effect may leave patients relatively unprotected early in treatment. According to 1 study, about 12% of patients had a fracture in the 2 years following initiation of TPTD use, even in persistent users, and most of those fractures (64%) occurred during the first year on therapy (Bonafede et al, 2015). Furthermore, transitioning patients from a bisphosphonate to TPTD, which is more common than use of TPTD as first-line treatment, can lead to significantly reduced or delayed gains in BMD over the first year of treatment relative to treatment-naïve subjects, particularly at the hip (Miller et al, 2008; Obermayer-Pietsch et al, 2008; Ettinger et al, 2004). In the USA, another bone-building agent has been recently approved, abaloparatide (Tymlos™, Radius Health, Inc, MA, USA) for postmenopausal women with osteoporosis at high risk for fracture due to a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have not responded to or are intolerant to other available osteoporosis therapy (Food and Drug Administration approval date: 28 Apr 2017). This product is not currently approved in EU or China, and like TPTD, abaloparatide is administered by daily injection.

2.3.5 Current treatment approach for osteoporosis in China

In China, the updated guideline of diagnosis/treatment of osteoporosis has been published in 2017 by the Osteoporosis And Bone Mineral Research Society of the Chinese Medical Association.

The diagnosis of osteoporosis is based on BMD and history of fragility fracture. For BMD, DXA exam at the lumbar spine or proximal femur is the gold standard for diagnosis. The T-score evaluation is based on the World Health Organization (WHO) criteria (2007) and using database of healthy peak BMD. Other than BMD exams and fragility fractures, BTMs and blood tests are

used for supportive and differential diagnosis. The BMD assessments can be used as a surrogate for efficacy evaluation and fracture risk evaluation, consistent with Western countries.

Besides the basic treatment including lifestyle change, calcium and vitamin D supplementation, pharmacologic therapies are indicated to manage osteoporosis patients. There are 3 categories of drugs available in China: i) antiresorptive agents, ii) bone-forming agents, and iii) others. The majority of available pharmacologic therapies belong in the category of antiresorptive agents, among which, bisphosphonates are the most widely used (Table 2–2). Further information on the antiresorptive and bone-forming agents is presented in Section 2.3.4. In China, ALN has an indication of osteoporosis in males. Calcitonin has good efficacy on ostalgia, but has a limitation of 3 months continuous usage due to risk of malignancies.

Overall, even though some treatment options available elsewhere are not yet available in China (eg, abaloparatide, bazedoxifene, denosumab), the basic treatment approach for osteoporosis in the elderly in China is basically similar to other countries. Thus, there remains an unmet medical need in China for a therapy that rapidly increases bone mass and bone strength and delivers fracture risk protection, which is particularly important in patients who have already suffered a fracture or are otherwise at increased risk for fracture in the near term.

Table 2–2: Pharmacologic therapies for postmenopausal osteoporosis available in China, EU, and USA

Drug category	Drug class	Drug name	China	EU	USA
Antiresorptive	Bisphosphonates	Alendronate	Yes	Yes	Yes
		Ibandronate	Yes	Yes	Yes
		Risedronate	Yes	Yes	Yes
		Zoledronic acid	Yes	Yes	Yes
	Calcitonin	Calcitonin	Yes	Yes	Yes
	Hormone replacement therapy	Estrogen	Yes	Yes	Yes
	Selective estrogen receptor modulator	Raloxifene	Yes	Yes	Yes
		Bazedoxifene	No	Yes	Yes
	RANK ligand inhibitor	Denosumab	Yes	Yes	Yes
Bone-forming agent	Parathyroid hormone	Teriparatide	Yes	Yes	Yes
	Parathyroid hormone-related protein (PTHrP)	Abaloparatide	No	No	Yes
Other		Vitamin D analogous	Yes	Yes	Yes
		Strontium	No[a]	No[a]	No

RANK=receptor activator of nuclear factor kappa-B
[a] Servier (manufacturer of strontium ranelate) withdrew their brand medicine Protelos (strontium ranelate) in 2017.

2.4 Rationale for the study

UCB proposes to conduct a Phase 3 study to evaluate the efficacy and safety of romosozumab treatment in postmenopausal Chinese women with osteoporosis. The requirements for this study and the study design were discussed between the sponsor and Center of Drug Evaluation (CDE) at the Chinese Agency in 2018.

3 STUDY OBJECTIVES

3.1 Objectives for the Double-Blind, Placebo-Controlled Period

3.1.1 Primary objective

The primary objective is to evaluate the effect of treatment with romosozumab for 6 months compared with placebo on the percent change in BMD at the lumbar spine in postmenopausal Chinese women with osteoporosis.

3.1.2 Secondary objective

The secondary objective is to evaluate the effect of treatment with romosozumab for 6 months compared with placebo on the percent change in BMD at the total hip and femoral neck in postmenopausal Chinese women with osteoporosis.

3.1.3 Other objectives

The other objectives are as follows:

- To evaluate the effect of treatment with romosozumab for 3 months compared to placebo on the percent change in BMD at the lumbar spine, total hip, and femoral neck in postmenopausal Chinese women with osteoporosis.
- To evaluate the effect of treatment with romosozumab at 1-, 3-, and 6-month time points compared with placebo on the percent changes in BTMs in postmenopausal Chinese women with osteoporosis. The BTMs include the bone formation marker P1NP and the bone resorption marker sCTX.
- To characterize serum concentrations of romosozumab in postmenopausal Chinese women with osteoporosis who are randomized to romosozumab treatment.

3.1.4 Safety objective

The safety objective is to characterize the safety and tolerability of romosozumab treatment for 6 months compared with placebo in postmenopausal Chinese women with osteoporosis.

3.2 Objectives for the Open-Label Treatment Period

3.2.1 Secondary objective

The secondary objective is to describe the percent change in BMD at the lumbar spine, total hip, and femoral neck in postmenopausal Chinese women with osteoporosis who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (a total of 12 months of romosozumab treatment).

3.2.2 Other objectives

The other objectives are as follows:

- To describe the percent change in BMD at the lumbar spine, total hip, and femoral neck in postmenopausal Chinese women with osteoporosis who transition to 6 months of romosozumab treatment after initially being randomized to placebo in the Double-Blind, Placebo-Controlled Period.
- To describe the percent changes in BTMs in postmenopausal Chinese women with osteoporosis who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment). The BTMs include bone formation marker P1NP and bone resorption marker sCTX.
- To describe the percent changes in BTMs in postmenopausal Chinese women with osteoporosis who transition to 6 months of romosozumab treatment after initially being randomized to placebo in the Double-Blind, Placebo-Controlled Period. The BTMs include bone formation marker P1NP and bone resorption marker sCTX.
- To describe area under the curve (AUC) for the entire 12-month treatment for P1NP in postmenopausal Chinese women with osteoporosis who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment).
- To characterize the serum concentrations of romosozumab in postmenopausal Chinese women with osteoporosis who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment).
- To characterize the serum concentrations of romosozumab in postmenopausal Chinese women with osteoporosis who are initially randomized to placebo in the Double-Blind, Placebo-controlled Period and transition to romosozumab treatment.

3.2.3 Safety objectives

The safety objectives will be presented for the OL Treatment Period (up to Month 12) and for the overall study period that includes the 3-month Follow-Up Period (for a total of 15 months) as follows:

- To characterize the safety and tolerability of romosozumab treatment in postmenopausal Chinese women with osteoporosis who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment).
- To characterize the safety and tolerability of romosozumab treatment in postmenopausal Chinese women with osteoporosis who are initially randomized to placebo in the Double-Blind, Placebo-Controlled Period and transition to romosozumab treatment.

4 STUDY VARIABLES

4.1 Study variables for the Double-Blind, Placebo-Controlled Period

4.1.1 Efficacy variables

4.1.1.1 Primary efficacy variable

The primary efficacy variable is percent change from baseline in BMD at the lumbar spine at the end of the Double-Blind, Placebo-Controlled Period (Month 6) as assessed by DXA.

4.1.1.2 Secondary efficacy variables

The secondary efficacy variables are as follows:

- Percent change from baseline in BMD at the total hip at the end of the Double-Blind, Placebo-Controlled Period (Month 6) as assessed by DXA.
- Percent change from baseline in BMD at the femoral neck at the end of the Double-Blind, Placebo-Controlled Period (Month 6) as assessed by DXA.

4.1.1.3 Other efficacy variables

The other efficacy variables are percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at Month 3 as assessed by DXA.

4.1.2 Pharmacokinetic and pharmacodynamic variables

4.1.2.1 Other pharmacokinetic variables

The other PK variables are serum trough concentrations of romosozumab at Day 1 (baseline) and at Months 1, 3, and 6.

4.1.2.2 Other pharmacodynamic variables

The other PD variables are percent changes from baseline in P1NP and sCTX at Months 1, 3, and 6.

4.1.3 Safety variables

4.1.3.1 Primary safety variable

The primary safety variable is the overall incidence of treatment-emergent adverse events (TEAEs).

4.1.3.2 Other safety variables

The other safety variables are as follows:

- Changes from baseline in laboratory assessments (serum chemistry and hematology) and shifts from baseline to the worst value between baseline and Month 6.
- Changes from baseline in vital signs.
- Changes from baseline in ECG parameters.
- Clinically significant physical examination findings from baseline through Month 6.
- Incidence of subjects with antiromosozumab antibodies at Day 1 (baseline) and at Months 1, 3, and 6.

4.2 Study variables for the Open-Label Treatment Period

4.2.1 Efficacy variables

4.2.1.1 Secondary efficacy variables

The secondary efficacy variables are as follows:

- Percent change from baseline in BMD at the lumbar spine at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment).
- Percent change from baseline in BMD at the total hip at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment).
- Percent change from baseline in BMD at the femoral neck at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment).

4.2.1.2 Other efficacy variables

The other efficacy variables are percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are initially randomized to placebo in the Double-Blind, Placebo-Controlled Period and transition to romosozumab treatment for 6 months.

4.2.2 Pharmacokinetic and pharmacodynamic variables

4.2.2.1 Other pharmacokinetic variables

The other PK variables are as follows:

- Serum trough concentrations of romosozumab at Months 7, 9, and 12 in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab in the Double-Blind, Placebo-Controlled Period (a total of 12 months of romosozumab treatment).
- Serum trough concentrations of romosozumab at Months 7, 9, and 12 (1, 3, and 6 months of romosozumab exposure, respectively) in subjects who are initially randomized to placebo in the Double-Blind, Placebo-Controlled Period and transition to romosozumab treatment for 6 months.

4.2.2.2 Other pharmacodynamic variables

The other PD variables are as follows:

- Percent changes from baseline in P1NP and sCTX at Months 7, 9, and 12 in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (a total of 12 months of romosozumab treatment).
- Percent changes from baseline in P1NP and sCTX at Months 7, 9, and 12 (1, 3, and 6 months of romosozumab exposure, respectively) in subjects who are initially randomized to placebo in the Double-Blind, Placebo-Controlled Period and transition to romosozumab treatment for 6 months.
- AUC for the entire 12-month treatment period for P1NP in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment).

4.2.3 Safety variables

The safety variables listed below will be assessed during the OL Treatment Period, including some selected safety variables that will be followed up to Month 15, in subjects who are initially randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period and continue with romosozumab for 6 months (for a total of 12 months of romosozumab treatment) and in subjects who are initially randomized to placebo in the Double-Blind, Placebo-Controlled Period and transition to romosozumab treatment for 6 months.

4.2.3.1 Primary safety variable

The primary safety variable is the overall incidence of TEAEs.

4.2.3.2 Other safety variables

The other safety variables are as follows:

- Changes from baseline in laboratory assessments (serum chemistry and hematology) and shifts from baseline to the worst value between baseline and Month 12.
- Changes from baseline in vital signs.
- Changes from baseline in ECG parameters.
- Clinically significant physical examination findings from baseline through Month 12.
- Incidence of subjects with antiromosozumab antibodies at Months 7, 9, and 12, and at the EOS Visit.

5 STUDY DESIGN

5.1 Study description

OP0002 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study followed by an OL Treatment Period to evaluate the efficacy, safety and tolerability of romosozumab treatment in postmenopausal Chinese women with osteoporosis.

The study consists of 4 study periods: a Screening Period (Day -35 to Day -1); a 6-month Double-Blind, Placebo-Controlled Period; a 6-month OL Treatment Period, and a 3-month Follow-Up Period. The overall study design including treatment assignments is depicted in Figure 5–1.

5.1.1 Screening Period

After the subject has been informed about the study and signed the Informed Consent form (ICF), the Screening procedures and assessments will be performed as described in Table 5–1 within a period of 35 days prior to IMP administration. To be eligible to participate in the study, subjects must be postmenopausal Chinese women, 55 to 90 years of age (inclusive), have a BMD T-score ≤-2.50 at the lumbar spine, total hip, or femoral neck and an independent risk factor for fracture at Screening, with at least 2 vertebrae in the lumbar (L)1 through L4 region and at least 1 hip evaluable by DXA. After consent, subjects should undergo BMD by DXA and lateral spine x-rays to confirm they fulfill the BMD criteria before any other Screening evaluations are conducted.

In addition, before enrolling subjects in the study, a careful individual assessment of the CV risk profile should be performed. For more information on the potential CV risk, see the results of 20110142 in Section 2.2.

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be eligible to participate in the study. A complete list of the eligibility criteria is provided in Section 6.

From Screening until the EOS Visit, subjects will be required to take daily calcium and vitamin D supplementation. Refer to Section 7.8.1.1 for further information on the dosing and management of these supplements. Subjects who fail the serum 25 hydroxy (OH) vitamin D eligibility criterion at Screening may be retested once following vitamin D repletion.

5.1.2 Double-Blind, Placebo-Controlled Period

Approximately 300 subjects will be randomized, stratified by age (<75 years, ≥75 years), in a 2:1 ratio to receive romosozumab 210mg sc QM (200 subjects) or matched placebo sc QM (100 subjects) in a blinded manner for 6 months to evaluate if romosozumab treatment compared with placebo is effective in increasing BMD, as assessed by DXA at the lumbar spine, total hip, and femoral neck.

During this period, in addition to efficacy (BMD measurements) and safety assessments (eg, physical examinations, vital sign measurements, and ECG parameters) being performed, blood samples will be collected to analyze PK, immunogenicity, BTMs (P1NP and sCTX) and laboratory data (including intact parathyroid hormone [iPTH] and lipids) at the time points specified in the schedule of study assessments (Table 5–1). Only Lunar or Hologic densitometers should be used to measure BMD during the study.

The 6-month analysis, which will include the analyses of the primary and secondary efficacy variables, PK variables, PD variables, and safety variables will be performed using the data obtained from the 6-month, Double-Blind, Placebo-Controlled Period.

5.1.3 Open-Label Treatment Period

Upon completion of the 6-month Double-Blind, Placebo-Controlled Period, subjects will enter the OL Treatment Period and receive romosozumab 210mg sc QM for 6 months in an

OL fashion. During this period, all subjects will receive active treatment (romosozumab) allowing for the collection of efficacy and safety data for an additional 6 months (a total of 12 months for subjects randomized to romosozumab and 6 months for those randomized to placebo). Refer to the schedule of study assessments for the efficacy and safety assessments to be performed during this period (Table 5–1).

In addition to the efficacy and safety assessments, blood samples for BTM (P1NP and sCTX), PK, immunogenicity, and laboratory (including iPTH and lipids) testing will be collected at specified time points during the OL Treatment Period (see Table 5–1).

5.1.4 Follow-Up Period

After completing the OL Treatment Period (Month 12), subjects will be followed up for an additional 3 months and should complete the EOS Visit at Month 15. The assessments for this visit are specified in Table 5–1. Subject participation in the study is concluded once the EOS procedures and assessments are completed. Subjects who test positive for neutralizing antibodies to romosozumab at the EOS Visit or ET Visit will be asked to return for additional follow-up testing for up to 1 year after final administration of IMP. Additional information on antiromosozumab antibody testing procedures is presented in Section 11.7.5.

The final analysis will be performed after completion of the Follow-Up Period. The remaining efficacy, PK, PD, and safety analyses for Month 12 and the safety analysis for the overall study period, ie, the period from the start of double-blind treatment to the Month 15 Visit for each subject, will be evaluated.

Subjects can decide to discontinue IMP but continue participation in the study. However, subjects who withdraw early from the study should return to the study to complete the ET Visit (see Section 8.5). Subjects who withdraw from the study will not be replaced.

An independent DMC will monitor the safety of subjects in OP0002 on an ongoing basis. Further information on the DMC is provided in Section 13.7.

No interim analysis is planned for this study.

5.1.5 Study duration per subject

For each individual subject, the study will last approximately 16 months, as follows:

- Screening Period – up to 35 days
- Double-Blind, Placebo-Controlled Period – 6 months (final administration of IMP [romosozumab or placebo] at Month 5)
- OL Treatment Period – 6 months (final administration of romosozumab at Month 11)
- Follow-Up Period – 3 months with the EOS Visit at Month 15

A subject's participation in the study may be extended up to 1 year after the final IMP administration if the subject tests positive for neutralizing antibodies to romosozumab at the EOS Visit or ET Visit (see Section 11.7.5).

The end of the study is defined as the date of the last visit of the last subject in the study.

5.1.6 Planned number of subjects and sites

Approximately 300 subjects are to be randomized in the study, ensuring approximately 200 subjects in the romosozumab group and approximately 100 subjects in the placebo group. The planned number of study sites is approximately 30.

5.1.7 Anticipated regions and countries

The study will be conducted in mainland China.

5.2 Schedule of study assessments

The study procedures and assessments to be conducted at each visit are presented in the schedule of study assessments (Table 5–1).

Table 5–1: Schedule of study assessments

Activity	Screening Period	Double-Blind, Placebo-Controlled Period						Open-Label Treatment Period								Follow-Up Period
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**ET**	**15 /EOS**
Day/month[a]	**Within 35 days of D1[b]**	**D1**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**--**	**M15**
Windows (days)	**-35**	**--**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**--**	**-14**
Informed Consent	X															
Inclusion/exclusion criteria	X	X														
Withdrawal criteria		X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Demographic data	X															
Medical history	X															
Medical fracture history	X															
Discuss signs and symptoms of myocardial infarction and stroke[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior medications	X															
Lifestyle[e]	X															
Physical examination	X							X						X	X	
Height and weight	X							X						X	X	
Vital signs[f]	X		X					X	X					X	X	
ECG[g]	X		X		X			X			X			X	X	
Safety laboratory tests[h]	X	X	X		X			X	X		X			X	X	

Table 5–1: Schedule of study assessments

Activity	Screening Period	Double-Blind, Placebo-Controlled Period						Open-Label Treatment Period								Follow-Up Period
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**ET**	**15 /EOS**
Day/month[a]	**Within 35 days of D1[b]**	**D1**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**--**	**M15**
Windows (days)	**-35**	**--**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**--**	**-14**
Lipid profile		X[i]						X						X		
Serology[j]	X															
Serum 25 (OH) vitamin D	X	X														
TSH, free T4	X															
iPTH	X	X	X		X			X	X		X			X	X	
Blood sample for PK analyses[k]		X[l]	X		X			X	X		X			X	X	
Blood sample for antibodies to romosozumab		X[l]	X		X			X	X		X			X	X[m]	X[m]
Lateral spine x-rays (lumbar and thoracic)	X															
Bone mineral scan (DXA lumbar spine, total hip, and femoral neck)[n]	X				X			X						X	X	
P1NP		X[l]	X		X			X	X		X			X	X	
sCTX[o]		X[l]	X		X			X	X		X			X	X	

Table 5–1: Schedule of study assessments

Activity	Screening Period	Double-Blind, Placebo-Controlled Period						Open-Label Treatment Period								Follow-Up Period
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**ET**	**15 /EOS**
Day/month[a]	**Within 35 days of D1[b]**	**D1**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**--**	**M15**
Windows (days)	**-35**	**--**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**--**	**-14**
Concomitant medications	← entire study period →															
Concomitant medical procedures	← entire study period →															
Recording of AEs	← entire study period →															
IMP administration[p] (double-blind treatment)		X	X	X	X	X	X									
Romosozumab administration[p] (OL treatment)								X	X	X	X	X	X			
Instructions on daily calcium and vitamin D supplementation[q]	X															X
Vitamin D loading dose (if required)		X[r]														
Daily calcium and vitamin D supplementation[q]	← entire study period →															

AE=adverse event; BMD=bone mineral density; BP=blood pressure; BTM=bone turnover marker; D=day; DXA=dual-energy x-ray absorptiometry; eCRF=electronic Case Report form; ECG=electrocardiogram; EOS=End-of-Study; ET=Early Termination; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HDL=high density lipoprotein; HIV=human immunodeficiency virus; IMP=investigational

medicinal product; iPTH=intact parathyroid hormone; LDL=low density lipoprotein; M=month; OH=hydroxy; OL=open-label; P1NP=procollagen type 1 N-telopeptide; PK=pharmacokinetic(s); sCTX=serum type I collagen C-telopeptide; T4=thyroxine; TSH=thyroid-stimulating hormone

[a] For the purpose of this study, a month is defined as 30 days.

[b] After consent, subjects should undergo BMD by DXA and lateral spine x-rays to confirm they fulfill BMD criteria before any other Screening evaluations are conducted.

[c] After randomization, confirm that the subject fulfills none of the withdrawal criteria.

[d] Before enrolling subjects in the study, a careful individual assessment of the cardiovascular risk profile should be performed.

[e] Lifestyle records subject's alcohol use, tobacco use, and caffeinated beverage use.

[f] Vital signs include BP, pulse rate, and temperature; vital signs are to be measured after the subject has been in a seated or semi-recumbent position for at least 3 minutes. Vital signs should be measured prior to blood sampling and prior to IMP administration, where applicable.

[g] A 12-lead ECG will be recorded after the subject has been in a seated or semi-recumbent position for at least 3 minutes. The ECG should be recorded prior to blood sampling and prior to IMP administration, where applicable.

[h] Safety laboratory tests include hematology and serum chemistry. A complete list of the clinical laboratory parameters is provided in Table 11–2.

[i] A blood sample for lipid testing (total cholesterol, LDL, HDL, and triglycerides) will be collected with the subject in a fasted state. Fasting state is defined as overnight fasting, with a minimum of 8h of fasting required.

[j] Subjects who have evidence of or test positive for any of the following are excluded from the study: HBsAg, HBcAb, HCV antibody, and HIV antibody.

[k] PK samples will be analyzed to determine serum concentrations of romosozumab.

[l] On D1, samples for PK, BTMs, and antibodies are to be collected prior to IMP administration.

[m] Subjects who test positive for neutralizing antibodies to romosozumab at the EOS Visit or ET Visit will be asked to return for additional follow-up testing. This testing is to occur every 3 months starting from when the site has been notified of the positive results until 1) neutralizing antibodies are no longer detectable or 2) the subject has been followed for a period of at least 1 year (±4 weeks) postadministration of romosozumab.

[n] Only Lunar or Hologic densitometers should be used to measure BMD during the study. Previous BMD scans by DXA may be used for Screening if the criteria in Section 10.1 are met.

[o] Blood samples for determination of sCTX must be collected from subjects in a fasted state and before noon. Fasting state is defined as overnight fasting, with a minimum of 8h of fasting required.

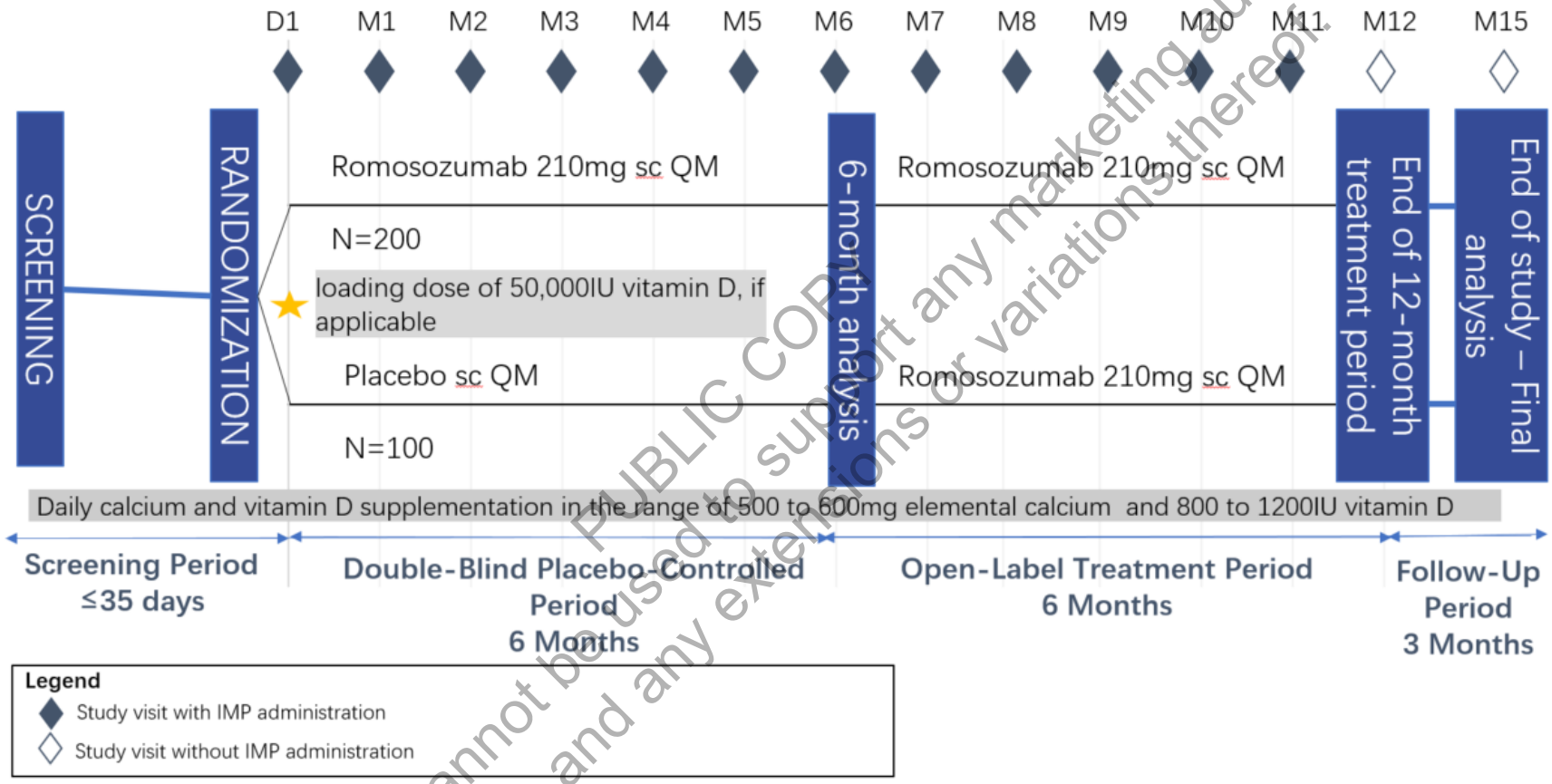
[p] Administration of IMP must be the final procedure at each applicable visit. Injections are to be administered by trained study personnel at the study site. Open-label romosozumab administration at Month 6 is the first dose of the OL Treatment Period.

[q] All subjects will be required to take daily calcium and vitamin D supplementation during the study. Details of the calcium and vitamin D supplementation are to be recorded in the subject's eCRF (refer to Section 7.8.1.1).

[r] If a loading dose of vitamin D is required, then this should be administered within 1 week of D1. However, if the vitamin D loading dose is missed in this timeframe, it should be given as soon as possible thereafter.

5.3 Schematic diagram

Figure 5–1: Overall study design for OP0002



D=day; IMP=investigational medicinal product; IU=international unit; M=month; N=number of subjects in each treatment arm; QM=every month; sc=subcutaneous(ly)

Note: Final analysis will include the remaining efficacy and safety analyses for Month 12 and the safety analyses for the overall study period, ie, the period from the start of double-blind treatment to the Month 15 Visit for each subject will be evaluated.

5.4 Rationale for study design and selection of dose

A randomized double-blind, placebo-controlled treatment period followed by an OL design has been selected to demonstrate the efficacy and safety of romosozumab in postmenopausal Chinese women with osteoporosis.

5.4.1 Rationale for the dose selected for romosozumab

The romosozumab 210-mg sc QM regimen was selected based on the following reasons:

- The 210-mg sc QM dosing regimen resulted in rapid and greatest increases in BMD at the lumbar spine, total hip, and femoral neck compared with the other romosozumab dosing regimens tested (70 and 140mg QM) in the Phase 2 studies. Other evaluations such as BTMs, also support the use of 210mg sc QM as summarized in Section 2.2.
- In the global Phase 3 program, the romosozumab 210-mg sc QM dosing regimen demonstrated fracture risk reduction, which persisted after transitioning to antiresorptive therapy, while for safety, the 210-mg sc QM regimen was well tolerated as described in Section 2.2.

5.4.2 Rationale for selecting the BMD endpoint

The primary efficacy variable selected for this study is change from baseline in BMD by DXA at 6 months at the lumbar spine based on the following:

- BMD by DXA is a key predictor of future fracture and Chinese treatment guidelines recommend use of BMD for the diagnosis of osteoporosis (Osteoporosis and Bone Mineral Research Society of the Chinese Medical Association, 2017).
- BMD by DXA is also used in clinical practice to monitor the effect of osteoporosis pharmacological treatment and for clinical research purposes. Lumbar spine and hip are the recommended regions for measuring BMD in routine clinical practice.
- It is acknowledged that osteoporotic fractures most commonly occur at the spine and hip, so BMD measurements at these anatomical sites are predictors of fracture risk at these sites (Lofman et al, 2000; Faulkner, 1998; Nelson et al, 1998; Marshall et al, 1996).
- BMD by DXA represents a reliable surrogate endpoint for romosozumab as BMD gains translate into efficacy by reducing fracture risk, and this has been confirmed in the global Phase 3 fracture studies (20070337 and 20110142) where fracture risk reduction was demonstrated together with BMD increases with romosozumab treatment.
- To extrapolate the global fracture data to China, the BMD endpoint is considered to be the most suitable endpoint to support efficacy under the International Council for Harmonisation (ICH) bridging concept and to avoid unnecessary medical resources and patient burden in performing large-scale fracture studies in China.
- There is already strong evidence of fracture risk reduction with romosozumab treatment from the clinical development program outside China and as recommended for consideration in osteoporosis clinical study design by CDE officers in 2011 (Zhang et al, 2011), BMD is proposed as an alternative primary efficacy variable for local studies in China to bridge the evidence of fracture protection.

- In the previous romosozumab studies, the greatest BMD gains were observed at the lumbar spine compared with other anatomical sites (total hip and femoral neck); therefore, BMD at the lumbar spine is selected as the primary efficacy measure.

5.4.3 Rationale for 6-month duration of Double-Blind Period as primary efficacy endpoint

Onset of action is considered relatively early with romosozumab treatment. The following evidence supports a 6-month duration for the primary efficacy assessment, BMD:

- Changes in BTMs were noted early with romosozumab treatment. In the clinical studies in postmenopausal women with osteoporosis, romosozumab 210mg sc QM showed that the bone formation marker (P1NP) increased from baseline immediately and achieved peak levels by Month 1, then decreased towards baseline levels by approximately Month 6 to Month 9. The bone resorption marker (sCTX) decreased within a month after the first dose and generally remained below placebo at Month 12, but above the sCTX levels of the antiresorptive therapy ALN in the active-controlled study (20110142).
- BMD data showed that romosozumab 210mg sc QM resulted in rapid and robust increases in BMD from baseline compared with both placebo and ALN within 12 months. BMD increases were observed at the lumbar spine, total hip, and femoral neck (nominal $p < 0.001$) in the 2 Phase 3 studies in postmenopausal women (20070337 and 20110142). Additionally, the significant and progressive increases from baseline in BMD were apparent at Month 6 of the 12-month treatment period in the global Phase 2 and 3 studies conducted so far.
- In accordance with BTM and BMD changes, the efficacy of romosozumab in reducing fracture risk has been seen relatively early. In 20070337, romosozumab 210mg sc QM significantly reduced the risk of new vertebral fracture compared with placebo through Month 12 (odds ratio=0.27, $p < 0.001$), with a relative risk reduction of 73% (95% confidence interval [CI]: 53%, 84%). Romosozumab significantly reduced the risk of clinical fracture compared with placebo through Month 12, with a relative risk reduction of 36% (95% CI:11%, 54%; p=0.008). In 20110142, a reduction in risk of new vertebral fracture for romosozumab 210mg sc QM vs ALN 70mg po QW was observed during the 12-month double-blind treatment period (odds ratio=0.63, p=0.008), with a relative risk reduction for new vertebral fracture of 36% (95% CI: 11%, 54%). There was also a reduction in the risk of clinical fracture compared with ALN through Month 12 in 20110142, with a relative risk reduction of 28% (95% CI: 4%, 46%; nominal p=0.027). In addition, in 20070337 further early onset of antifracture effect was seen. Through Month 6, 14 subjects (0.4%) in the romosozumab group and 26 subjects (0.8%) in the placebo group had a new vertebral fracture; the relative risk reduction for romosozumab compared with placebo was 46% (95% CI: -3%, 72%; odds ratio=0.54; nominal p=0.056).
- Based on the data presented above, placebo use can be minimized to 6 months compared to the previous studies with much longer duration where new fracture remained a concern for placebo subjects.

5.4.4 Rationale for placebo-controlled study with an Open-Label Treatment Period.

The rationale for the choice of placebo as a comparator during the Double-Blind Period with an OL Treatment Period is as follows:

- A placebo-controlled study was chosen because it permits a minimally confounded demonstration of efficacy and safety of romosozumab in the treatment of postmenopausal Chinese women with osteoporosis.
- The use of a placebo control is also consistent with regulatory guidance, as recommended for consideration in osteoporosis clinical study design by CDE officers (Zhang et al, 2011).
- To minimize subject exposure to placebo, a 6-month treatment duration has been selected. (see Section 5.4.3 for the rationale for 6-month duration)
- The randomization ratio is 2:1 between active treatment and placebo which reduces placebo exposure while maintaining sufficient sensitivity in the study.
- The most severe osteoporotic population with a history of hip fracture and severe or moderate vertebral fracture and those with a BMD T-score of ≤-3.50 at the total hip or femoral neck have been excluded by the inclusion/exclusion criteria.
- In addition, to maintain the integrity of the bone, subjects will receive a loading dose of vitamin D (50,000IU) at the start of the study in the case of low serum vitamin D levels and all subjects will receive daily calcium and vitamin D supplements throughout the study. These supplements have been shown to have a protective effect on the skeleton.
- Inclusion of the 6-month OL Treatment Period will provide an opportunity for those subjects who are randomized to placebo to receive active treatment. This extension will generate additional safety and efficacy data in postmenopausal Chinese women resulting in a more consistent and robust efficacy and safety profile.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written ICF is signed and dated by the subject or legal representative prior to initiation of any study-specific activities/procedures.
2. Subject is considered reliable and capable of adhering to the protocol, visit schedule, and medication intake according to the judgment of the investigator.

3a. Subject is an ambulatory postmenopausal Chinese women, 55 to 90 years of age (inclusive) at the time of Screening. Postmenopause is defined as no spontaneous vaginal bleeding or spotting for 12 or more consecutive months prior to Screening.

4. Subject has a BMD T-score ≤-2.50 at the lumbar spine, total hip, or femoral neck, as assessed by the central imaging vendor at the time of Screening based on DXA scans, and using data for Caucasian women from the National Health and Nutritional Examination Survey (NHANES, 1998).

5. Subject must have at least 1 of following independent risk factors for fracture:
   - History of fragility fracture (except hip fracture, a severe [SQ3] vertebral fracture or more than 2 moderate [SQ2] vertebral fractures [see exclusion criteria]);
   - Parental history of hip fracture;
   - Low body weight (body mass index ≤19kg/m^2);
   - Elderly (age ≥65 years);
   - Current smoker
6. Subject has at least 2 vertebrae in the L1 to L4 region and at least 1 hip that are evaluable by DXA, as assessed by the central imaging vendor.

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject has a BMD T-score of ≤-3.50 at the total hip or femoral neck, as assessed by the central imaging vendor at the time of Screening based on DXA scans, and using data for Caucasian women from NHANES 1998.
2. Subject has a known history of hip fracture.
3. Subject has any severe (SQ3) or more than 2 moderate (SQ2) vertebral fractures, as assessed by the central imaging vendor based on the lateral spine x-ray at Screening (Visit 1).
4. Subject has a history of myocardial infarction (MI).
5. Subject has a history of stroke.
6. Subject has a vitamin D insufficiency, defined as 25 (OH) vitamin D levels <20ng/mL, as assessed by the central laboratory at Screening. Vitamin D repletion will be permitted and the subject may be retested once within the Screening Period.
7. Subject has used oral bisphosphonates:
   - Any doses received within 3 months prior to randomization (Day 1).
   - More than 1 month of cumulative use between 3 and 12 months prior to randomization.
   - More than 3 years of cumulative use, unless the last dose was received ≥5 years prior to randomization.
8. Subject has used intravenous (iv) bisphosphonates:
   - zoledronic acid
     - Any doses received within 3 years prior to randomization.
     - More than 1 dose received within 5 years prior to randomization.
   - iv ibandronate, iv pamidronate, or iv ALN
     - Any doses received within 12 months prior to randomization.
     - More than 3 years of cumulative use, unless the last dose was received ≥5 years prior to randomization.

9. Subject has used denosumab or any cathepsin K inhibitor:
   - Any doses received within 18 months prior to randomization.
10. Subject has used tibolone, cinacalcet, or calcitonin:
   - Any doses received within 3 months prior to randomization.
11. Subject has used TPTD or any PTH derivative:
   - Any doses received within 3 months prior to randomization.
   - More than 1 month of cumulative use between 3 and 12 months prior to randomization.
12. Subject has used systemic oral or transdermal estrogen or selective estrogen receptor modulators (SERMs):
   - More than 1 month of cumulative use within 6 months prior to randomization.
13. Subject has used strontium ranelate or fluoride:
   - More than 1 month of cumulative use within 5 years prior to randomization.
14. Subject has used hormonal ablation therapy:
   - More than 1 month of cumulative use within 6 months prior to randomization.
15. Subject has used systemic glucocorticosteroids:
   - ≥5mg prednisone equivalent per day for more than 14 days within 3 months prior to randomization.
16. Subject has a history of metabolic or bone disease (except osteoporosis) that may interfere with the interpretation of the results, such as sclerosteosis, Paget's disease, rheumatoid arthritis, osteomalacia, osteogenesis imperfecta, osteopetrosis, ankylosing spondylitis, Cushing's disease, hyperprolactinemia, and malabsorption syndrome.
17. Subject has a history of solid organ or bone marrow transplants.
18. Subject has a history of ONJ or AFF.
19. Subject has a confirmed diagnosis or under investigation for multiple myeloma or related lymphoproliferative disorder at the Screening Visit.
20. Subject has evidence of any of the following:
    a. Current, uncontrolled hyper- or hypothyroidism. Uncontrolled hyperthyroidism is defined as thyroid-stimulating hormone (TSH) and thyroxine (T4) outside of the normal range. Uncontrolled hypothyroidism is defined as TSH >10.
    b. Current, uncontrolled hyperparathyroidism or history of hypoparathyroidism. Uncontrolled hyperparathyroidism is defined as PTH outside the normal range in subjects with concurrent hypercalcemia or PTH values >20% above upper limit of normal (ULN) in normocalcemic subjects.
    c. Current hypercalcemia or hypocalcemia, defined as albumin-adjusted serum calcium outside the normal range, as assessed by the central laboratory at the time of Screening. Albumin-adjusted serum calcium levels may be retested once in case of an elevated

albumin-adjusted serum calcium level within 1.1xULN of the laboratory's reference ranges.

d. Subject has ≥3xULN of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

   For randomized subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

   If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at Screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

21. Subject is currently receiving treatment in another investigational device or drug study, or less than 30 days or 5 half-lives (whichever is longer) since ending treatment on another investigational device or drug study(ies).
22. Subject is undergoing other investigational procedures while participating in this study.
23. Subject has previously entered this study or has previously participated in a study with a sclerostin antibody product.
24. Subject has had a malignancy within the last 5 years, except nonmelanoma skin cancers, cervical or breast ductal carcinoma in situ.
25. Subjects has a known hypersensitivity to any of the products to be administered during dosing (calcium supplements, vitamin D products, or mammalian cell derived products).
26. Subject who is breastfeeding or plans to become pregnant or breastfeed during the study or within 12 weeks of the final dose of study drug.
27. Subject has a history or evidence of any other clinically significant disorder, condition or disease (eg, untreated or unstable, with the exception of those outlined above) that, in the opinion of the investigator, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
28. Subject shows a positive result for human immunodeficiency virus (HIV), hepatitis C virus, or hepatitis B infection at Screening (Visit 1).
29. Subject has an active tuberculosis infection within 6 months of signing the ICF.
30. Subject has active pneumonia.
31. Subject has a reported history of hearing loss associated with cranial nerve VIII compression due to excessive bone growth (eg, as seen in conditions such as Paget's disease, sclerosteosis, and osteopetrosis).

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Subjects have the option to either discontinue IMP but continue participation in the study (withdrawal of IMP) or discontinue IMP and withdraw participation from the study (withdrawal from study). Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

6.3.1 Withdrawal of IMP

Subjects can decide to discontinue IMP but continue participation in the study. If IMP is discontinued, the investigator should encourage the subject to continue participation by attending scheduled study visits to have procedures/assessments performed and data collected including endpoints and AEs. The investigator must document any changes to the scheduled visits and assessments (Table 5–1) and the plan for follow up that is agreed by the subject.

Subjects might have IMP withdrawn if any of the following events occur (but not limited to):

- Subject request.
- Decision of the sponsor or investigator.
- Safety concern (eg, due to an AE, ineligibility determined, protocol deviation, noncompliance, requirement for alternative therapy, protocol-specified criteria).
- Clinical fracture or BMD decrease from baseline of 7% or more at the lumbar spine, total hip, or femoral neck.

  In the event that a subject experiences a clinical fracture or a BMD decrease from baseline of 7% or more at the lumbar spine, total hip or femoral neck at any time during the study, the investigator is required to discuss the subject's individual fracture risk and alternative treatment options with the subject and to note the discussion in the subject's records. If a decision is made to begin an alternative approved therapy, the subjects must discontinue IMP and every effort should be made to have the subject complete the remaining study visits and assessments.

6.3.2 Withdrawal from study

Subjects can be withdrawn from the study if any of the following events occur:

- Subject develops a serious illness that would interfere with her continued participation.
- Subject is noncompliant with the study procedures or medications in the opinion of the investigator.
- Subject withdraws her consent.
- There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
- The sponsor or a regulatory agency requests withdrawal of the subject.

Withdrawal of consent for a study means that the subject does not wish to continue in the study. Subject data up to withdrawal of consent will be included in the analysis of the study.

Subjects who withdraw from the study should complete the ET Visit. Refer to the schedule of assessments for the procedures to be performed at this visit (Table 5–1). These subjects will be encouraged to return to the study site to complete the procedures and assessments for the EOS Visit, 4 months after the final administration of IMP.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow up, the investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Subjects who withdraw from the study will not be replaced.

6.3.3 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥8xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 11.6.1.2.1 are followed.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x baseline) and <8xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 11.6.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if

applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

6.4 Retesting

During the Screening Period, any laboratory values can be retested once to determine subject's eligibility for the study and to ensure that there is no further ongoing clinical relevance.

All retests must be confirmed by the central laboratory and the subject must be randomized within the 35-day Screening Period.

6.5 Lateral spine x-ray at Screening

The x-rays of the lateral thoracic and lumbar spine will be acquired according to specific instructions provided by the central imaging vendor.

For assessment of prevalent vertebral fractures at Screening, which will be performed by a radiologist at the central imaging center, a visual semiquantitative grading scale as defined in Table 6–1 will be used (Genant et al, 1993).

Table 6–1: Semiquantitive (SQ) grading scale

Grade	Fracture severity	Definition
0	Normal	Approximately less than 20% reduction in anterior, middle, and/or posterior height
1	Mild	Approximately 20% to 25% reduction in anterior, middle, and/or posterior height
2	Moderate	Approximately 25% to 40% reduction in anterior, middle, and/or posterior height
3	Severe	Approximately 40% or greater reduction in anterior, middle, and/or posterior height

7 STUDY TREATMENT

7.1 Description of investigational medicinal product

For this study, romosozumab and placebo are considered IMP.

Subjects will be administered either romosozumab or placebo in a blinded manner for 6 months after which time, all subjects will receive active treatment (romosozumab) in an OL manner for 6 months.

Romosozumab will be supplied as a sterile, clear to opalescent, colorless to light yellow, preservative-free solution for sc injection in a single-use prefilled syringe (PFS). Each PFS contains 90mg/mL of romosozumab in 55mM acetate and 13mM calcium containing 6.0% w/v sucrose and 0.006% w/v polysorbate 20 at pH 5.2, with a deliverable volume of 1.17mL (105mg romosozumab solution for injection).

Placebo is supplied in a 1.17-mL PFS identical in appearance to romosozumab. Placebo will be stored and packaged the same as romosozumab.

Details of the IMP are provided in the IMP Handling Manual.

Subjects will be required to take daily calcium and vitamin D supplementation during the study; however, these protocol-required products are not considered IMP. Further information on the calcium and vitamin D supplementation is provided in Section 7.8.1.1.

7.2 Treatments to be administered

Procedures for dose administration are provided in the IMP Handling Manual. All IMP will be administered to subjects at the study site by trained study personnel.

The IMP (romosozumab or placebo) will be administered over 2 study periods: the Double-Blind, Placebo-Controlled Period immediately followed by the OL Treatment Period as detailed below.

- Double-Blind, Placebo-Controlled Period
  - Approximately 300 subjects will be randomized, stratified by age (<75 years, ≥75 years), in a 2:1 ratio to receive romosozumab 210mg sc QM (approximately 200 subjects) or matched placebo sc QM (approximately 100 subjects) in a blinded manner for 6 months, with the final administration of double-blind IMP at Month 5.
- OL Treatment Period
  - At Month 6, all subjects will receive romosozumab 210mg sc QM for 6 months in an OL fashion, with the final administration of OL romosozumab at Month 11.

Subjects will receive 2 sc injections of romosozumab QM (ie, 2 injections of 105mg romosozumab for a total dose of 210mg) or 2 injections of matched placebo QM for 6 months during the Double-Blind, Placebo-Controlled Period. The 2 sc injections will be administered one immediately after the other. During the OL Treatment Period, all subjects will receive 2 sc injections of romosozumab QM (ie, 2 injections of 105mg romosozumab each administered one immediately after the other for a total dose of 210mg) for 6 months. A separate 1.17-mL PFS will be used for each injection. Thus, to administer the IMP at each dosing visit, 2 PFS (romosozumab or placebo) will be supplied in a single box.

Injections will be administered sc into different sites on the subject's anterior abdominal wall, upper thigh, or upper arm by an individual at the study site who has been trained in the injection technique. The injection should not be administered in the same arm from which blood is drawn. The IMP injections must be administered after all other study visit procedures have been completed.

The first dose of IMP must be administered on the day of randomization (Day 1). Details of the IMP administered including the date and time are to be recorded on each subject's eCRF.

Over the course of the study, a physician must be available during administration of romosozumab or placebo. It is recommended that all subjects be closely observed for approximately 30 minutes after dosing. In the unlikely event of overdose, refer to Section 11.4 for further information.

7.3 Packaging

The IMP will be manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. The IMP will be suitably packaged in such a way as to protect it from deterioration during transport and storage.

Romosozumab and placebo injections will be identical in appearance and will be presented in indistinguishable containers (PFS) and boxes during the Double-Blind, Placebo-Controlled Period. The 2 PFS required for each IMP administration will be supplied in a single box, as assigned by the interactive response technology (IRT) system.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current ICH guidelines and Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

Refer to the IMP Handling Manual for the storage conditions of the IMP.

The investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing actual and minimum/maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

To administer the injections, study personnel must be appropriately trained and licensed (per country guidelines).

The investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The investigator may assign some of the investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The investigator must ensure that the IMP is used only in accordance with the protocol.

After completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures (SOPs) or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

The IMP will be administered at the study site by staff trained in the injection technique. Date and time of IMP administration will be recorded in the subject's eCRF. Drug accountability must be recorded on the Drug Accountability form.

7.8 Concomitant medications/treatments

Any treatment administered from the time of signing the ICF to the EOS Visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

Any concomitant medication use reported by the subject during the study will be recorded in the eCRF.

7.8.1 Permitted concomitant treatments (medications and therapies)

Throughout the study, the investigator may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.8.2.

Subjects taking concomitant Chinese herbal medication as indicated by the investigator for osteoporosis must be on a stable dose prior to study entry and continue on that dose throughout the study.

7.8.1.1 Calcium and vitamin D supplementation

All subjects will be required to take daily calcium and vitamin D supplementation by the oral route during the study. Details of daily calcium and vitamin D supplementation are to be recorded in the subject's eCRF.

The calcium and vitamin D supplements are not considered IMP. The investigator will be responsible for ensuring that subjects have access to these protocol-required therapies. Where available, vitamin D_3 preparations should be used; if vitamin D_3 is not available, use of vitamin D_2 preparations is acceptable.

From Screening through the EOS Visit, subjects should be taking between 500 to 600mg of elemental calcium along with 800 to 1200IU of vitamin D daily.

Subjects with a serum 25 (OH) vitamin D level of ≥20ng/mL and ≤40ng/mL at Screening will receive an initial loading dose of 50,000IU of vitamin D on Day 1 (or within 1 week of Day 1) by the oral route. Subjects with a serum 25 (OH) vitamin D level of >40ng/mL at Screening may also receive the vitamin D loading dose at the investigator's discretion. Subjects whose serum 25 (OH) vitamin D at Screening is <20ng/mL may be given vitamin D supplementation and retested once during the Screening Period to determine subject's eligibility.

If a subject develops hypercalcemia over the course of the study, the investigator may use his or her medical judgment and reduce the calcium and/or vitamin D supplementation to maintain serum calcium concentration within the normal range. If a subject develops hypocalcemia over the course of the study, appropriate additional supplementation should be instituted as deemed acceptable by local guidelines, to maintain serum calcium concentration within the normal range. If a subject is unable to tolerate the daily calcium or vitamin D supplementation, the formulation may be changed or the dosage lowered. The intolerance as well as the resolution (ie, change in formulation or dosage) should be documented in the subject's chart.

7.8.2 Prohibited concomitant treatments (medications and therapies)

Chinese herbal medicine for treating osteoporosis must not be initiated at any time during the study.

In addition, the following concomitant medications are prohibited until the end of the OL Treatment Period (Month 12 Visit) or until 1 month after the early termination of study medication:

- Strontium (including strontium ranelate and over-the-counter strontium preparations)
- Fluoride
- Vitamin K and vitamin K analogs (for the treatment of osteoporosis)
- Activated vitamin D (1,25-di[OH] vitamin D or 1 [OH] vitamin D)
- iv bisphosphonates
- Oral bisphosphonates (cumulative dosing regimens of ≤1 month are acceptable)
- Denosumab
- TPTD or any PTH analogs
- Systemic oral or transdermal estrogen (cumulative dosing regimens of ≤1 month are acceptable; vaginal preparations and estrogen creams will be allowed at any time)
- SERMs (cumulative dosing regimens of ≤1 month are acceptable)
- Calcitonin (cumulative dosing regimens of ≤1 month are acceptable)
- Tibolone
- Prolonged (ie, >3 months) oral glucocorticoid therapy at a prednisone equivalent dose of ≥5.0mg/day (tapering glucocorticoid courses of ≤1-month duration is permitted regardless of dose; inhaled or topical glucocorticoids are permitted)
- Any cathepsin K inhibitor, such as odanacatib (MK-0822)
- Hormonal ablation therapy
- Cinacalcet

7.8.3 Rescue medication

No alternative osteoporosis medication will be allowed during this study and no change in the dose and frequency of romosozumab administration is permitted. In the event that a subject experiences a clinical fracture during the study, the investigator may discuss alternative treatment options. If the decision is made to begin an alternative approved therapy, the subject must discontinue IMP. Every effort should be made to have the subject complete the remaining study visits and assessments.

7.9 Blinding

This is a Phase 3 multicenter, randomized, 6-month double-blind, placebo-controlled study followed by a 6-month OL Treatment Period. Details on maintaining the blind during the

Double-Blind, Placebo-Controlled Period and minimizing any bias during the OL Treatment Period are provided in Section 7.9.1.1 and Section 7.9.1.2, respectively.

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Double-Blind, Placebo-Controlled Period

All IMP injections administered during the Double-Blind, Placebo-Controlled Period (romosozumab and placebo) will be identical in appearance, presented in identical containers (PFS), and stored and packaged in the same manner in order to maintain the blind.

All sponsor, contract research organization (CRO), and investigator site personnel involved in the study will be blinded to the IMP assignment during the Double-Blind, Placebo-Controlled Period with the following exceptions:

- Sponsor Patient Safety (PS) staff reporting SAEs to regulatory authorities
- Bioanalytical laboratory staff (analyzing blood samples for PK, antibodies, and BTMs)
- Unblinded CRO Randomization Biostatistician (to produce the randomization list)
- Unblinded Medical Monitor (only when deemed necessary to provide appropriate medical care to a subject)

7.9.1.2 Open-Label Treatment Period

After the last subject has completed the final visit in the Double-Blind, Placebo-Controlled Period, individuals at the sponsor and CRO who will be involved in the data management and data cleaning, statistical analysis of the 6-month double-blind data, and the writing of the associated Clinical Study Report (CSR), will be unblinded to initial IMP assignments. Upon finalization of the CSR (6-month analysis), investigators will be unblinded to subject level treatment assignments. Investigators are obliged not to disclose to subjects their initial IMP assignment so that subjects will remain blinded during both the Double-Blind, Placebo-Controlled and OL Treatment Periods of the study.

7.9.1.3 Maintenance of study treatment blind

All subject treatment details (romosozumab and placebo) will be allocated and maintained by the IRT system.

Under normal circumstances, the blinded treatment must not be revealed. In the case of a medical emergency, UCB or its representatives must be notified immediately if the blind is broken.

7.9.1.4 Breaking the treatment blind in an emergency situation

The integrity of the clinical study must be maintained by observing the treatment blind. In the event of an emergency, it will be possible to determine to which treatment arm the subject has been allocated by contacting the IRT system. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

The Clinical Project Manager (CPM) will be informed immediately via the IRT system when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the

IMP performed by the investigator must be recorded in the source documents and on the Study Termination eCRF page.

7.10 Randomization and numbering of subjects

An IRT system will be used for assigning subjects to treatment based on a predetermined production randomization list provided by the CRO. A CRO Randomization Biostatistician who is not involved otherwise in the study will write the randomization code using a validated program and produce the randomization list. The randomized list will be retained at the CRO in a secure location until database lock. The CRO team and UCB team directly involved in the conduct of the study will not have access to the productive randomization list up to the unblinding of the study. Before the start of the study, copies of the randomization list will be sent in a secure fashion to the IRT system and to the unblinded personnel identified in Section 7.9.1.1. The IRT system will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

Subjects will be randomized, stratified by age (<75 years, ≥75 years), in a 2:1 ratio of romosozumab to placebo during the Double-Blind, Placebo-Controlled Period, after which, all subjects will receive romosozumab during the OL Treatment Period.

At Screening (Visit 1), after signing the ICF, the investigator or designee will contact the IRT system to enter a subject in the study. Each subject will be assigned a 5-digit number via the IRT system that serves as the subject identifier throughout the study. The subject number will be required in all communication between the investigator or designee and the IRT system regarding a particular subject.

To randomize a subject to treatment on Visit 2 (Day 1), the investigator or designee will contact the IRT system to obtain the subject's randomization number. The randomization number must be incorporated into the subject's eCRF.

The IRT system will allocate kit numbers based on the subject number for both the Double-Blind, Placebo-Controlled Period and the OL Treatment Period. Subject number and kit numbers will be tracked via the IRT system.

The investigator or designee will contact the IRT system when a subject discontinues IMP and/or discontinues the study. Subjects who withdraw from the study will not be replaced.

8 STUDY PROCEDURES BY VISIT

A general overview of the study assessments is provided in Table 5–1. An outline of the study procedures and assessments to be performed at each visit is provided below.

Every effort should be made to keep subjects on the study schedule. However, when this is not feasible, romosozumab or placebo may be administered within ±7 days of the study-defined visits. Also, subjects can complete with EOS Visit up to 14 days prior to Month 15.

For the purpose of this study, a month is defined as 30 days.

8.1 Screening Visit (Visit 1) (up to 35 days)

The Screening Visit (Visit 1) should be completed within the 35-day period prior to the first administration of IMP.

Prior to any study specific activities, subjects will be asked to read, sign, and date an ICF that has been approved by the sponsor and an IEC/IRB and that complies with regulatory requirements. Subjects will be given adequate time to consider any information concerning the study given to them by the investigator or designee. As part of the informed consent procedure, subjects will be given the opportunity to ask the investigator any questions regarding potential risks and benefits of participation in the study.

After written informed consent is obtained from the subject, the investigator or designee will contact the IRT system to enter the subject in the study. The following procedures and assessments will be performed/recorded at this visit.

Investigator or designee is advised to perform the BMD by DXA and lateral spine x-rays (lumbar and thoracic) first and only subjects who fulfill BMD criteria should undergo the remaining Screening assessments. Calcium and vitamin D supplements should be prescribed after or at this visit.

- Collect and record demographic data
- Obtain a medical history
- Collect and record medical fracture history
- Collect and record prior medications
- Complete the lifestyle questions
- Perform a physical examination
- Measure the subject's height and weight
- Measure vital signs (blood pressure [BP], pulse rate, and temperature)
- Perform a 12-lead ECG
- Obtain blood samples for the following:
  - Safety laboratory tests (hematology and serum chemistry)
  - Serology
  - Serum 25 (OH) vitamin D (can be retested once during the Screening Period)
  - TSH, free T4 (if required for confirmation of thyroid status)
  - iPTH
- Perform lateral spine x-rays (lumbar and thoracic) (instructions are provided in Section 6.5)
- Perform BMD DXA scans at the lumbar spine, total hip, and femoral neck
- Recording of concomitant medications
- Recording of concomitant medical procedures
- Recording of AEs
- Instruct the subject to start taking for study purposes daily calcium and vitamin D supplementation

- Record information on the subject's daily calcium and vitamin D supplementation

In addition, before enrolling subjects in the study, a careful individual assessment of the CV risk profile should be performed.

Based on the results of the Screening assessments and procedures at Visit 1, eligible subjects are instructed to return to the study site on Visit 2 (Day 1) to be randomized to receive the first dose of IMP.

8.2 Double-Blind, Placebo-Controlled Period

8.2.1 Visit 2 (Day 1)

The following procedures and assessments will be performed/recorded prior to administration of IMP:

- Confirm that the subject fulfills all the inclusion criteria and none of the exclusion criteria
- Obtain blood samples for the following:
  - Safety laboratory tests (hematology and serum chemistry)
  - Lipids (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL], and triglycerides) - sample should be collected under fasting conditions. Fasting state is defined as overnight fasting, with a minimum of 8h of fasting required.
  - Serum 25 (OH) vitamin D
  - iPTH
  - PK (serum romosozumab concentration)
  - Antiromosozumab antibodies
  - BTMs (P1NP and sCTX) - sample for sCTX must be collected from subjects in a fasting state and before noon. Fasting state is defined as overnight fasting, with a minimum of 8h of fasting required.
- Recording of concomitant medications
- Recording of concomitant medical procedures
- Recording of AEs
- Discuss signs and symptoms of MI and stroke
- Record any change in the subject's daily calcium and vitamin D supplementation
- Loading dose of vitamin D, if required - should be administered within 1 week of Day 1

In addition, before enrolling subjects in the study, a careful individual assessment of the CV risk profile should be performed.

After completion of these procedures and assessments, the investigator or designee should contact the IRT system to obtain the subject's randomization number and the IMP kit number assigned to the subject. The IMP will be administered by trained study personnel.

After the subject has been randomized:

- Confirm that the subject fulfills none of the withdrawal criteria

8.2.2 Visit 3 (Month 1) and Visit 5 (Month 3)

At these visits, the following procedures and assessments will be performed/recorded prior to administration of IMP:

- Confirm that the subject fulfills none of the withdrawal criteria
- Measure vital signs (BP, pulse rate, and temperature) (Visit 3 only)
- Perform a 12-lead ECG
- Obtain blood samples for the following:
  - Safety laboratory tests (hematology and serum chemistry)
  - iPTH
  - PK (serum romosozumab concentration)
  - Antiromosozumab antibodies
  - BTMs (P1NP and sCTX) - sample for sCTX must be collected from subjects in a fasting state and before noon. Fasting state is defined as overnight fasting, with a minimum of 8h of fasting required.
- Perform BMD DXA scans at the lumbar spine, total hip, and femoral neck (Visit 5 only)
- Recording of concomitant medications
- Recording of concomitant medical procedures
- Recording of AEs
- Discuss signs and symptoms of MI and stroke
- Record any change in the subject's daily calcium and vitamin D supplementation

After completion of these procedures and assessments at each visit, IMP will be administered by trained study personnel.

8.2.3 Visit 4 (Month 2), Visit 6 (Month 4), and Visit 7 (Month 5)

At these visits, the following assessments will be performed prior to administration of IMP:

- Confirm that the subject fulfills none of the withdrawal criteria
- Recording of concomitant medications
- Recording of concomitant medical procedures
- Recording of AEs
- Discuss signs and symptoms of MI and stroke
- Record any change in the subject's daily calcium and vitamin D supplementation

After completion of these assessments at each visit, IMP will be administered by trained study personnel. The final administration of IMP during the Double-Blind, Placebo-Controlled Period will occur at Visit 7 (Month 5).

8.2.4 Visit 8 (Month 6)

The following procedures and assessments will be performed/recorded prior to the first administration of OL romosozumab to all subjects:

- Confirm that the subject fulfills none of the withdrawal criteria
- Perform a physical examination
- Measure the subject's height and weight
- Measure vital signs (BP, pulse rate, and temperature)
- Perform a 12-lead ECG
- Obtain blood samples for the following:
  - Safety laboratory tests (hematology and serum chemistry)
  - Lipids (total cholesterol, HDL, LDL, and triglycerides)
  - iPTH
  - PK (serum romosozumab concentration)
  - Antiromosozumab antibodies
  - BTMs (P1NP and sCTX) - sample for sCTX must be collected from subjects in a fasting state and before noon. Fasting state is defined as overnight fasting, with a minimum of 8h of fasting required.
- Perform BMD DXA scans at the lumbar spine, total hip, and femoral neck
- Recording of concomitant medications
- Recording of concomitant medical procedures
- Recording of AEs
- Discuss signs and symptoms of MI and stroke
- Record any change in the subject's daily calcium and vitamin D supplementation

After completion of these procedures and assessments, all subjects will receive the first dose of OL romosozumab administered by trained study personnel and transition to the OL Treatment Period of the study.

8.3 Open-Label Treatment Period

8.3.1 Visit 9 (Month 7) and Visit 11 (Month 9)

At these visits, the following procedures and assessments will be performed/recorded prior to administration of OL romosozumab:

- Confirm that subject fulfills none of the withdrawal criteria

- Measure vital signs (BP, pulse rate, and temperature) (Visit 9 only)
- Perform a 12-lead ECG (Visit 11 only)
- Obtain blood samples for:
  - Safety laboratory tests (hematology and serum chemistry)
  - iPTH
  - PK (serum romosozumab concentration)
  - Antiromosozumab antibodies
  - BTMs (P1NP and sCTX) - sample for sCTX must be collected from subjects in a fasting state and before noon. Fasting state is defined as overnight fasting, with a minimum of 8h of fasting required.
- Recording of concomitant medications
- Recording of concomitant medical procedures
- Recording of AEs
- Discuss signs and symptoms of MI and stroke
- Record any change in the subject's daily calcium and vitamin D supplementation

After completion of these procedures and assessments at each visit, OL romosozumab will be administered by trained study personnel.

8.3.2 Visit 10 (Month 8), Visit 12 (Month 10), and Visit 13 (Month 11)

At these visits, the following assessments will be recorded prior to administration of OL romosozumab:

- Confirm that the subject fulfills none of the withdrawal criteria
- Recording of concomitant medications
- Recording of concomitant medical procedures
- Recording of AEs
- Discuss signs and symptoms of MI and stroke
- Record any change in the subject's daily calcium and vitamin D supplementation

After completion of these assessments at each visit, OL romosozumab will be administered by trained study personnel. The final administration of romosozumab during the OL Treatment Period will occur at Visit 13 (Month 11).

8.3.3 Visit 14 (Month 12)

The following procedures and assessments will be performed/recorded:

- Confirm that the subject fulfills none of the withdrawal criteria
- Perform a physical examination

- Measure the subject's height and weight
- Measure vital signs (BP, pulse rate, and temperature)
- Perform a 12-lead ECG
- Obtain blood samples for the following:
  - Safety laboratory tests (hematology and serum chemistry)
  - Lipids (total cholesterol, HDL, LDL, and triglycerides)
  - iPTH
  - PK (serum romosozumab concentration)
  - Antiromosozumab antibodies
  - BTMs (P1NP and sCTX) - sample for sCTX must be collected from subjects in a fasting state and before noon. Fasting state is defined as overnight fasting, with a minimum of 8h of fasting required.
- Perform BMD DXA scans at the lumbar spine, total hip, and femoral neck
- Recording of concomitant medications
- Recording of concomitant medical procedures
- Recording of AEs
- Discuss signs and symptoms of MI and stroke
- Record any change in the subject's daily calcium and vitamin D supplementation

8.4 Follow-Up Period

8.4.1 Visit 15 (Month 15) – End-of-Study Visit

The EOS Visit will occur 4 months after the final administration of OL romosozumab (Visit 13) and 3 months after the final study visit (Visit 14) in the OL Treatment Period. At this visit, the following procedure and assessments will be performed/recorded:

- Obtain a blood sample for antiromosozumab antibody testing
- Recording of concomitant medications
- Recording of concomitant medical procedures
- Recording of AEs
- Record any change in the subject's daily calcium and vitamin D supplementation before instructing the subject for study purposes to stop taking the supplements

8.5 Early Termination Visit

Subjects who withdraw from the study for any reason prior to the EOS Visit should complete the ET Visit. The procedures and assessments to be performed at this visit are the same as those listed for the final study visit (Visit 14) in the OL Treatment Period, with the exception of lipids

(see Section 8.3.3). These subjects will be encouraged to return to the study site for the EOS Visit (see Section 8.4.1).

8.6 Unscheduled Visit

At the investigator's discretion, an Unscheduled Visit may be completed at any time during the study but prior to the EOS Visit, if deemed necessary for the subject's safety and well-being. Details of this visit should be recorded on the subject's chart.

At this visit, any of the following assessments may be performed, depending on the reason for the visit:

- Confirm that the subject fulfills none of the withdrawal criteria
- Perform a physical examination
- Measure vital signs (BP, pulse rate, and temperature)
- Perform a 12-lead ECG
- Safety laboratory tests (hematology and serum chemistry)
- Recording of AEs
- Recording of concomitant medications
- Any other assessments that the investigator deems necessary

8.7 Study conduct during coronavirus disease 2019

The protocol mandated visit schedule should be followed to the closest extent possible, based on the judgment of the investigator. However, during the coronavirus disease 2019 (COVID-19) epidemic or under other exceptional circumstances, remote follow-up may be conducted and the subjects may be contacted by telephone/video to assess as many details as possible, according to the protocol scheduling, to verify that the subject is suitable for continuing study treatment. In-person follow-up at an alternative study site or a home visit is acceptable. Some procedures may be collected by other remote means, if feasible. Study sites should make efforts to inform the sponsor or the CRO in the event that protocol procedures cannot be completed due to COVID-19.

In those situations when the subject cannot return to the study site, the investigators are to assess the subject's safety by telephone/video contact.

Ad hoc subject contact may be warranted to understand the current health status of the subjects, to follow up on AEs, and inform them of any protective measures taken by the clinical site as a result of the COVID-19 pandemic (eg, any measures that may limit access to the site or may require additional actions by the subject prior to entry to the site).

If a subject visits another facility for a medical issue, the investigator should request a detailed explanation of the subject's condition and her participation in the clinical study from the subject or caregiver. Subjects or caregivers shall be reminded to completely collect and keep records of this visit.

9 ASSESSMENT OF PHARMACOKINETIC/PHARMACODYNAMIC VARIABLES

9.1 Assessment of pharmacokinetic variables

Blood samples for the determination of serum concentrations of romosozumab will be collected at the time points specified in the schedule of study assessments (Table 5–1).

At the visits where IMP is administered, the PK samples will be drawn prior to dosing. For those visits where samples for PK testing are collected, vital signs are measured, and 12-lead ECG are recorded, the vital sign measurements and 12-lead ECG readings should be taken prior to the collection of the PK samples.

The dates and times of IMP administration and PK collection will be recorded in the eCRF.

A fully validated bioanalytical method will be utilized to determine concentration of romosozumab. Detailed information on sample analysis will be provided in a separate bioanalytical report.

The PK samples will be processed and analyzed by the bioanalytical laboratory.

Methods for collecting, processing, storing, and shipping of the PK samples are presented in further detail in the bioanalytical laboratory manual.

The PK results will not be made available to the investigator and study-related site personnel at any time after the first administration of double-blind IMP to avoid any potential unblinding during the Double-Blind Placebo-Controlled Period and to minimize any bias being introduced during the OL Treatment Period, once the investigator is unblinded to individual treatment assignments.

9.2 Assessment of pharmacodynamic variables

The PD assessment is the concentration of BTMs, the bone formation marker, P1NP and the bone resorption marker, sCTX.

Blood samples for BTM analyses will be collected from subjects at the visits specified in Table 5–1. Blood samples to determine sCTX should be collected from the subject in a fasting state and before noon. Fasting state is defined as overnight fasting, with a minimum of 8h of fasting required. Blood samples should not be drawn from the same arm where IMP is administered.

Blood samples for BTMs will be processed and analyzed by a central laboratory.

Methods for collecting, processing, storing, and shipping of the BTM samples are presented in further detail in the laboratory manual.

At any time after the first administration of double-blind IMP, BTM results will not be reported to the investigator and study-related site personnel to avoid any potential unblinding during the Double-Blind Placebo-Controlled Period and to minimize any bias being introduced during the OL Treatment Period, once the investigator is unblinded to individual treatment assignments.

10 ASSESSMENT OF EFFICACY

The efficacy assessment in this study is BMD as measured by DXA scan at the lumbar spine, total hip, and femoral neck.

10.1 Bone mineral density measurements

Bone density measurements will be performed by DXA at the time points outlined in the schedule of study assessments (Table 5–1). All DXA scans will be analyzed by the central imaging vendor. Only Lunar or Hologic densitometers will be allowed in the study. All DXA scan data will be submitted electronically to the central imaging laboratory for analysis. Sites unable to submit data electronically can submit a compact disc or other media as specified in the DXA procedural manual, but electronic submission is preferred. After analysis by the central imaging vendor, the study site may be asked to re-acquire a scan due to malpositioning or other technical reasons. The study site must comply with these requests.

A separate DXA procedure manual provided by the central imaging vendor will give specific instructions for acquisition of scans as well as performance of Instrument Quality Control.

Bone density will be measured at the lumbar spine, total hip, and proximal femur. The DXA scans of the lumbar spine will be performed in duplicate (ie, subjects will be removed from the table inbetween scans). Lumbar spine scans must include L1 through L4. For total hip and proximal femur DXA scans, the left side should be used for all scans at all visits. If the right side must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study. If a subject fractures the hip that has been scanned during the study up to the time of fracture, no further scans will be obtained for the affected location. The same DXA machine must be used for a particular subject for the duration of the study.

For Screening purposes, DXA scans of the lumbar spine and proximal femur taken up to 35 days prior to the beginning of the Screening Period may be used if the following criteria are met:

- Images were obtained as part of the routine standard of care or following appropriate informed consent procedures
- Images were obtained by a trained technician using the parameters specified by the imaging vendor (refer to the appropriate imaging manual provided by the imaging vendor
- DXA images were obtained using the same DXA scanner that will be used for this study

To determine subject's eligibility based on BMD T-scores, lumbar spine and proximal femur DXA scans will be analyzed by the central imaging vendor. Subjects must have at least 2 evaluable lumbar vertebrae (L1-L4) and at least 1 evaluable hip as assessed by the central imaging vendor.

All BMD data will be analyzed by the central imaging vendor and these results will not be reported to the investigator and study-related site personnel at any time after the first administration of double-blind IMP to avoid any potential unblinding during the Double-Blind Placebo-Controlled Period and to minimize the introduction of any bias during the OL Treatment Period, once the investigator is unblinded to individual treatment assignments.

Investigators will be alerted if a subject experiences a BMD decrease from baseline of 7% or more at the lumbar spine, total hip, or femoral neck at any time during the study. The

investigator is required to discuss the implications for individual fracture risk and alternative treatment options and this discussion should be documented in the subject's records. If a decision is made to begin alternative treatment, the subject should discontinue IMP and every effort will be made for the subject to complete the remaining study visits and assessments (see Section 6.3.1).

11 ASSESSMENT OF SAFETY

In this study, the safety variables include the number and incidence of TEAEs; vital sign measurements; 12-lead ECG parameters; laboratory test results (hematology and serum chemistry), physical examination findings, and incidence of antibodies to romosozumab. The assessments of the safety variables are described below.

11.1 Adverse events

11.1.1 Definitions

11.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the investigator from the subject's history or the Baseline Period.

11.1.1.2 Serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)

- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 11.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

11.1.1.2.1 Anticipated serious adverse events

The Anticipated SAEs in Table 11–1 have been identified as these events are anticipated to occur in the osteoporotic population at some frequency that is independent of drug exposure.

This list does not change the investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 11.1.2.3.

Table 11–1: Anticipated SAEs for osteoporotic population

Population	Anticipated SAE
Osteoporotic	Pneumonia
	Osteoarthritis
	Femur fracture
	Chronic obstructive pulmonary disease
	Cholelithiasis
	Urinary tract infection
	Radius fracture
	Femoral neck fracture
	Lung neoplasm malignant

ISS=Integrated Summary of Safety; SAE=serious adverse event
Note: Anticipated SAEs are based on treatment-emergent SAEs with an exposure-adjusted incidence rate ≥0.2/100 subject-years in the placebo arm of placebo-controlled studies, with the exception of study endpoints, cerebrovascular event, and death (Source: ISS 2017, Table 14-6.7.2).

11.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

11.1.1.4 Adverse events of interest

The following AEs have been prospectively identified as AEs of interest for romosozumab:

- Injection site reactions
- Events potentially related to hypersensitivity
- Hypocalcemia
- Hyperostosis
- Osteoarthritis
- Malignancy
- Positively-adjudicated ONJ, AFF, and CV events

Details of the adjudication processes for ONJ, AFF, and CV events are provided in Section 13.4.3.1.

11.1.2 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the investigator should review any self-assessment procedures (eg, diary cards) employed in the study.

11.1.2.1 Description of adverse events

When recording an AE, the investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the AE eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

11.1.2.2 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

11.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the SAE Reporting section at the front of the protocol). The investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE Report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE Report form will be provided to the investigator. The Investigator SAE Report form must be completed in English.

It is important for the investigator, when completing the SAE Report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a

translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report form.

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE Report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the IB.

11.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 11.6.1.4.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the investigator must provide a justification. The follow up will usually be continued for 4 months after the subject has discontinued her IMP.

Information on SAEs obtained after clinical database lock will be captured through the PS database without limitation of time.

11.2 Pregnancy

Since the study population is postmenopausal women, it is not expected that any subject will become pregnant during the study. However, in the event that a pregnancy occurs, the procedures outlined in this section should be followed.

If an investigator is notified that a subject has become pregnant after the first intake of any IMP, the investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome form (for contact details see SAE reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an ET Visit and have the ET assessments performed with the exception of the BMD measurement by DXA (which is not to be performed).
- The investigator should immediately stop any further administration of the IMP at the ET Visit.
- An EOS Visit should be scheduled 4 months after the subject's final dose of IMP.

The investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the investigator. The progression of the pregnancy and the eventual birth (if applicable) must be

followed up using the Pregnancy Report and Outcome form in which the investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

11.3 Suspected transmission of an infectious agent

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

11.4 Overdose of investigational medicinal product

Overdose with this product has not been reported. The effects of overdose of this product are not known. An antidote to overdose of this product is not known. The maximum amount of romosozumab that can be safely administered in a single dose has not been determined, and there is currently insufficient information to draw any conclusions about the safety of doses higher than those studied in clinical studies. The highest single dose of romosozumab tested in clinical studies is 10mg/kg sc.

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

11.5 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

An independent DMC will be formed to monitor the ongoing safety of subjects in the study. Further details on the DMC is provided in Section 13.7.

11.6 Laboratory measurements

Blood samples will be collected for laboratory assessments at the time points specified in the schedule of study assessments (Table 5–1). Blood will be drawn by venipuncture before each IMP administration. The clinical laboratory parameters to be measured are presented in Table 11–2.

Serology (hepatitis/HIV) testing, laboratory tests (hematology and serum chemistry), an endocrine test (serum 25 [OH] vitamin D), and some hormone tests (iPTH, TSH, and T4) will be performed at Screening to determine the subject's eligibility for the study.

The central laboratory will be responsible for all clinical laboratory testing.

Details on the collection, storage, preparation, and shipping of samples to the central laboratory will be presented in the laboratory manual provided separately.

The following laboratory parameters will be measured:

Table 11–2: Clinical laboratory measurements

Hematology	RBC count, hemoglobin, hematocrit, platelet count, total WBC count and differentials consisting of absolute counts of the following leukocyte types: neutrophils, lymphocytes, monocytes, eosinophils, and basophils
Serum chemistry	Sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, albumin-adjusted calcium, magnesium, phosphorus, glucose, BUN, creatinine, total bilirubin, ALP, AST, and ALT
Lipids	Total cholesterol, LDL, HDL, and triglycerides
Serology[a]	HBsAg, HBcAb, HCV antibody, HIV 1 and 2 antibodies
Hormone	iPTH TSH and T4[a]
Endocrine[b]	Serum 25 (OH) vitamin D

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HDL=high density lipoprotein; HIV=human immunodeficiency virus; iPTH=intact parathyroid hormone; LDL=low density lipoprotein; OH=hydroxy; RBC=red blood cell; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell

[a] Testing will be performed only at Screening (Visit 1).

[b] Testing will be performed at Screening (Visit 1) and Visit 2 (Day 1).

The original printouts from the laboratory, signed or initialed by the investigator, will be kept at the study site. The laboratory data will be transferred electronically to UCB.

Results of laboratory assessments for serum calcium, albumin-adjusted calcium, phosphorus, ALP, P1NP, CTX, iPTH, romosozumab levels, and antiromosozumab antibodies are considered potentially unblinding and will not be reported to any study-related personnel after Day 1 in order to maintain the integrity of the study blind. However, in the event of an abnormal value of clinical relevance (panic value) for serum calcium, albumin-adjusted calcium, phosphorus, or

ALP, sites will be notified of the unblinded value by the central laboratory. After such notification is issued, the sites may perform additional follow-up blood draws for local analysis as required to support subject medical care.

All clinically significant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the investigator and the sponsor, or until the abnormality is explained by an appropriate diagnosis. All clinically significant values will be reported as AEs.

11.6.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.3, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 11.1.1.3), and, if applicable, also reported as an SAE (see Section 11.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11–3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 11.6.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 11.6.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.3.3), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 11.6.1.2.1 are met, rechallenge with IMP may be appropriate.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below (Table 11–3) summarizes the approach to investigate PDILI.

Table 11–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.6.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 11.6.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	

Table 11–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Hepatology consult if there is no evidence of resolution (see Follow up requirements).[c] Discussion with Medical Monitor required.	IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase during 2-week monitoring period. • Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 2-week monitoring period.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 11.6.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • Discontinue IMP if levels remain ≥5xULN (and ≥2x baseline); monitor until values normalize, stabilize, or return to within baseline values.[d] • Continue IMP if levels are no longer ≥5xULN (and ≥2x baseline); continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values.[d]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 11.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

11.6.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 11.6.1.3) and SAE report (if applicable).

11.6.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.3 and Table 11–3 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

11.6.1.2.1 IMP restart/rechallenge (if applicable)

Rechallenge in a subject in whom a potentially causing drug-induced liver injury event is suspected, is dangerous, may be fatal, and must not occur.

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 11-3), but for whom an alternative diagnosis is confirmed, ie, drug-induced liver injury is excluded, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 11.6.1.3 and Section 11.6.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician, DMC, and a hepatologist. The hepatologist must be external to UCB but may be a member of the DMC. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the investigator-recommended monitoring plan and understands their individual benefit risk for restarting IMP and this is adequately documented.

11.6.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 11–4 (laboratory measurements) and Table 11–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 11–4: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic(s); RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 11–5: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

11.6.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 11–3. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

11.7 Other safety measurements

Other safety measurements will include vital signs, 12-lead ECG readings, physical examination findings, and the incidence of antibodies to romosozumab.

11.7.1 Vital sign measurements

Vital signs (BP [systolic and diastolic], pulse rate, and body temperature [oral or otic]) should be measured at the time points specified in Table 5–1.

Vital sign measurements will be recorded after the subject is in a seated or semi-recumbent position for at least 3 minutes. The subject's preferred position should remain consistent

throughout the study. The BP readings should be taken from the same arm by the same qualified individual throughout the study.

The method used for measuring the subject's body temperature should be consistent throughout the study and documented in the subject's eCRF.

11.7.2 12-lead ECG recordings

Standard 12-lead ECGs will be recorded at the time points specified in Table 5–1. All ECGs will be recorded after the subject is in a seated or in a semi-recumbent position for at least 3 minutes.

The ECGs will be read by a central reader. The PR, RR, QRS, QT, and corrected QT (QTc) intervals and heart rate will be assessed.

At any time during the study, the investigator may consult with the cardiologist at the central ECG laboratory to confirm the presence of a clinically significant ECG abnormality. It remains the responsibility of the investigator to decide whether an ECG finding is of clinical significance on the basis of the complete clinical picture and whether this finding influences the subject's participation in the study.

11.7.3 Physical examination

Physical examinations will be performed at the time points specified in Table 5–1. Findings considered as clinically significant changes since the physical examination at Screening (Visit 1) will be recorded as AEs.

11.7.4 Body weight and height

Body weight (subject in underwear or light clothing, without shoes) and height (subject without shoes) will be recorded at the time points specified in the schedule of study assessments in Table 5–1. The subject's BW will be rounded to the nearest 0.1kg. The subject's height will be rounded to the nearest 0.5cm.

11.7.5 Antibodies to romosozumab

Blood samples for antiromosozumab antibody testing will be collected from subjects at the time points indicated in Table 5–1. However, only samples from subjects who receive romosozumab will be analyzed for antiromosozumab binding antibodies.

A fully validated bioanalytical method will be utilized to determine antibodies to romosozumab. Detailed information on sample analysis will be provided in a separate bioanalytical report.

The investigator will be notified of any positive neutralizing antibody results to romosozumab detected at the EOS Visit or ET Visit. Subjects who test positive for neutralizing antibodies to romosozumab at the EOS Visit or ET Visit will be asked to return for additional follow-up testing. This testing should occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (±4 weeks) after IMP administration. All follow-up results both positive and negative will be communicated to the site. More frequent testing (eg, QM) or testing over a longer period may be requested in the event of safety-related concerns.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an antiromosozumab antibody response may also be asked to return for additional follow-up testing.

Blood samples for antibody determination will be processed and analyzed by the bioanalytical laboratory.

Methods for collecting, processing, storing, and shipping of the samples are presented in further detail in the bioanalytical laboratory manual.

No notifications of a positive antibody status will be sent to the investigator before the EOS Visit or ET Visit to avoid any potential unblinding during the Double-Blind Placebo-Controlled Period and to minimize any bias being introduced during the OL Treatment Period, once the investigator is unblinded to individual treatment assignments.

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Adherence to protocol

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the investigator must notify the CPM of the sponsor within 24 hours and follow any local regulatory requirements.

12.2 Monitoring

Monitoring of the study will be delegated by UCB to a CRO. The CRO will monitor the study to meet the CRO's monitoring SOPs, ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate.

The investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each subject). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

12.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments

(such as removable self-stick notes). Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the investigator and become a permanent part of the subject's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

12.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes).

12.3 Data handling

12.3.1 Case Report form completion

The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the investigator's review and approval (by means of a password/electronic signature) will be reapproved by the investigator.

The investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

12.3.2 Database entry and reconciliation

External electronic data will be loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eCRFs once and are subsequently verified if the study is performed using electronic data capture.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

12.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The investigator will keep a Subject Identification Code list. This list remains with the investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

12.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

12.5 Archiving and data retention

The investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the investigator for 5 years after the completion/discontinuation of the study, or at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP (whichever is longest). These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's trial master file (TMF).

12.6 Audit and inspection

The investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing

study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the investigator will immediately inform UCB (or designee).

12.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the investigator, institution, institution staff, or designees of the sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

13 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

13.1 Definition of analysis sets

The following analysis sets are defined for this study:

- Enrolled Set (ES) will consist of subjects who signed the ICF.
- Randomized Set (RS) will consist of subjects who have been randomized. Disposition data are based on the ES and the RS.
- Safety Set (SS) will consist of all randomized subjects who received at least 1 dose of IMP. These subjects will be analyzed according to the actual treatment received, where subjects who receive at least 1 dose of romosozumab will be analyzed in the romosozumab treatment group regardless of the randomized treatment. Data on safety and exposure will be based on the SS.
- The Full Analysis Set (FAS) will consist of all randomized subjects who received at least 1 dose of IMP and provided at least 1 baseline and post-baseline BMD measurement. In the case of dosing administration error, analyses of the FAS will be conducted according to randomized treatment. This will be the primary efficacy analysis set. The FAS will be used for demographics, disease characteristics, and BMD efficacy analysis.
- The Per-Protocol Set (PPS) will consist of subjects in the FAS who have completed a minimal exposure of 6 months of a treatment regimen without any important protocol deviations that may influence the validity of the data for the primary efficacy variable. Post-baseline deviations will not necessarily lead to exclusion of a subject from PPS analysis but may lead to exclusion of data. The PPS will be used as sensitivity analyses for BMD efficacy analysis.
- The Pharmacokinetic Per-Protocol Set (PK-PPS) will include all subjects in the SS who have at least 1 evaluable serum romosozumab concentration measurement with no further PK-related important protocol deviations. This analysis set will be used in the PK analyses.

- The Pharmacodynamic Per-Protocol Set (PD-PPS) will include all subjects in the SS who have at least 1 evaluable BTM measurement with no further PD-related important protocol deviations. This analysis set will be used in the analyses of BTMs.

13.2 General statistical considerations

Statistical evaluation will be performed by the biostatistics department at UCB and/or CRO. All computations will be performed using SAS® version 9.4 or later (SAS Institute, NC, USA).

Summary statistics will consist of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, standard deviation (SD), median, minimum and maximum, coefficient of variation) will be tabulated. Data may be summarized by treatment group, and in addition, may be summarized by time.

If not otherwise stated, baseline will be the predose value or, if missing, the Screening value. Baseline characteristics (eg, gender, age, weight, height, body mass index) for the SS will be summarized descriptively.

For addressing multiplicity issues, a hierarchical testing procedure will be implemented which consists of 3 steps:

1. Lumbar spine BMD percent change from baseline at 6 months
2. Total hip BMD percent change from baseline at 6 months
3. Femoral neck BMD percent change from baseline at 6 months

Step 2 will be executed in a confirmatory sense only if the statistical test in Step 1 was statistically significant using a 2-sided type I error rate of 0.05.

Step 3 will be executed in a confirmatory sense only if the test in Step 1 and the test in Step 2 are statistically significant on a level of 0.05 (2-sided).

Data listings will be prepared for subjects with available data (ES, RS, SS, FAS, PD-PPS, and PK-PPS), depending on the domain.

13.3 Planned analyses

13.3.1 6-month analysis

The 6-month analysis of efficacy and safety will be performed after all subjects have completed the 6-month Double-Blind, Placebo-Controlled Period. After the last subject last visit of the 6-month Double-Blind Placebo-Controlled Period and after data cleaning, a database snapshot will be taken for the 6-month analysis. Following the snapshot, the study will be unblinded to the individuals at the sponsor and CRO involved in conducting the statistical analysis and in the compilation of the statistical analysis report and the CSR. The investigators and sponsors initially remain blinded. After internal finalization of the CSR, the unblinding of the investigators is required to conduct the stamping process. However, the investigators are still obliged not to disclose the initial double-blind treatment assignment to the individual subjects as long as the subjects are included in the OL Treatment Period. Subjects will remain blinded to the Double-Blind, Placebo-Controlled Period treatment assignment throughout the study.

The primary variable of the 6-month analysis is the evaluation of the effect of treatment with romosozumab compared with placebo on the percent change in BMD at the lumbar spine in

postmenopausal Chinese women with osteoporosis. Formal statistical testing will be performed (see Section 13.2).

The secondary variables of the 6-month analysis are to evaluate the effects of treatment with romosozumab compared with placebo on the percent change in BMD at the total hip and femoral neck. For these endpoints, confirmatory testing will be performed as outlined in Section 13.2.

Other variables of the 6-month analysis include the evaluation of the effect of treatment with romosozumab compared with placebo at 3 months on the percent change in BMD at the lumbar spine, total hip and femoral neck, the evaluation of the effect of treatment with romosozumab compared with placebo at 1-, 3-, and 6-month time points on the percent changes in BTMs, and to characterize serum concentrations of romosozumab in subjects who are randomized to romosozumab for 6 months. For the other variables, statistical testing will be performed in an exploratory manner.

The safety analyses of the 6-month analysis will compare the safety of romosozumab treatment with placebo in postmenopausal Chinese women with osteoporosis. The safety analyses in the 6-month analysis will include all available data collected up to the time of 6-month data snapshot.

13.3.2 Final analysis

After all subjects have the opportunity to complete the Month 15 Visit, a further database snapshot or database lock will be executed. Based on these data, the remaining efficacy and safety analyses for Month 12 and the safety analyses for the overall study period, ie, the period from the start of double-blind treatment to the Month 15 Visit for each subject will be evaluated.

13.4 Planned efficacy analysis

13.4.1 Analysis of the primary efficacy variable

The comparison of the percent change from baseline in lumbar spine DXA BMD at Month 6 between treatment groups will be evaluated using an analysis of covariance (ANCOVA) model. The ANCOVA model will include treatment group, baseline BMD value, machine type at baseline, and interaction of baseline BMD value and machine type at baseline as independent variables. Summaries of the results will include least squares (LS) means point estimates of the percent change from baseline for each treatment arm. The 2-sided 95% CI and associated p-value will be provided for the difference between the LS means for romosozumab and placebo.

A sensitivity analysis with a repeated measurements model will be fit with the percent change from baseline at Months 3 and 6 in BMD of the lumbar spine as the dependent variable, and baseline BMD, machine type, interaction of baseline BMD and machine type, visit (categorical), treatment (categorical), and interaction of treatment and visit as the independent variables. The variance structure will allow for heteroskedasticity of variance between treatment groups. Due to the sensitivity nature of this analysis, formal significance testing will not be conducted.

A blinded data review process will be implemented in which the missingness of data, statistical assumptions, and eligibility of definition of categorical variables/thresholds will be assessed. If it turns out that the number of randomized subjects without baseline and/or without BMD measurement at an on-treatment visit is high, then a sensitivity analysis under blinded conditions will be executed using multiple imputation strategies under the “missing at random” assumption.

Furthermore, depending on the amount of missingness and on frequencies of treatment discontinuations, additional sensitivity analyses under "missing not at random" assumptions may be defined as well. If such analyses are needed, they will be prespecified in the SAP before unblinding and database lock.

For these BMD analyses, the FAS will be used. The results from the central imaging vendor will be used in the BMD analyses.

13.4.1.1 Analysis of secondary variables

For the secondary efficacy BMD endpoints (at total hip and femoral neck at Month 6), a percent change from baseline in DXA BMD will employ an ANCOVA model. The ANCOVA model will include treatment group, baseline value of BMD, machine type at baseline and interaction of baseline BMD value and machine type at baseline as independent variables. Summaries of the results will include LS means point estimates of the percent change from baseline for each treatment arm. The variance structure will allow for heterogeneity between treatments. The 2-sided 95% CI and associated p-value will be provided for the difference between the LS means for romosozumab and placebo. The FAS will be used for these analyses.

A sensitivity analysis with a repeated measurements model will be fit with the percent change from baseline at Months 3 and 6 in BMD of the corresponding skeletal location (ie, total hip or femoral neck) as the dependent variable and baseline BMD, machine type, interaction of baseline BMD and machine type, visit (categorical), treatment (categorical), and interaction of treatment and visit as the independent variables. The variance structure will allow for heteroskedasticity of variance between treatment groups. Due to the sensitivity nature of this analysis, formal significance testing will not be conducted.

13.4.2 Planned pharmacokinetic and pharmacodynamic analyses

13.4.2.1 Planned pharmacokinetic analyses

The serum trough concentrations of romosozumab will be summarized using descriptive statistics for those subjects who continued with 6 months of romosozumab after initially being randomized to 6 months of romosozumab treatment and for those subjects who are initially randomized to placebo for 6 months and transition to romosozumab for 6 months.

Geometric mean (geometric coefficient of variation) and mean (±SD) romosozumab serum concentration time profiles will be displayed graphically.

Individual concentration-time profiles will be displayed graphically on a linear scale and semi-logarithmic scale.

The PK-PPS will be used in this analysis.

13.4.2.2 Planned pharmacodynamic analyses

For the BTMs (P1NP and sCTX), descriptive statistics will be presented by treatment group at selected time points for both the romosozumab and placebo group. Descriptive statistics (eg, mean, median) will be displayed for the actual values (ie, observed variables without further imputation), change from baseline, and the percent changes from baseline in BTMs at each time point. In addition, AUC through Month 12 in P1NP will be produced by treatment group.

Pharmacodynamic-time plots will be generated for each PD parameter at selected time points for both the romosozumab and placebo group and these plots will be displayed on the same figure.

Pharmacodynamic-time plots will be generated for the percent change from baseline for each PD parameter at selected time points for both the romosozumab and placebo group and these plots will be displayed on the same figure.

The PD-PPS will be used for these analyses.

13.4.3 Planned safety and other analyses

13.4.3.1 Safety analyses

The number and incidence of TEAEs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term (PT). The incidence of TEAEs will also be summarized by intensity and relationship to IMP. In accordance with routine pharmacovigilance activities for romosozumab, any serious CV, ONJ, or AFF events will be subject to independent adjudication.

Three separate independent adjudication committees will review and adjudicate on potential ONJ events, potential AFF events, and potentially serious CV events, respectively. Each adjudication committee will comprise of experts in that specific field. All events of ONJ and AFF reported during the study and those potential events identified through a predefined search of MedDRA terms will be submitted for blind review and adjudication to the relevant adjudication committee. All deaths and SAEs deemed by the investigator to be of potential CV origin or etiology and SAEs with terms mapping to a predefined MedDRA PT list potentially indicative of CV etiology will be submitted to the CV committee for review and adjudication.

Vital sign variables and ECG parameters and changes from baseline will be descriptively summarized by scheduled time points.

Laboratory parameters (hematology and serum chemistry) and changes from baseline will be descriptively summarized at each time point. Shift tables from baseline to each post-baseline time point will be presented.

The incidence and percentage of subjects who develop antiromosozumab antibodies (binding and neutralizing) at any time will be tabulated only for the romosozumab group.

Physical examination abnormalities will be listed by treatment.

13.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy (effectiveness), key safety, or PK/PD outcomes for an individual subject. The criteria for identifying important protocol deviations will be predefined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to unblinding to confirm exclusion of data from analyses and subjects from analysis sets.

13.6 Handling of dropouts or missing data

In general, even if the study treatment is discontinued, the subjects will be encouraged to continue the study schedule up to the planned final visit. For all subjects, all available data will

be included in analysis, regardless of whether the data are collected before or after the subject discontinues study treatment or before or after the subject takes alternative or prohibited medication. Potentially, (few) deaths could occur under this study protocol. However, these events mostly likely will not be linked to the study indication so that data in all the missed assessments after occurrence of death will be seen as missing.

Missing baseline BMD by DXA at any anatomical site will not be imputed and evaluated for the BMD analysis.

Missing post-baseline BMD will be imputed using the LOCF approach (by carrying forward the last nonmissing post-baseline value prior to the missing value from the same anatomical site) in the 6-month analysis. For the OL Treatment Period variables, only the OL Treatment Period value will be used for imputation, the values in the Double-Blind, Placebo-Controlled Period will not be carried forward into the OL Treatment Period. To ensure that the imputation approach provides valid results, sensitivity analyses with varying imputation methods will be defined. Those will include repeated measurement model and multiple imputation strategies as needed.

If a subject has BMD values from different DXA machine types (ie, Hologic and Lunar) only those BMD values that are collected from the same machine type as the baseline BMD will be used for analyses and imputation. For anatomical sites that can be measured on different body sides (ie, left and right), only those BMD values that are collected from the same body side as the baseline BMD will be used for analyses and imputation.

Missing BTMs (either baseline or post-baseline values) or PK will not be imputed. Any values below the lower limit of quantification (LLOQ) will be imputed using the LLOQ/2 for analysis.

The impact of COVID-19 and COVID-19 vaccination will be evaluated at the blinded data evaluation meetings and details of analysis will be provided in the SAP.

13.7 Planned interim analysis and data monitoring

No interim analysis is planned for this study.

An independent DMC will be formed to monitor the ongoing safety of subjects in the study. The DMC will periodically review study data for potential safety issues.

At each DMC meeting, safety and tolerability data will be available. Other data eg, PK data, may be provided to the DMC, if requested. In the case the DMC needs information that requires unblinding of individuals, an independent unblinded analysis group will be established consisting of personnel not otherwise involved in the conduct of this study who have access to the critical data. The data that requires unblinding will be disclosed and discussed in the closed session to which no sponsor or CRO personnel will have access. The precautions to preserve the blinding will be detailed in the DMC charter.

Data will be presented by individuals not otherwise involved in the conduct of the study. The deliberations and decisions of the DMC will be formally minuted/documented.

Ad hoc DMC meetings can be held for other reasons if deemed appropriate by the sponsor or the DMC members.

Details of the role, scope, composition, responsibilities, and operation of the DMC, as well as the identity of the DMC members, will be defined in a separate DMC Charter.

13.8 Determination of sample size

The sample size calculations were done using historical BMD data of all 3 anatomical sites taken into account from the romosozumab studies 20070337 and 20120156.

- Assumptions for BMD of the lumbar spine:

Postmenopausal women with osteoporosis in 20120156 showed a treatment difference of 8.4 with 95% CI: 6.9 to 9.9 when compared with placebo BMD response at lumbar spine. Furthermore, postmenopausal women with osteoporosis in 20070337 showed a treatment difference of 9.4 (95% CI: 7.9 to 10.8). Taking the minimum of the lower confidence bound (conservative approach) results in an assumption of 6.9 for the treatment difference in percentage change from baseline at Month 6.

For postmenopausal women with osteoporosis in 20120156, the upper bounds of the SDs were 4.94 for the romosozumab group and 3.93 for the placebo group; in 20070337, the upper bounds of the SDs were 6.10 and 3.32, respectively. This indicates that SDs were differing between romosozumab and placebo necessitating a statistical test accounting for differing SDs. To merge the SDs of 20070337 and 20120156, the pooled common SDs were calculated separately for romosozumab and placebo taking the upper bound in each study and each arm (conservative approach). As a result, the assumptions for the SDs are 5.26 for the romosozumab arm and 3.34 for the placebo arm.

- Assumptions for BMD of the total hip

Studies 20070337 and 20120156 showed a minimum treatment difference on total hip BMD of 3.5 (95% CI: 2.5 to 4.4) when compared with placebo. The combined upper bounds of the SDs for 20070337 and 20120156 were 3.80 for the romosozumab group and 3.03 for the placebo group.

- Assumptions for BMD of the femoral neck:

Studies 20070337 and 20120156 showed a minimum treatment difference on femoral neck BMD of 3.2 (95% CI: 2.0 to 4.3) when compared with placebo. The combined upper bounds of the SDs for 20070337 and 20120156 were 4.39 for the romosozumab group and 4.10 for the placebo group.

- Resulting sample size:

For the sample size calculations, a 2-group Satterthwaite t-test will be assumed (2-sided on a 5% significance level) which allows for unequal SDs and unequal sample size ratios. Taking into account the upper bounds pooled common SDs and the minimum effect size as assumptions (BMD of the femoral neck outlined above), the sample size of 146 subjects for romosozumab and 73 subjects for placebo would preserve at least 90% power for the percent change from baseline in BMD of the lumbar spine, total hip and femoral neck at Month 6.

To give a reasonable chance to show significance, at least 90% power for all 3 anatomical sites, following a hierarchical testing procedure (see Section 13.2) with safety objectives and dropout taken into account, a total sample size of 300 subjects (ie, 200 subjects in the romosozumab group and 100 subjects in the placebo group) seemed appropriate.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the investigator.

Prior to participation in the study, the ICF should be signed and personally dated by the subject, or her legal representative, and by the person who conducted the informed consent discussion (investigator or designee). The subject or her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each subject must consent to direct access to her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the ICF is amended during the study, the investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IRB/IEC and use of the amended form.

The subject may withdraw her consent to participate in the study at any time. A subject is considered as enrolled in the study when she has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained her written consent to participate in the study.

14.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The investigator will fill in the subject identifying information and medical emergency contact information. The investigator will instruct the subject to keep the card with her at all times.

14.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, ICF, IB, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the investigator or the sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the sponsor (or its representative) with evidence of such IRB/IEC notification.

14.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

14.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

15 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the investigator and/or CRO agreements, as applicable.

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17 APPENDICES

17.1 Protocol Amendment 1

Rationale for this amendment

In this amendment, the definition of "month" has been revised to ensure that the analysis windows defined for this study are similar to those utilized in the global clinical program. Minor inconsistencies have been corrected. This amendment is considered nonsubstantial as these changes do not impact the efficacy, safety, or the conduct of the study.

Specific changes to the protocol

Section	Original text	Revised text	Reason for change
Table 5-1, footnote [a]	[a] For the purpose of this study, a month is defined as a 4-week period of 28 days.	[a] For the purpose of this study, a month is defined as 30 days.	To be similar to the global clinical program
Section 6.3.2	These subjects will be encouraged to return to the study site to complete the procedures and assessments for the EOS Visit, 16 weeks after the final administration of IMP.	These subjects will be encouraged to return to the study site to complete the procedures and assessments for the EOS Visit, 4 months after the final administration of IMP.	Timing of EOS Visit or follow up after subject's final administration of IMP to be consistent throughout the protocol
Section 8	For the purpose of this study, a month is defined as a 4-week period of 28 days.	For the purpose of this study, a month is defined as 30 days.	To be similar to the global clinical program
Section 11.1.3	The follow up will usually be continued for 12 weeks after the subject has discontinued her IMP.	The follow up will usually be continued for 4 months after the subject has discontinued her IMP.	Timing of EOS Visit or follow up after subject's final administration of IMP to be consistent throughout the protocol
Section 11.2, 3rd bullet	• An EOS Visit should be scheduled 16 weeks after the subject's final dose of IMP.	• An EOS Visit should be scheduled 4 months after the subject's final dose of IMP.	Timing of EOS Visit or follow up after subject's final administration of IMP to be consistent throughout the protocol

17.2 Protocol Amendment 2

Rationale for this amendment

This amendment is considered substantial as the changes will impact the safety of the subjects in the study. In this context, specific inclusion and exclusion criteria have been added to affirm that the patient population in the study is osteoporosis in postmenopausal women with high risk of fracture, and to ensure that patients who are at the highest cardiovascular risk are excluded from the study. To be included in the study, patients must present with at least 1 independent risk factor for fracture and have no history of MI or stroke. In addition, a careful individual assessment of the patient's CV risk profile must be completed by the investigator in accordance with their routine clinical practice, with discussion of the signs and symptoms of MI and stroke on an ongoing basis, thereafter.

Other changes include removal of 1 of the PK variables (normalized serum trough concentration of romosozumab by BW) as this is already covered in the planned PK-PPS analysis; removal of serum protein electrophoresis testing as multiple myeloma or related lymphoproliferative disorder is no longer assessed at Screening; removal of serum pregnancy test to identify a PDILI event given that the study population is postmenopausal women and also planned pregnancy is exclusionary; clarification of the process in the event of a clinical significant (panic value) for selected laboratory results, and clarification of the model to be used in the sensitivity analyses.

Specific changes

Details are presented in the following table.

Section	Original text	Revised/new text	Reason for change
Title Page	UCB Biopharma SPRL Allée de la Recherche 60 1070 Brussels BELGIUM	UCB Biopharma SRL Allée de la Recherche 60 1070 Brussels BELGIUM	Company name legally changed
Study Contact Information, Sponsor	UCB Biopharma SPRL Allée de la Recherche 60 1070 Brussels BELGIUM	UCB Biopharma SRL Allée de la Recherche 60 1070 Brussels BELGIUM	Company name legally changed
List of Abbreviations	None	MI myocardial infarction	Abbreviated in text
Section 1, Summary	Eligible subjects will be randomized, stratified by age and prevalent vertebral fracture, in a 2:1 ratio to receive romosozumab 210mg subcutaneously (sc) every month (QM) or matched placebo sc QM in a blinded manner for 6 months.	Eligible subjects will be randomized, stratified by age, in a 2:1 ratio to receive romosozumab 210mg subcutaneously (sc) every month (QM) or matched placebo sc QM in a blinded manner for 6 months.	Stratification by prevalent vertebral fracture no longer necessary due to the new inclusion criterion #5
Section 4.1.2.1, Other pharmacokinetic variables	The other PK variables are serum trough concentrations of romosozumab and normalized serum trough concentrations by BW at Day 1 (baseline) and at Months 1, 3, and 6.	The other PK variables are serum trough concentrations of romosozumab at Day 1 (baseline) and at Months 1, 3, and 6.	Variable considered unnecessary as the normalized serum trough concentration by BW will be accounted for in the planned PK-PPS analysis

Section	Original text	Revised/new text	Reason for change
Section 4.2.2.1, Other pharmacokinetic variables	• Serum trough concentrations of romosozumab and normalized serum trough concentrations by BW at Months 7, 9, and 12 in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab in the Double-Blind, Placebo-Controlled Period (a total of 12 months of romosozumab treatment). • Serum trough concentrations of romosozumab and normalized serum trough concentrations by BW at Months 7, 9, and 12 (1, 3, and 6 months of romosozumab exposure, respectively) in subjects who are initially randomized to placebo in the Double-Blind, Placebo-Controlled Period and transition to romosozumab treatment for 6 months.	• Serum trough concentrations of romosozumab at Months 7, 9, and 12 in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab in the Double-Blind, Placebo-Controlled Period (a total of 12 months of romosozumab treatment). • Serum trough concentrations of romosozumab at Months 7, 9, and 12 (1, 3, and 6 months of romosozumab exposure, respectively) in subjects who are initially randomized to placebo in the Double-Blind, Placebo-Controlled Period and transition to romosozumab treatment for 6 months.	Variable considered unnecessary as the normalized serum trough concentration by BW will be accounted for in the planned PK-PPS analysis
Section 5.1.1, Screening Period	To be eligible to participate in the study, subjects must be postmenopausal Chinese women, 55 to 90 years of age (inclusive), and have a BMD T-score ≤-2.50 at the lumbar spine, total hip, or femoral neck at Screening, with at least 2 vertebrae in the lumbar (L)1 through L4 region and at least 1 hip evaluable by DXA.	To be eligible to participate in the study, subjects must be postmenopausal Chinese women, 55 to 90 years of age (inclusive), have a BMD T-score ≤-2.50 at the lumbar spine, total hip, or femoral neck and an independent risk factor for fracture at Screening, with at least 2 vertebrae in the lumbar (L)1 through L4 region and at least 1 hip evaluable by DXA.	To affirm that the patient population in the study is osteoporosis in postmenopausal women with high risk of fracture
Section 5.1.1, Screening Period	In addition, before enrolling subjects in the study, a careful individual assessment of the CV risk profile should be performed (including evaluation of CV history, CV risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking and severe renal impairment and other relevant results from the Screening investigations such as ECG).	In addition, before enrolling subjects in the study, a careful individual assessment of the CV risk profile should be performed.	Examples of CV risk provided were not exhaustive. Removal of these examples allows the investigator to conduct an individualized assessment in accordance with their routine clinical practice

Section	Original text	Revised/new text	Reason for change
Section 5.1.2, Double-Blind, Placebo-Controlled Period	Approximately 300 subjects will be randomized, stratified by age (<75 years, ≥75 years) and prevalent vertebral fracture (yes, no), in a 2:1 ratio to receive romosozumab 210mg sc QM (200 subjects) or matched placebo sc QM (100 subjects) in a blinded manner for 6 months to evaluate if romosozumab treatment compared with placebo is effective in increasing BMD, as assessed by DXA at the lumbar spine, total hip, and femoral neck.	Approximately 300 subjects will be randomized, stratified by age (<75 years, ≥75 years), in a 2:1 ratio to receive romosozumab 210mg sc QM (200 subjects) or matched placebo sc QM (100 subjects) in a blinded manner for 6 months to evaluate if romosozumab treatment compared with placebo is effective in increasing BMD, as assessed by DXA at the lumbar spine, total hip, and femoral neck.	Stratification by prevalent vertebral fracture no longer necessary due to the new inclusion criterion #5
Section 5.2, Table 5-1, Schedule of study assessments	None	Activity added: Discuss signs and symptoms of myocardial infarction and stroke[d] - at all visits except Screening (Visit 1) and Visit 15/EOS	Patient assessment added to align with the risk minimization measures and warnings and precautions for use for romosozumab
Section 5.2, Table 5-1, Schedule of study assessments	Activity removed: Serum protein electrophoresis[i]	None	Serum protein electrophoresis has been removed since multiple myeloma or related lymphoproliferative disorder is no longer assessed at Screening (revised exclusion criterion #19)
Section 5.2, Table 5-1, Schedule of study assessments	Footnote [d]: Lifestyle records subject's alcohol use, tobacco use, and caffeinated beverage use. (now footnote [e])	Footnote [d]: Before enrolling subjects in the study, a careful individual assessment of the cardiovascular risk profile should be performed.	Patient assessment added to align with the risk minimization measures and warnings and precautions for use for romosozumab

Section	Original text	Revised/new text	Reason for change
Section 5.2, Table 5-1, Schedule of study assessments	Footnote [i]: This test will be performed to exclude subjects with multiple myeloma or related lymphoproliferative disorder. Serum protein electrophoresis can be performed by the local laboratory in the case electrophoresis results are available within 6 months of signing ICF. If no serum protein electrophoresis data available within 6 months, serum protein electrophoresis should be performed by the central laboratory at the Screening Visit (removed).	Footnote [i]: A blood sample for lipid testing (total cholesterol, LDL, HDL, and triglycerides) will be collected with the subject in a fasted state. Fasting state is defined as overnight fasting, with a minimum of 8h of fasting required. (previously footnote [h])	Serum protein electrophoresis has been removed since multiple myeloma or related lymphoproliferative disorder is no longer assessed at Screening (revised exclusion criterion #19)
Section 6.1, Inclusion criteria (#5)	5. Subject has at least 2 vertebrae in the L1 to L4 region and at least 1 hip that are evaluable by DXA, as assessed by the central imaging vendor. (now inclusion criterion #6)	New criterion: 5. Subject must have at least 1 of following independent risk factors for fracture: • History of fragility fracture (except hip fracture, a severe [SQ3] vertebral fracture or more than 2 moderate [SQ2] vertebral fractures [see exclusion criteria]); • Parental history of hip fracture; • Low body weight (body mass index ≤19kg/m^2); • Elderly (age ≥65 years); • Current smoker	To affirm that the patient population in the study is osteoporosis in postmenopausal women with high risk of fracture
Section 6.2, Exclusion criteria (#4)	4. Subject has used oral bisphosphonates: - Any doses received within 3 months prior to randomization (Day 1). - More than 1 month of cumulative use between 3 and 12 months prior to randomization. - More than 3 years of cumulative use, unless the last dose was received ≥5 years prior to randomization. (now exclusion criterion #7)	New criterion: 4. Subject has a history of myocardial infarction (MI).	To exclude patients at highest risk of future MI events

Section	Original text	Revised/new text	Reason for change
Section 6.2, Exclusion criteria (#5)	5. Subject has used intravenous (iv) bisphosphonates: - zoledronic acid ◦ Any doses received within 3 years prior to randomization. ◦ More than 1 dose received within 5 years prior to randomization. - iv ibandronate, iv pamidronate, or iv ALN ◦ Any doses received within 12 months prior to randomization. ◦ More than 3 years of cumulative use, unless the last dose was received ≥5 years prior to randomization. (now exclusion criteria #8)	New criterion: 5. Subject has a history of stroke.	To exclude patients at highest risk of future stroke events
Section 6.2, Exclusion criteria (#6)	6. Subject has used denosumab or any cathepsin K inhibitor: - Any doses received within 18 months prior to randomization. (now exclusion criterion #9)	6. Subject has a vitamin D insufficiency, defined as 25 (OH) vitamin D levels <20ng/mL, as assessed by the central laboratory at Screening. Vitamin D repletion will be permitted and the subject may be retested once within the Screening Period. (previously exclusion criterion #18)	Exclusion criterion was moved up from #18 to #6 to maximize the operationalization of Screening activities
Section 6.2, Exclusion criteria (#10)	Criterion removed: 10. Subject has used activated vitamin D_3 or vitamin K2: - More than 1 month of cumulative use within 6 months prior to randomization.	10. Subject has used tibolone, cinacalcet, or calcitonin: - Any doses received within 3 months prior to randomization. (previously exclusion criterion #7)	Criterion determined as not necessary for regional study participation

Section	Original text	Revised/new text	Reason for change
Section 6.2, Exclusion criteria (#17)	17. Subject has a possible diagnosis of multiple myeloma or related lymphoproliferative disorder, as assessed by serum protein electrophoresis (Serum protein electrophoresis can be performed by the local laboratory in the case electrophoresis results are available within 6 months of signing ICF. If no serum protein electrophoresis data are available within 6 months, serum protein electrophoresis should be performed by the central laboratory at the Screening Visit.)	19. Subject has a confirmed diagnosis or under investigation for multiple myeloma or related lymphoproliferative disorder at the Screening Visit.	Clarified that subjects with a confirmed diagnosis or under investigation for multiple myeloma or related lymphoproliferative disorder are excluded from the study. Disease activity is not being assessed at Screening
Section 6.2, Exclusion criteria (#18)	Criterion moved to #6: 18. Subject has a vitamin D insufficiency, defined as 25 (OH) vitamin D levels <20ng/mL, as assessed by the central laboratory at Screening. Vitamin D repletion will be permitted and the subject may be retested once within the Screening Period.	18. Subject has a history of ONJ or AFF. (previously exclusion criterion #16)	Exclusion criterion was moved up from #18 to #6 to maximize the operationalization of Screening activities
Section 7.2, Treatments to be administered	• Double-Blind, Placebo-Controlled Period - Approximately 300 subjects will be randomized, stratified by age (<75 years, ≥75 years) and prevalent vertebral fracture (yes, no), in a 2:1 ratio to receive romosozumab 210mg sc QM (approximately 200 subjects) or matched placebo sc QM (approximately 100 subjects) in a blinded manner for 6 months, with the final administration of double-blind IMP at Month 5.	• Double-Blind, Placebo-Controlled Period - Approximately 300 subjects will be randomized, stratified by age (<75 years, ≥75 years), in a 2:1 ratio to receive romosozumab 210mg sc QM (approximately 200 subjects) or matched placebo sc QM (approximately 100 subjects) in a blinded manner for 6 months, with the final administration of double-blind IMP at Month 5.	Stratification by prevalent vertebral fracture no longer necessary due to the new inclusion criterion #5

Section	Original text	Revised/new text	Reason for change
Section 7.9.1.1, Double-Blind Placebo-Controlled Period	In addition, to maintain the blind, BMD, BTM, PK, immunogenicity, and selected laboratory results (ie, serum calcium, albumin-adjusted calcium, phosphorus, ALP, and iPTH) will not be reported to the investigator and study-related site personnel during the Double-Blind, Placebo-Controlled Period. However, if there is a clinically significant laboratory value noted for the selected laboratory values, the investigator will be notified by the central laboratory in order to treat the subject appropriately. The investigator may perform additional follow-up blood draws for local analysis as required to support subject medical care. Notifications will be issued for subjects who test positive for neutralizing antiromosozumab antibodies at the EOS or ET Visit.	None	Text was removed as these processes are described adequately in their respective sections
Section 7.9.1.2, Open-Label Treatment Period	In an effort to avoid introducing any bias and to maintain the quality of the data during the OL Treatment Period, BMD, BTM, PK, immunogenicity, and selected laboratory results (ie, serum calcium, albumin-adjusted calcium, phosphorus, ALP, and iPTH) will not be reported to the investigator and study-related site personnel during the OL Treatment Period, using the same process as described for the Double-Blind, Placebo-Controlled Period in Section 7.9.1.1. However, if there is a clinically significant laboratory value noted for the selected laboratory values, the investigator will be notified by the central laboratory in order to treat the subject appropriately. Notifications will be issued for subjects who test positive for neutralizing antiromosozumab antibodies at the EOS or ET Visit.	None	Text was removed as these processes are described adequately in their respective sections

Section	Original text	Revised/new text	Reason for change
Section 7.10, Randomization and numbering of subjects	Subjects will be randomized, stratified by age (<75 years, ≥75 years) and prevalent vertebral fracture (yes, no), in a 2:1 ratio of romosozumab to placebo during the Double-Blind, Placebo-Controlled Period, after which, all subjects will receive romosozumab during the OL Treatment Period.	Subjects will be randomized, stratified by age (<75 years, ≥75 years), in a 2:1 ratio of romosozumab to placebo during the Double-Blind, Placebo-Controlled Period, after which, all subjects will receive romosozumab during the OL Treatment Period.	Stratification by prevalent vertebral fracture no longer necessary due to the new inclusion criterion #5
Section 8.1, Screening Visit (Visit 1) (up to 35 days)	• Obtain blood samples for the following: - Safety laboratory tests (hematology and serum chemistry) - Serum protein electrophoresis – Serum protein electrophoresis can be performed by the local laboratory in the case electrophoresis results are available within 6 months of signing ICF. If no serum protein electrophoresis data are available within 6 months, serum protein electrophoresis should be performed by the central laboratory. - Serology - Serum 25 (OH) vitamin D (can be retested once during the Screening Period) - TSH, free T4 (if required for confirmation of thyroid status) - FSH - iPTH	• Obtain blood samples for the following: - Safety laboratory tests (hematology and serum chemistry) - Serology - Serum 25 (OH) vitamin D (can be retested once during the Screening Period) - TSH, free T4 (if required for confirmation of thyroid status) - FSH - iPTH	Serum protein electrophoresis has been removed since multiple myeloma or related lymphoproliferative disorder is no longer assessed at Screening (revised exclusion criterion #19)
Section 8.1, Screening Visit (Visit 1) (up to 35 days)	In addition, before enrolling subjects in the study, a careful individual assessment of the CV risk profile should be performed (including evaluation of CV history, CV risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking and severe renal impairment and other relevant results from the Screening investigations such as ECG).	In addition, before enrolling subjects in the study, a careful individual assessment of the CV risk profile should be performed.	Examples of CV risk provided were not exhaustive. Removal of these examples allows the investigator to conduct an individualized assessment in accordance with their routine clinical practice

Section	Original text	Revised/new text	Reason for change
Section 8.2.1, Visit 2 (Day 1)	In addition, before enrolling subjects in the study, a careful individual assessment of the CV risk profile should be performed (including evaluation of CV history, CV risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking and severe renal impairment and other relevant results from the Screening investigations such as ECG).	In addition, before enrolling subjects in the study, a careful individual assessment of the CV risk profile should be performed.	Examples of CV risk provided were not exhaustive. Removal of these examples allows the investigator to conduct an individualized assessment in accordance with their routine clinical practice
Section 8.2.1, Visit 2 (Day 1) through Section 8.3.3, Visit 14 (Month 12)	None	• Discuss signs and symptoms of MI and stroke	Patient assessment added to align with the risk minimization measures and warnings and precautions for use for romosozumab
Section 11.6, Laboratory measurements	Serology (hepatitis/HIV) testing, laboratory tests (hematology and serum chemistry including serum protein electrophoresis), an endocrine test (serum 25 [OH] vitamin D), and some hormone tests (iPTH, FSH, TSH, and T4) will be performed at Screening to determine the subject's eligibility for the study.	Serology (hepatitis/HIV) testing, laboratory tests (hematology and serum chemistry), an endocrine test (serum 25 [OH] vitamin D), and some hormone tests (iPTH, FSH, TSH, and T4) will be performed at Screening to determine the subject's eligibility for the study.	Serum protein electrophoresis has been removed since multiple myeloma or related lymphoproliferative disorder is no longer assessed at Screening (revised exclusion criterion #19)
Section 11.6, Table 11-2, Clinical laboratory measurements	Serum chemistry: Serum protein electrophoresis[a]	Removed	Serum protein electrophoresis has been removed since multiple myeloma or related lymphoproliferative disorder is no longer assessed at Screening (revised exclusion criterion #19)

Section	Original text	Revised/new text	Reason for change
Section 11.6, Laboratory measurements	Results of laboratory assessments for serum calcium, albumin-adjusted calcium, phosphorus, iPTH, and ALP will not be reported to the investigator and study-related site personnel at any time after the first administration of double-blind IMP to avoid any potentially unblinding during the Double-Blind, Placebo-Controlled Period and to minimize the introduction of any bias during the OL Treatment Period once the investigator is unblinded to individual treatment assignments. However, in the event of an abnormal value of clinical significance for serum calcium, albumin-adjusted calcium, phosphorus, iPTH, or ALP, the investigator or designee will be notified of the unblinded value by the central laboratory.	Results of laboratory assessments for serum calcium, albumin-adjusted calcium, phosphorus, ALP, P1NP, CTX, iPTH, romosozumab levels, and antiromosozumab antibodies are considered potentially unblinding and will not be reported to any study-related personnel after Day 1 in order to maintain the integrity of the study blind. However, in the event of an abnormal value of clinical relevance (panic value) for serum calcium, albumin-adjusted calcium, phosphorus, or ALP, sites will be notified of the unblinded value by the central laboratory. After such notification is issued, the sites may perform additional follow-up blood draws for local analysis as required to support subject medical care.	Clarification of the process in the event of an abnormal value of clinical relevance (panic value) for serum calcium, albumin-adjusted calcium, phosphorus, or ALP
Section 11.6.1.3, Table 11-4, PDILI laboratory measurements	Additional: Prothrombin time/INR[a] Serum pregnancy test PK sample	Additional: Prothrombin time/INR[a] PK sample	Removed serum pregnancy test since the study population is postmenopausal women and planned pregnancy is excluded (exclusion criterion #26)
Section 13.4.1, Analysis of the primary efficacy variable	A sensitivity analysis of repeated measures model will be fit with the percent change from baseline at Months 3 and 6 in BMD of the lumbar spine as the dependent variable, and baseline BMD, machine type, interaction of baseline BMD and machine type, visit (categorical), treatment (categorical), and interaction of treatment and visit as the independent variables.	A sensitivity analysis with a repeated measurements model will be fit with the percent change from baseline at Months 3 and 6 in BMD of the lumbar spine as the dependent variable, and baseline BMD, machine type, interaction of baseline BMD and machine type, visit (categorical), treatment (categorical), and interaction of treatment and visit as the independent variables.	Clarification of model used for the sensitivity analysis

Section	Original text	Revised/new text	Reason for change
Section 13.4.1.1, Analysis of secondary variables	A sensitivity analysis of repeated measures model will be fit with the percent change from baseline at Months 3 and 6 in BMD of the corresponding skeletal location (ie, total hip or femoral neck) as the dependent variable and baseline BMD, machine type, interaction of baseline BMD and machine type, visit (categorical), treatment (categorical), and interaction of treatment and visit as the independent variables.	A sensitivity analysis with a repeated measurements model will be fit with the percent change from baseline at Months 3 and 6 in BMD of the corresponding skeletal location (ie, total hip or femoral neck) as the dependent variable and baseline BMD, machine type, interaction of baseline BMD and machine type, visit (categorical), treatment (categorical), and interaction of treatment and visit as the independent variables.	Clarification of model used for the sensitivity analysis
Section 13.4.2.1 Planned pharmacokinetic analyses	The serum trough concentrations and normalized serum trough concentrations of romosozumab by BW will be summarized using descriptive statistics for those subjects who continued with 6 months of romosozumab after initially being randomized to 6 months of romosozumab treatment and for those subjects who are initially randomized to placebo for 6 months and transition to romosozumab for 6 months.	The serum trough concentrations of romosozumab will be summarized using descriptive statistics for those subjects who continued with 6 months of romosozumab after initially being randomized to 6 months of romosozumab treatment and for those subjects who are initially randomized to placebo for 6 months and transition to romosozumab for 6 months.	Variable considered unnecessary as the normalized serum trough concentration by BW will be accounted for in the planned PK-PPS analysis
Section 19, Sponsor Declaration	Clinical Trial Biostatistician	Statistical Representative	In compliance with Standard Operating Procedure and associated documents

Note: In Table 5-2, the addition of the new footnote [d] shifted the footnotes accordingly from [d] through [h] (previous version: Protocol Amendment 1) to [e] through [i] only (Protocol Amendment 2).

Note: The numbering of the inclusion and exclusion criteria has changed from Protocol Amendment 1. With the addition of an inclusion criterion, the inclusion criteria are now numbered 1 through 6 (previously 1 through 5). With additions, deletions, and revisions to the exclusion criteria, the exclusion criteria are now numbered 1 through 31 (previously 1 through 30).

17.3 Protocol Amendment 3

Rationale for this amendment

This amendment is considered substantial. The main purpose for this amendment is to clarify Inclusion Criterion #3. In line with Chinese and international guidelines (eg, Menopause Group, 2018), the diagnosis of menopause is to be made by clinical assessment, ie, without taking into acount the follicle-stimulating hormone (FSH) value. Following this, the subcriterion on the FSH value has been deleted. In addition, there is a new paragraph concerning the study conduct in case of restrictions imposed during exceptional circumstances (eg, COVID-19).

Specific changes to the protocol

Section	Original text	Revised text	Reason for change
Study Contact Information	Study Physician, Clinical Project Manager, and Clinical Trial Biostatistician were changed.	Lead Clinical Development Representative role was added.	To update the study team.
Section 1, Section 5.1.6	OP0002 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study followed by an Open-Label (OL) Treatment Period to evaluate the efficacy, safety and tolerability of romosozumab treatment in postmenopausal Chinese women with osteoporosis across approximately 20 study sites in mainland China. The planned number of study sites is approximately 20.	OP0002 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study followed by an Open-Label (OL) Treatment Period to evaluate the efficacy, safety and tolerability of romosozumab treatment in postmenopausal Chinese women with osteoporosis across approximately 30 study sites in mainland China. The planned number of study sites is approximately 30.	To update the anticipated number of study sites.
Section 2.3.5, Table 2.2	Denosomab approval status listed as “No” in China.	Denosomab approval status listed as “Yes” in China.	Update to reflect current available therapies in China.
Section 5.2, Table 5-1, Section 8.1	FSH sample collected at the Screening Visit.	FSH sample removed from the Screening Visit.	Reference to FSH has been removed throughout the protocol.
Section 6.1	3. Subject is an ambulatory postmenopausal Chinese women, 55 to 90 years of age (inclusive) at the time of Screening. Postmenopause is defined as no spontaneous vaginal bleeding or spotting for 12 or more consecutive months prior to Screening, verified by a serum follicle stimulating hormone (FSH) level >40mUI/mL at Screening (Visit 1).	3a. Subject is an ambulatory postmenopausal Chinese women, 55 to 90 years of age (inclusive) at the time of Screening. Postmenopause is defined as no spontaneous vaginal bleeding or spotting for 12 or more consecutive months prior to Screening.	In line with Chinese and international guidelines (Menopause Group, 2018), the diagnosis of menopause is to be made by clinical assessment, ie, without taking into acount the FSH value. Reference to FSH has been removed throughout the protocol.
Section 8.6	None.	• Any other assessments that the investigator deems necessary	To allow for any additional assessments at the discretion of the investigator.

Section	Original text	Revised text	Reason for change
Section 8.7	None.	The protocol mandated visit schedule should be followed to the closest extent possible, based on the judgment of the investigator. However, during the coronavirus disease 2019 (COVID-19) epidemic or under other exceptional circumstances, remote follow-up may be conducted and the subjects may be contacted by telephone/video contact to assess as many details as possible, according to the protocol scheduling, to verify that the subject is suitable for continuing study treatment. In-person follow-up at an alternative study site or a home visit is acceptable. Some procedures may be collected by other remote means if feasible. Study sites should make efforts to inform the sponsor or the CRO in the event that protocol procedures cannot be completed due to COVID-19. In those situations when the subject cannot return to the study site, the investigators will assess the subject's safety by telephone/video contact. Ad hoc subject contact may be warranted to understand the current health status of the subjects, to follow up on AEs, and inform them of any protective measures taken by the clinical site as a result of the COVID 19 pandemic (eg, any measures that may limit access to the site or may require additional actions by the subject prior to entry to the site). If a subject visits another facility for a medical issue, the investigator should request a detailed explanation of the subject's condition and his/her participation in the clinical study from the subject or caregiver. Subjects or caregivers shall be reminded to completely collect and keep records of this visit.	To clarify study conduct during COVID-19.

Section	Original text	Revised text	Reason for change
Section 11.6, Table 11-2	FSH included in clinical laboratory measurements.	FSH removed from clinical laboratory measurements.	Reference to FSH has been removed throughout the protocol.
Section 13.3.1	The safety objective of the 6-month analysis will compare the safety of romozosumab treatment with placebo in postmenopausal Chinese women with osteoporosis. The safety variables to be analyzed in the 6-month analysis are presented in Section 4.1.3.	The safety analyses of the 6-month analysis will compare the safety of romozosumab treatment with placebo in postmenopausal Chinese women with osteoporosis. The safety analyses in the 6-month analysis will include all available data collected up to the time of 6-month data snapshot.	Clarification of the data to be included in the 6-month analysis safety analyses.
Section 13.6	None.	The impact of COVID-19 and COVID-19 vaccination will be evaluated at the blinded data evaluation meetings and details of analysis will be provided in the SAP.	To clarify that details of any analyses of the impact of COVID-19 will be provided in the SAP.
Section 16	None.	Menopause Group in the Chinese Society of Obstetrics and Gynecology. Chinese guideline (2018) on menopausal management and menopausal hormone therapy [J]. Chinese Journal of Obstetrics and Gynecology. 2018,53:729-739.	New reference added.

18 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

19 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Lead Clinical Development Representative

[redacted]

Date/Signature [redacted]

Statistical Representative

[redacted]

Date/Signature [redacted]

Program Physician

[redacted]

Date/Signature [redacted]