Protocol Title: A Phase 2b, Multicentre, Multinational, Double-blind, Dose-finding Study, incorporating an open label substudy, in Adult Patients with Type I, III or IV Osteogenesis Imperfecta Treated with setrusumab (BPS804).

Protocol Number: MBPS205 Amendment 6

Please see appendix 9 for summaries of amendment changes

Compound Number: BPS804

Sponsor Name and Legal Registered Address: Mereo BioPharma 3 Ltd. 1 Cavendish Place, London, W1G 0QF

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1. Synopsis

Protocol Title: A Phase 2b, Multicentre, Multinational, Double-blind, Dose-finding Study, incorporating an open label substudy, in Adult Patients with Type I, III or IV Osteogenesis Imperfecta Treated with setrusumab (BPS804)

Rationale:

There is limited clinical experience with setrusumab (BPS804) in the Osteogenesis Imperfecta (OI) patient population. MBPS205 will be the first study to investigate dose-response to setrusumab in a large cohort of Type I, III and IV OI patients.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate that setrusumab increases radial trabecular volumetric bone mineral density (Tr. vBMD) on high resolution peripheral quantitative computed tomography (HRpQCT) and bone strength on finite element analysis (FEA) in patients with OI Type I, III or IV	• Tr. vBMD (radius) on HRpQCT and bone strength on FEA at 12 months.
Secondary	
• To determine the dose-response relationship of Tr. vBMD to setrusumab after 12 months of treatment	• Tr. vBMD (radius) on HRpQCT at 12 months.
• To evaluate the onset of treatment effect	• Tr. vBMD (tibia & radius) on HRpQCT and bone strength on FEA at 6 months. • Tr. vBMD (tibia & radius) on HRpQCT and bone strength on FEA at 3, 6 & 12 months in the open-label treatment arm.
• To evaluate the effect of setrusumab on fracture rate (peripheral, major [long-bone], and vertebral fractures)	• Total fracture rate at 12 months • Peripheral fracture rate at 12 months • Vertebral fracture rate at 12 months • Long-bone fracture rate at 12 months

Objectives	Endpoints
• To evaluate the effect of setrusumab on vertebral fractures and vertebral height	• Changes in vertebral fractures and vertebral height with Genant's semi-quantitative method and 6-point quantitative morphometry from baseline at 6 and 12 months
• To evaluate the effect of setrusumab on bone mineral density (BMD)	• Changes in lumbar, whole body, and proximal femur dual-energy x-ray absorptiometry (DXA) BMD (absolute and T-score) from baseline at Month 6 and Month 12.
• To evaluate the effect of setrusumab on bone quality	• Changes in bone histomorphometry
• To evaluate changes in radial Tr. vBMD on HRpQCT and bone strength FEA during the 12 months post-setrusumab treatment period	• Tr. vBMD (tibia & radius) on HRpQCT and bone strength on FEA at 18 and 24 months
• To evaluate the effect of setrusumab on HRpQCT parameters	• Changes (tibial and radial) in Total vBMD, cortical vBMD, bone volume fraction (BV/TV), peripheral to medullary trabecular bone density ratio (Met/Inn), trabecular thickness (TbTh), trabecular number (TbN), Inhomogeneity, cortical thickness, and cortical porosity from baseline at 6, 12, 18, and 24 months • Changes in Tr. vBMD (tibia) from baseline at 12, 18, and 24 months • Changes (tibial and radial) in Total vBMD, cortical vBMD, bone volume fraction (BV/TV), peripheral to medullary trabecular bone density ratio (Met/Inn), trabecular thickness (TbTh), trabecular number (TbN), Inhomogeneity, cortical thickness, and cortical porosity on HRpQCT and bone strength on FEA at 3 months in the open-label treatment arm.
• To evaluate the effect of setrusumab on body composition	• Changes in body height, weight and body mass index from baseline at 6 and 12 months • Changes in lean and fat body mass from whole body DXA

Objectives	Endpoints
• To evaluate the effect of setrusumab on markers of bone composition	• Changes in bone turnover markers and metabolic biomarkers associated with bone (parathyroid hormone [PTH], amino-terminal propeptide of type 1 procollagen [P1NP], carboxy-terminal propeptide of type 1 procollagen [P1CP], osteocalcin [OC], bone-specific alkaline phosphatase [BSAP], carboxy-terminal telo-peptide [CTX-1], amino-terminal telo-peptide [NTX-1], receptor activator of nuclear factor kappa-B ligand [RANKL], osteoprotegerin, transforming growth factor beta [TGF-β], sclerostin, released C-terminal pro-peptide of Type V collagen [Pro-C5], neo-epitope of MMP-2,9 mediated degradation of Type V collagen [C5M]) from baseline and each visit
• To evaluate the effect of setrusumab on Patient-Reported Outcomes (PROs) and Quality of Life (QoL)	• Change in total scores from baseline to Month 6 and 12 on Short Form 12 Health Survey (SF-12), EuroQol 5-dimension 5-level descriptive system (EQ-5D-5L) and Osteogenesis Imperfecta specific Quality of Life Questionnaire for Adults (OIQoL-A) • Change in OIQoL-A pain and activity sub-scale scores from baseline to Month 6 and 12
• To evaluate the pharmacokinetics (PK) of setrusumab	• Serum concentrations of setrusumab
• To evaluate potential induction of anti-drug antibodies (ADAs) by setrusumab and their effect on safety and PK	• Serum concentrations of anti-setrusumab antibodies • Serum concentrations of setrusumab neutralising antibodies
• To evaluate safety and tolerability of setrusumab	• Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs) • Infusion site reactions • Vital signs • Physical examinations

Objectives	Endpoints
	• Electrocardiogram • Clinical laboratory tests
Tertiary/Exploratory	
• To evaluate the effect of setrusumab on bone quality	• Changes in Trabecular Bone Score from baseline at 6 and 12 months
• To evaluate the effect of setrusumab on changes in use of physical aids	• Changes in usage or need for physical aids from baseline at 12 months
• To evaluate the effect of setrusumab on hearing	• Change in auditory function from baseline at 12 months in a subset of patients

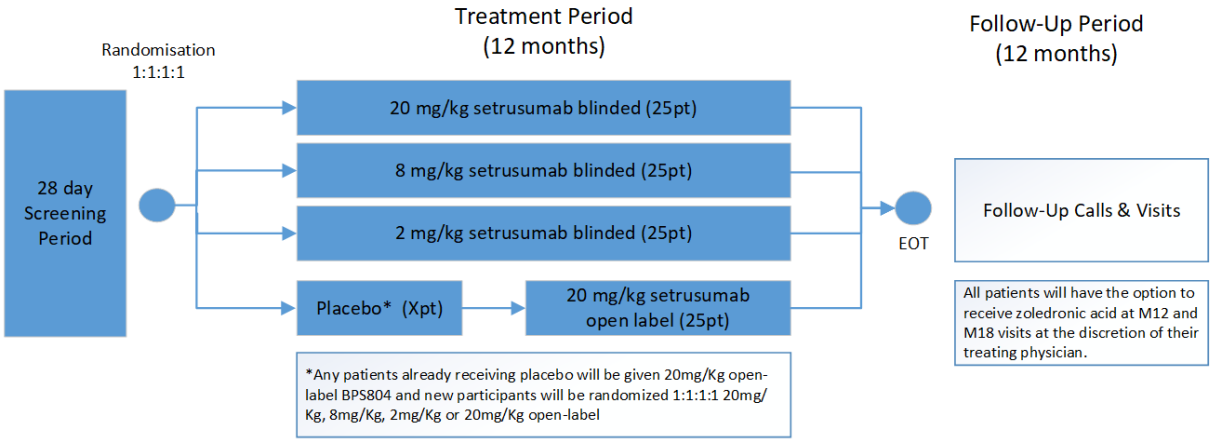
• To evaluate the effect of setrusumab on bone formation and resorption parameters measured by HRpQCT	• Change in bone formation from baseline at 6 and 12 months
	  • Normalised newly mineralised bone volume (MV/BV)
	  • Normalised newly mineralised surface area (MS/BS)
	  • Mineralised thickness (MTh)
	  • Normalised formation patch number density (N.F. Patch/BV)
	  • Formation patch volume (F.PatchVol.)
	  • 3D bone formation rate (3D BFR/BS)
	  • 3D mineral apposition rate (3D MAR)
	• Change in bone resorption from baseline at 6 and 12 months
	  • Normalised newly eroded bone volume (EV/BV)
	  • Normalised newly eroded surface area (ES/BS)
	  • Erosion depth (ED)
	  • Normalised resorption cavity number density (N.R.Cav./BV)
	  • Resorption cavity volume (R.Cav.Vol.)
	  • 3D bone resorption rate (3D BRR/BS)

Objectives	Endpoints
	• 3D mineral resorption rates (3D MRR)

Overall Design:

- MBPS205 is a phase 2b, multicentre, multinational, double-blind, dose-finding study with 3 blinded doses of setrusumab (20 mg/kg, 8 mg/kg and 2 mg/kg) and an open-label treatment arm (20 mg/kg) in patients diagnosed with Type I, III or IV OI.
- Participants will be adults clinically diagnosed with either Type I, III or IV OI and a confirmed COL1A1/COL1A2 mutation who have fractured in the previous 5 years.
- Participants will be excluded if they are over 75 years old, have a history of certain cardiac events, have confounding skeletal or other medical conditions and/or have been treated with bisphosphonates in the previous 3 months or other anabolic or anti-reabsorptive medications in the previous 6 months.
- Participants will have HRpQCT scans of their non-dominant distal radius at baseline, 3-month (for open-label participants only), 6-month and 12-month time points to determine the effect of treatment on Tr. vBMD with the primary analysis and dose determination being made after all enrolled patients have completed their 12-month HRpQCT scan.
- Other investigations include study of sparse PK, monitoring for safety and tolerability including immunogenicity, and measurement of the effect of treatment on bone quality, fractures, QoL and utilisation of resources e.g. physical aids and hospitalisation.
- Following completion of the study treatment participants will enter 12 months follow-up and will have visits at Months 14, 18 and 24. Participants will also receive follow-up telephone calls at Months 16 and 21.
- During the follow-up period all participants will have the option to receive zoledronic acid at Month 12 and Month 18 at the discretion of their treating physician.
- During the follow-up period participants will have HRpQCT scans of their non-dominant distal radius and tibia at Month 18 and Month 24.
- For the purposes of the study protocol 1 month is defined as 28 days.
- An Independent Data Monitoring Committee will monitor safety throughout the study and make recommendations on the selected dose.

MBPS205 Study Schematic



Number of Participants:

The number of participants is based on power considerations for the trabecular vBMD (radius) derived from HRpQCT at Month 12. The primary analysis method for this endpoint will be on the change from baseline within each treatment group, so the primary hypothesis to be tested is

$$H_0: \mu_T \leq 0 \text{ vs. } H1: \mu_T > 0$$

where μ_T denotes the change from baseline for each dose of Setrusumab. Under the assumptions of a maximum change from baseline of [redacted], a standard deviation at both timepoints of [redacted] and a correlation between both measurements of [redacted], a sample size of 25 patients per group yields approximately 80% power for a one-sided test with significance level 0.025, if the data are analysed on the log scale using a t-test.

For a change from baseline of [redacted], with standard deviation as above the one-sided test would have a probability of 80% to yield a p-value below 5%, being considered indicative of a trend.

Following a review of the trabecular vBMD (radius) derived from HRpQCT at Month 6 of those subjects within the 20 mg/kg Setrusumab open label treatment group, a change from baseline standard deviation of [redacted][3] was observed. This yields to a correlation between baseline and Month 6 visits of [redacted] (much higher than the [redacted] that was originally assumed). If such a correlation is observed at Month 12, given 25 subjects per arm, the one-sided test would have a probability of 80% to yield a p-value below 5% for a change in baseline of [redacted].

As a secondary analysis, the MCPMod approach will be applied to the data in order to assess a non-flat dose-response curve and to obtain information about the underlying dose-response curve. Due to the missing placebo group, the power of this approach depends heavily on the underlying dose-response curve.

The following candidate models will be used:

- EMax (ED_{50} of 1.5 mg)
- Exponential ($\delta = 2$)

Under the assumptions of each of the two candidate models being the true dose-response curve, and in addition an Sigmoid EMax model with parameters $ED_{50} = 10$ mg and $h = 2.4$, a contrast test at a one-sided significance level of 2.5% has the following power for each of the three models:

Model	EMax	Exponential	Sigmoid EMax
Power	13.7%	73.2%	60.7%

The total sample size required is therefore determined as 100:

- 25 participants on open-label setrusumab (20 mg/kg)
- 25 participants on each of the active arms (2 mg/kg, 8 mg/kg, 20 mg/kg)

Approximately 100 participants will be randomised.

Treatment Groups and Duration:

- Participants will be qualified during a 28-day screening period, followed by 12 months of study treatment. At the end of treatment in MBPS205, participants will continue into the follow-up period for 12 months. Participants discontinuing setrusumab treatment prior to the end of the treatment phase for any reason will complete the end of treatment visit and the 60-day follow-up visit.
- After screening, participants will be randomised to 1:1:1:1 to blinded 20 mg/kg, 8 mg/kg and 2 mg/kg setrusumab or to open label 20 mg/kg setrusumab.
- Any participants assigned to placebo according to the previous MBPS205 protocol design will be transferred to open-label 20 mg/kg treatment for 12 months.
- Allocation of treatment will be via Interactive Web Response System (IWRS), which will also calculate total doses of setrusumab based on participant body weight and track vials allocation to patients.
- Investigators and participants will be blinded to the blinded active arms study treatment allocation throughout the study; pharmacists will be unblinded to study allocation to allow for dispensing and reconstitution. The sponsor will be initially blinded but become unblinded after the primary analysis at which time all the participants will have been enrolled.
- All participants will receive monthly 60-minute infusions of 250 mL 5% dextrose with setrusumab.

Statistical Methods:

General Statistical Methods

The evaluation of the primary efficacy endpoint will be performed on the full analysis set (FAS, intention to treat analysis). Results for the per-protocol analysis set will be considered supportive. Safety endpoints will be analysed on the safety analysis set. The primary analysis will be performed after all patients have completed their initial 12-month study period or have withdrawn prior to completion. Analyses for the follow-up period will be carried out separately to the primary analysis once all patients have completed the 12 months follow-up period, or have withdrawn from it.

Generally, data will be tabulated by treatment group. Both descriptive and inferential statistics will be presented as appropriate. Categorical data will be described using absolute and relative frequencies; for continuous variables, the following descriptive summary statistics will be presented: number of observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Continuous variables will be log transformed where appropriate. Time to event variables (e.g., time to first fracture) will be analysed using Kaplan-Meier methods, and quartiles for the median time to event will be presented together with their 95% confidence intervals.

Data for placebo participants and open-label BPS804 20 mg/kg participants will be reported separately from the comparison between the randomized, blinded treatment groups. In particular for the primary analysis, the open-label BPS804 20 mg/kg participants' data will not be pooled with the blinded BPS804 20 mg/kg participants' data.

Efficacy Analysis

The HRpQCT results will be log transformed and an ANCOVA model will be used to calculate Least Square Means (LSMeans) for the change from baseline, using baseline values as a covariate and treatment group and stratum as a factor. LSMeans for each treatment group will be calculated and tested against the null hypothesis of 0 in an a priori hierarchical approach, starting with the highest dose. Differences between LSMeans will also be displayed but will be analysed in an exploratory fashion only. The type I error rate will be 5% two-sided. P-values above 5% but below 10% (two-sided) will be considered as indicative for a trend.

The LSMeans will further be analysed using the MCPMod methodology, using the following candidate models:

- EMax (ED_{50} of 1.5 mg)
- Exponential ($\delta = 2$)
- Sigmoid EMax model with parameters ED50 = 10 mg and h = 2.4

Parameter estimates and predicted values for each dose will be calculated for all models. These analyses will be done primarily on the trabecular vBMD (radius). It will be repeated for the bone strength on FEA for supportive evidence.

LSMeans and LSMean differences between treatment groups will be back-transformed to their original scale for descriptive purposes. After substracting the geometric mean of the log baseline values, the back-transformed LSMeans will correspond to the percentage change from baseline,

while the back-transformed LSMeans differences will correspond to the ratio of percentage changes from baseline.

The remaining efficacy variables will be analysed according to their scale using general methods as described above.

Exploratory Analyses

Exploratory endpoint variables will be analysed according to their scale using general methods as described above.

Safety Analyses

Variables will be analysed according to their scale using general methods as described above, and results will be presented overall and by treatment group.

Follow-Up Period Analyses

Variables will be analysed according to their scale using general methods as described above. Results will be presented overall and by initial treatment assignment. In addition, subgroup analyses will be performed for HRpQCT, DXA, vertebral radiograph, CTX-1 and P1NP based on the administration of zoledronic acid during the follow-up phase (none; at Month 12; at Month 18). Also, the frequency of administration of zoledronic acid during the follow-up phase will be related both to the site and to the 12 months outcome for both primary efficacy endpoints.

HRpQCT Validation Analysis

Validation analyses to the HRpQCT measurements will be described in a separate analysis plan.

2. Schedule of Activities (SoA) Treatment Period

Procedure	Screening (up to 28 days before Day 1)	Months												Notes All visits ± 4 days.
		Base-line	1	2	3	4	5	6	7	8	9	10	11	EOT/ 12	
COL1A1/COL1 A2 Mutation confirmation	X														If not available, consent can be obtained and test conducted prior to main study screening
Informed consent	X														Main study consent and bone biopsy
Inclusion and exclusion criteria	X														Re-confirm at Baseline
Demography	X														
Full physical examination including height and weight	X							X						X	
Brief physical examination		X	X	X	X	X	X		X	X	X	X	X		
Past and current medical conditions	X														
Prior medications	X														In the last 2 years

Procedure	Screening (up to 28 days before Day 1)	Months													Notes All visits ± 4 days.
		Base-line	1	2	3	4	5	6	7	8	9	10	11	EOT/ 12	
Serum pregnancy test (WOCBP only)	X														
Urine pregnancy tests (WOCBP)		X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Laboratory assessments	X	X	X	X	X			X			X			X	To be collected pre-dose
25-OH-Vitamin D	X	X	X		X			X			X			X	
12-lead ECG	X							X						X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomisation		X													
Study treatment		X	X	X	X	X	X	X	X	X	X	X	X		Weight will be measured to calculate dose
HRpQCT	X				X			X						X	M6 and M12 scans be conducted ±7days of visit M3 for open-label participants only
DXA	X							X						X	Calcium tablets should not be taken 2 hours prior to DXA lumbar scan

Procedure	Screening (up to 28 days before Day 1)	Months												Notes All visits ± 4 days.
		Base-line	1	2	3	4	5	6	7	8	9	10	11	EOT/ 12	
Vertebral Radiograph	X							X						X	
Fracture Assessment & Radiograph		←==========→													Radiographs will be taken in the event of a symptomatic fracture
Bone Biomarkers		X	X		X			X			X			X	Fasting pre-dose blood draw, Sub-set of patients will have additional blood draws at 8 d post- baseline (+4 days) and 14 d post-M9 visit.
Bone Biopsy								X						X	Sub-set of participants. Completed once either at M6 or M12
Audiometry	X													X	This procedure can be omitted if the investigative site does not have the capability to complete the audiometry assessment
Patient-Reported Outcomes		X	X		X			X			X			X	

Procedure	Screening (up to 28 days before Day 1)	Months												Notes All visits ± 4 days.
		Base-line	1	2	3	4	5	6	7	8	9	10	11	EOT/ 12	
Setrusumab PK		X	X	X	X			X						X	Sub-set of patients will have additional blood draws at 8 d post-baseline. Samples taken pre-dose and 10 mins post-dose at treatment visits. One sample taken at non-treatment visits
Anti-setrusumab Antibodies		X	X	X	X			X						X	Sub-set of patients will have additional blood draws at 8 d post baseline. Taken pre-dose for treatment visits
Zoledronic acid treatment														X	Optional. Can be administered up to 2 months following the visit
AE/SAE/AESI review		←==========→													
Concomitant medication & physical aid/treatment review		←==========→													

3. Schedule of Activities (SoA) Follow-Up Period

Procedure	Months					Notes All visits ± 4 days.
	14 (Follow-up visit +60 days)	16	18	21	24	
Follow-up call		X		X		
Brief physical examination	X		X		X	
Urine pregnancy tests (WOCBP)	X					
Safety Laboratory assessments	X		X		X	
25-OH-Vitamin D	X		X		X	
12-lead ECG	X					
Vital signs	X		X		X	
HRpQCT			X		X	Scans be conducted ±7 days of visit
DXA			X		X	Calcium tablets should not be taken 2 hours prior to DXA lumbar scan
Vertebral Radiograph			X		X	
Fracture Assessment & Radiograph	←==========→					Radiographs will be taken in the event of a symptomatic fracture
Patient-Reported Outcomes			X		X	
Setrusumab PK	X					One sample taken at non-treatment visits

Procedure	Months					Notes **All visits ± 4 days.**
	14 (Follow-up visit +60 days)	**16**	**18**	**21**	**24**	
Anti-setrusumab Antibodies	X					
CTX-1 & P1NP	X		X			Tested locally. ± 2 months of visit
Zoledronic acid treatment			X			Optional. Can be administered ± 1 month from visit
AE/SAE/AESI review	←==========→					Reporting only SAEs only after Month 14
Concomitant medication & physical aid/treatment review	←==========→					

4. Introduction

4.1. Background

Osteogenesis imperfecta (OI) is a serious and debilitating genetic disorder that is characterised by fragile bones that break easily, often with little or no physical trauma. Patients may suffer from recurrent fractures, bone deformity, bone pain, muscle weakness, hearing loss, fatigue, joint laxity, curved bones, scoliosis and short stature. In the most severe cases, OI can be life-threatening. It has been shown that patients with OI have a higher mortality rate, at all ages, with an increased risk of death from respiratory diseases, gastrointestinal diseases and trauma. Basilar invagination may lead to neurological consequences. Diagnosis of OI is based on the clinical features of the disease but may be confirmed by collagen or DNA testing. OI comprises of a group of disorders which primarily arise from mutation in the genes encoding Type I collagen. In about 85% of cases, autosomal dominant OI is caused by mutations in COL1A1 and COL1A2 genes (17q21.33 and 7q21.3) which encode the alpha 1and 2 chains of Type 1 collagen. Autosomal recessive forms of OI are also observed and are caused by mutations in the LEPRE1, CRTAP, and PPIB genes (1p34.1, 3p22 and 15q21-q22). Autosomal recessive forms are in most cases severe or even lethal (Willaert et al, 2009; Ward et al, 2002; Lindahl et al, 2014; Valadares et al, 2014).

Setrusumab is a fully human anti-sclerostin neutralising monoclonal antibody. Sclerostin, encoded for by the SOST gene, is an osteocyte-secreted glycoprotein and is functionally a negative regulator of bone formation. Lack of sclerostin in humans (sclerosteosis) (Online Mendelian Interitance in Man [OMIM] entry #269500) and van Buchem disease (OMIM entry #239100) results in life-long increased bone formation in the entire skeleton leading to increased bone mineral mass, density and strength (Balemans et al 2001; Brunkow et al 2001; Balemans et al 2002; Staehling-Hampton et al 2002).

Setrusumab has an affinity of 21 pM for human sclerostin and reverses the human sclerostin-mediated inhibition of canonical Wnt signalling and in vitro bone mineralisation, a surrogate assay for bone formation, with EC_{50} values of 13 nM and 150 nM, respectively.

Based on significantly increased bone remodeling (turnover) in untreated OI patients (Rauch et al 2000), it is hypothesised that OI patients who receive setrusumab will experience an increase in bone mineral density (BMD) via induction of osteoblast differentiation (a pathway that is blocked by sclerostin) (Winkler et al 2005), an improvement in bone structure and strength, and hence a reduction of fracture incidence. While setrusumab could increase matrix and collagen production, it should be noted that a change by setrusumab in the defective collagen structure is not expected.

Setrusumab has been studied in 4 clinical trials involving 106 participants, 83 of whom received setrusumab. Study CBPS804A2201 was a randomised, open-label intra-patient dose escalation study (5, 10, and 20 mg/kg) with an untreated reference group to evaluate safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple infusions of setrusumab in 14 adults (male and female participants between 18 and 75 years of age) with moderate OI. After administration of setrusumab, median amino-terminal propeptide of type 1 procollagen (P1NP), carboxy-terminal propeptide of type 1 procollagen (P1CP), bone-specific alkaline phosphatase

(BSAP) activity and osteocalcin (OC) levels were increased at Day 43 by 84%, 53%, 59% and 44%, respectively, while corresponding biomarkers remained unchanged or declined moderately in the untreated reference group. The most commonly reported adverse events (AEs) were headache, influenza, arthralgia and fatigue. None were considered related to the study drug and gave no indication of target organ toxicity. There were no clinically significant abnormalities of haematological, clinical chemistry, urinalysis, electrocardiogram (ECG) or vital sign data. Bioanalytical results showed that setrusumab had a very similar PK profile in adult participants with moderate OI when compared with other populations studied previously. Serum sclerostin levels increased following each dose of 5, 10 and 20 mg/kg with an insignificant increase between the 10 and 20 mg/kg doses and a peak time lag behind the PK profile. This is consistent with observations from studies in healthy postmenopausal women (CBPS804A2101) and participants with hypophosphatasia (CBPS804A2202). Thus, adult participants with moderate OI given escalating doses of setrusumab demonstrated significant increases in bone formation biomarkers and lumbar spine BMD indicating enhanced skeletal remodeling and bone formation. This was the first clinical evidence that an anti-sclerostin antibody can significantly improve bone metabolism in adult participants with moderate OI.

A detailed description of the chemistry, pharmacology, efficacy, and safety of setrusumab is provided in the Investigator's Brochure (IB).

4.2. Study Rationale

Current management of OI is directed towards preventing or controlling symptoms, maximising independent mobility and improving bone mass and muscle strength. Current interventions include exercise and physical therapy, rehabilitation, and pain management. Surgery may prove necessary for individuals with severe malformations or basilar impression. Rodding, a procedure in which metal rods are surgically placed in the long bones of patients with OI to prevent fractures, is often used to treat individuals with OI. However, none of these treatments affect the underlying bone pathology.

There are no FDA or EMA approved pharmacological therapies for the treatment of OI. Bisphosphonates are widely used in the treatment of OI patients, despite a lack of solid evidence that they are beneficial. Studies have shown increased BMD, but there is no strong evidence in adults that they improve clinical features of OI, especially fracture rate or other features such as deformities, pain, or mobility. Parathyroid hormone (PTH) and analogues have also been studied for the treatment of OI, but they do not seem to improve the clinical course of OI and their safety profile is a concern.

Therefore, there is a high unmet need for a safe and effective pharmacological treatment for OI. setrusumab has demonstrated an increase in bone formation markers, a decrease in bone resorption markers and an increase in BMD in non-clinical and early clinical studies. It is therefore considered a good candidate for further development in the treatment of OI.

The current study aims to determine whether treatment with setrusumab in participants with OI is able to improve parameters reflecting bone structure, as measured with high resolution peripheral quantitative computed tomography (HRpQCT), towards those of normal (unaffected) individuals. As described in Section 6.4, HRpQCT is able to measure not only total volumetric BMD (vBMD) but also to discriminate between the cortex and trabecular vBMD (Tr. vBMD),

which may be more reflective of the underlying pathology than the standard measure of areal BMD as measured by dual-energy x-ray absorptiometry (DXA). This method also provides a means by which bone strength can be calculated, using finite element analysis (FEA). Although these parameters are not of direct clinical relevance to patients' clinical wellbeing, they are considered to be appropriate at this stage of development because (a) they are objective measures, (b) they can be assessed within a reasonable timeframe and (c) they are likely to be predictive of clinical benefit.

In order to determine the most appropriate dose of setrusumab required to achieve these changes, 3 doses will be studied over a 10-fold dose range. At each dose level, a comparison will be made between post-treatment and baseline values. In order to determine the time-course of the effect, a substudy will be performed in which one quarter of the patients have additional scans at 3 months. Since an additional scan cannot be blinded, this part of the study will be open-label.

4.3. Benefit/Risk Assessment

Since there are no approved pharmacological therapies for OI, patients participating in this study have the possibility to receive a potentially beneficial treatment, at a potentially therapeutic dose for a period of time considered long enough to achieve a benefit. It is expected that at least one of the doses of setrusumab will be sub-therapeutic; therefore patients randomised to this dose are not expected to receive any therapeutic benefit from participation. However, no proven therapy will be withheld during the study until the final analysis is performed when all subjects in the blinded treatment arms have completed 12 months of treatment with setrusumab. Data from this study will provide confirmation about whether setrusumab is efficacious for the treatment in adult osteogenesis imperfecta.

The procedures being undertaken in the study are not expected to present any risk to participants. Radiation doses are kept to a minimum; HRpQCT uses a relatively low dose of radiation which is confined to the periphery and avoids exposure of radiologically sensitive organs. Bone biopsy may be unpleasant for participants, but this will not be mandatory and will be done as an optional sub-study.

In non-clinical and early clinical studies with setrusumab, no safety concerns have been identified and the maximum dose proposed for the current study is well below the NOAEL from non-clinical studies. Further information can be found in the IB.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of setrusumab may be found in the IB and Participant Information Leaflet.

5. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate that setrusumab increases radial trabecular volumetric bone mineral density (Tr. vBMD) on high resolution peripheral quantitative computed tomography (HRpQCT) and bone strength on finite element analysis (FEA) in patients with OI Type I, III or IV	• Tr. vBMD (radius) on HRpQCT and bone strength on FEA at 12 months.
Secondary	
• To determine the dose-response relationship of Tr. vBMD to setrusumab after 12 months of treatment	• Tr. vBMD (radius) on HRpQCT at 12 months.
• To evaluate the onset of treatment effect	• Tr. vBMD (tibia & radius) on HRpQCT and bone strength on FEA at 6 months. • Tr. vBMD (tibia & radius) on HRpQCT and bone strength on FEA at 3, 6 & 12 months in the open-label treatment arm.
• To evaluate the effect of setrusumab on fracture rate (peripheral, major [long-bone], and vertebral fractures)	• Total fracture rate at 12 months • Peripheral fracture rate at 12 months • Vertebral fracture rate at 12 months • Long-bone fracture rate at 12 months
• To evaluate the effect of setrusumab on vertebral fractures and vertebral height	• Changes in vertebral fractures and vertebral height with Genant's semi-quantitative method and 6-point quantitative morphometry from baseline at 6 and 12 months
• To evaluate the effect of setrusumab on BMD	• Changes in lumbar, whole body, and proximal femur DXA BMD (absolute and T-score) from baseline at Month 6 and Month 12.
• To evaluate the effect of setrusumab on bone quality	• Changes in bone histomorphometry

Objectives	Endpoints
• To evaluate changes in radial Tr.vBMD on HRpQCT and bone strength FEA during the 12 months post-setrusumab treatment period	• Tr.vBMD (tibia & radius) on HRpQCT and bone strength on FEA at 18 and 24 months
• To evaluate the effect of setrusumab on HRpQCT parameters	• Changes (tibial and radial) in Total vBMD, cortical vBMD, bone volume fraction (BV/TV), peripheral to medullary trabecular bone density ratio (Met/Inn), trabecular thickness (TbTh), trabecular number (TbN), Inhomogeneity, cortical thickness, and cortical porosity from baseline at 6, 12, 18, and 24 months • Changes in Tr. vBMD (tibia) from baseline at 12, 18, and 24 months • Changes (tibial and radial) in Total vBMD, cortical vBMD, bone volume fraction (BV/TV), peripheral to medullary trabecular bone density ratio (Met/Inn), trabecular thickness (TbTh), trabecular number (TbN), Inhomogeneity, cortical thickness, and cortical porosity on HRpQCT and bone strength on FEA at 3 months in the open-label treatment arm.
• To evaluate the effect of setrusumab on body composition	• Changes in body height, weight and body mass index (BMI) from baseline at 6 and 12 months • Changes in lean and fat body mass from whole body DXA
• To evaluate the effect of setrusumab on markers of bone composition	• Changes in bone turnover markers and metabolic biomarkers associated with bone (PTH, P1NP, P1CP, OC, BSAP, carboxy-terminal telo-peptide [CTX-1], amino-terminal telo-peptide [NTX-1], receptor activator of nuclear factor kappa-B ligand [RANKL], osteoprotegerin, transforming growth factor beta [TGF-β], sclerostin, released C-terminal pro-peptide of Type V collagen [Pro-C5], neo-epitope of MMP-2,9 mediated degradation of Type

Objectives	Endpoints
	V collagen [C5M]) from baseline and each visit.
• To evaluate the effect of setrusumab on Patient-Reported Outcomes (PROs) and Quality of Life (QoL)	• Change in total scores from baseline to Month 6 and 12 on Short Form 12 Health Survey (SF-12), EuroQol 5-dimension 5-level descriptive system (EQ-5D-5L) and Osteogenesis Imperfecta specific Quality of Life Questionnaire for Adults (OIQoL-A) • Change in OIQoL-A pain and activity sub-scale scores from baseline to Month 6 and 12.
• To evaluate the PK of setrusumab	• Serum concentrations of setrusumab
• To evaluate potential induction of anti-drug antibodies (ADAs) by setrusumab and their effect on safety and PK	• Serum concentrations of anti-setrusumab antibodies • Serum concentrations of setrusumab neutralising antibodies
• To evaluate safety and tolerability of setrusumab	• Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs) • Infusion site reactions • Vital signs • Physical examinations • ECG • Clinical laboratory tests
Tertiary/Exploratory	
• To evaluate the effect of setrusumab on bone quality	• Changes in Trabecular Bone Score (TBS) from baseline at 6 and 12 months
• To evaluate the effect of setrusumab on changes in use of physical aids	• Changes in usage or need for physical aids from baseline at 12 months
• To evaluate the effect of setrusumab on hearing	• Change in auditory function from baseline at 12 months in a sub-set of patients
• To evaluate the effect of setrusumab on bone formation and resorption parameters measured by HRpQCT	• Change in bone formation from baseline at 6 and 12 months • Normalised newly mineralised bone volume (MV/BV)

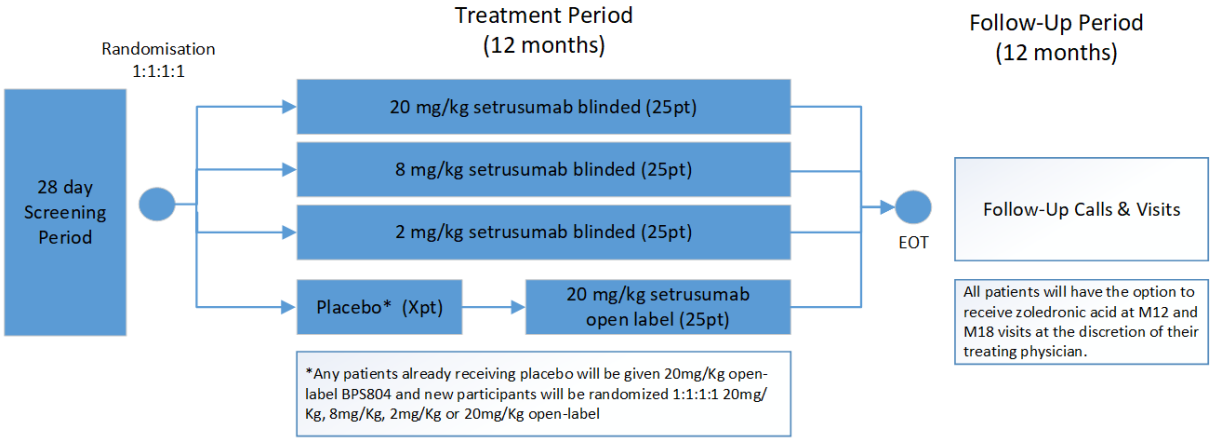
Objectives	Endpoints
	• Normalised newly mineralised surface area (MS/BS) • Mineralised thickness (MTh) • Normalised formation patch number density (N.F. Patch/BV) • Formation patch volume (F.PatchVol.) • 3D bone formation rate (3D BFR/BS) • 3D mineral apposition rate (3D MAR) • Change in bone resorption from baseline at 6 and 12 months • Normalised newly eroded bone volume (EV/BV) • Normalised newly eroded surface area (ES/BS) • Erosion depth (ED) • Normalised resorption cavity number density (N.R.Cav./BV) • Resorption cavity volume (R.Cav.Vol.) • 3D bone resorption rate (3D BRR/BS) • 3D mineral resorption rates (3D MRR)

6. Study Design

6.1. Overall Design

MBPS205 is a phase 2, multicentre, multinational, double-blind, dose range-finding study comparing 3 blinded doses of setrusumab (20 mg/kg, 8 mg/kg and 2 mg/kg) and an open-label treatment arm (20 mg/kg). Participants will be randomised 1:1:1:1 into the 4 treatment arms and will receive study treatment (setrusumab) for 12 months. Participants will have HRpQCT scans of their non-dominant distal radius at baseline, 3-month (for open-label participants only), 6-month and 12-month time points to determine the effect of treatment on Tr. vBMD. Following completion of the study treatment participants can receive an optional single dose of zoledronic acid and will enter 12 months follow-up period and will have visits at Months 14, 18 and 24 to establish the rate of offset of treatment effect. Participants will also receive follow-up telephone calls at Months 16 and 21. Participants can receive an optional further dose of zoledronic acid at Month 18 at the discretion of their treating physician. During the follow-up period participants will have HRpQCT scans of their non-dominant distal radius and tibia at Month 18 and Month 24. For the purposes of the study protocol 1 month is defined as 28 days.

Figure 1: MBPS205 Study Schematic



6.2. Number of Participants

Approximately 100 participants will be randomised to complete the study. It is anticipated that the study will be conducted in approximately 28 centres in 5 countries.

6.3. End of Study Definition

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

6.4. Scientific Rationale for Study Design

The study has been designed as a traditional parallel group dose-finding study, with 3 doses of setrusumab over a 10-fold dose range and an open-label arm. The setrusumab doses are predicted

to achieve approximately 50, 80 and 90% of maximal sclerostin inhibition and thereby provide sufficient information to allow a dose to be selected. At each dose level, a comparison will be made between post-treatment and baseline values. In order to determine the time-course of the effect, a substudy will be performed in which one quarter of the patients have additional scans at 3 months. Since an additional scan cannot be blinded, this part of the study will be open-label.

Fractures in adults with OI are likely to result from a combination of alterations in bone matrix quality, bone mass, bone microstructure and bone geometry. A variety of methodologies may be used to assess these bone parameters before and after treatment, thereby providing evidence of reduced fracture risk. The methodologies include measurement of soluble bone turnover biomarkers in the circulation, DXA, high resolution computed tomography, HRpQCT, bone biopsy, high resolution magnetic resonance imaging as well as microindentation and nanoindentation (OsteoProbe). However, HRpQCT appears to be the best option to measure treatment effects in this clinical study for the following reasons.

HRpQCT is a non-invasive technique that provides high resolution images of the bone that are directly amenable to quantification. By focussing on the extremities, HRpQCT not only reduces the radiation dose (compared to lumbar quantitative computed tomography (QCT)), but enhances patient comfort and compliance.

HRpQCT is able to measure not only total vBMD but also to discriminate between the cortex and trabecular vBMD. In addition, the microstructure of bone can be assessed (trabecular bone volume, number of trabeculae per millimetre, inhomogeneity of the network, trabecular thickness, cortical thickness and cortical porosity).

HRpQCT has been used in participants with OI and compared to healthy participants in 2 independent studies (Kocijan et al., 2015, Folkestad et al., 2012). The data were largely consistent between the studies and provide information on HRpQCT endpoints as follows:

- The relevant endpoints and their quantification in OI patients
- The expected variability of the endpoints
- The observed differences between OI and healthy bone provide an indication of potential clinically meaningful effect sizes
- The bone lesion in adults with OI resides largely in the trabecular region with the cortical region being similar to healthy participants
- Tr. vBMD is the parameter that most effectively differentiates bone density between OI and healthy bone
- BV/TV is the parameter that most effectively differentiates bone microstructure between OI and healthy bone

FEA is a well-established modelling technique that moves beyond measures of bone density and microstructure and provides a predictive measure of the whole bone strength (Engelke et al., 2013). HRpQCT provides images of sufficient resolution to allow effective FEA. FEA has been used in OI to determine bone strength as well as response to treatment with teriparatide (Orwoll et al., 2014). Accordingly, FEA can provide additional valuable information that is relevant for the determination of fracture risk in OI.

In addition to HRpQCT, the other methodologies for examining the likely impact of setrusumab on bone quality will be investigated. BMD measured by DXA, vertebral radiographs, bone turnover markers and qualitative examination of bone biopsies will also be studied in order to further characterise the effects of setrusumab and help to confirm the activity of the selected dose.

6.5. Justification for Dose Selection

Setrusumab doses targeting the EC_{50} (1.5 to 2 mg/kg monthly), $EC_{75\text{-}80}$ (6 to 8 mg/kg monthly) and EC_{90} (15 to 20 mg/kg) for sclerostin inhibition were identified through modelling and simulation using the available data from clinical studies with setrusumab. Adult participants with moderate OI given escalating doses of setrusumab demonstrated significant increases in bone formation biomarkers and lumbar spine BMD indicating enhanced skeletal remodeling and bone formation.

Therefore, study participants will receive either 2, 8 or 20 mg/kg setrusumab IV, administered monthly for 12 months. Since 90% of maximal sclerostin inhibition is expected to occur with the highest dose (20 mg/kg) this dose will be used for the open label group, which is designed to determine the rate of onset of effect with more frequent scans.

The dose with the most positive benefit/risk profile based on HRpQCT analysis and safety after 12 months of treatment will be selected for further study. Participants will continue on their allocated dose until 12 months to evaluate whether treatment effect is maintained at 12 months.

7. Study Population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

7.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Patients with a clinical diagnosis of OI Type I, III, or IV with a defect in COL1A1/COL1A2, as confirmed by genetic testing
2. Age ≥ 18 years
3. One or more non-traumatic long-bone, rib, hand/feet and/or vertebral fracture(s) in the past 5 years

Sex

4. Male and female

NOTE: The reliability of sexual abstinence for female enrolment eligibility needs to be evaluated in relation to **the duration of the clinical study and the preferred and usual lifestyle of the participant**. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Male participants:

5. There are no contraception requirements for male participants with female partners who are woman of childbearing potential (WOCBP) (See Appendix 5).

Female participants:

6. A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

a. Not a WOCBP as defined in Appendix 5

OR

b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 70 days after the last dose of setrusumab treatment.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

7.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Age > 75 years
2. History of skeletal malignancies or bone metastases at any time
3. History of neural foraminal stenosis (except if due to scoliosis)
4. History of myocardial infarction, angina pectoris, ischaemic stroke or transient ischaemic attack
5. History of or concomitant uncontrolled diseases such as hypo-/hyperparathyroidism, hypo-/hyperthyroidism, Paget's disease, abnormal thyroid function or thyroid disease or other endocrine disorders or conditions that could affect bone metabolism e.g. Stage IV/V renal disease
6. A history of rickets or osteomalacia or any skeletal condition (other than OI) leading to long-bone deformities and/or increased risk of fractures
7. Documented alcohol and/or drug abuse within 12 months prior to dosing or evidence of such abuse as indicated by the laboratory results during the screening/baseline assessments
8. Documented history of significant psychiatric or medical disorder that would prevent the participant complying with the requirements of the protocol or would make it unsafe for the participant to participate in the study as judged by the investigator
9. Current/previously reported allergy to the study drug or any of its excipients or the class of drug under investigation

Prior/Concomitant Therapy

10. History of external radiation
11. Treatment with any bisphosphonates 3 months prior to baseline and teriparatide, denosumab or other anabolic and anti-reabsorptive medications within 6 months prior to baseline. Note: treatment with zoledronic acid during the follow-up period is explicitly allowed at Months 12 and 18 only at the discretion of the treating physician.

Prior/Concurrent Clinical Study Experience

12. Participation in any clinical investigation within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initial dosing (or longer if required by local regulations)

7.3. Lifestyle Restrictions

7.3.1. Meals and Dietary Restrictions

Refrain from consumption of food or drinks (except water) for 8 hours prior to visits that require blood draws for bone biomarkers.

7.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAE) and adverse events of special interest (AESI).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

However, the screening period may be extended beyond 28 days in the following circumstances with the discussion and with the approval of the medical monitor:

- All screening inclusion/exclusion criteria are met but the participant's schedule, including genetic testing or HRpQCT scan, prevented them from being randomised within the screening period.

Additionally, individual lab parameters or screening test may be repeated if the result is considered aberrant or not clinically consistent with the patient's health status. Decisions to re-test should be made in conjunction with the study medical monitor.

Participants who have individual laboratory parameters re-tested should have the results entered in the electronic case report form (eCRF).

8. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

8.1. Treatments Administered

Study Treatment Name:	Setrusumab	Concomitant Vitamin D and Calcium Therapy	Zoledronic Acid
Dosage Formulation:	Lyophilised powder for solution	Calcium tablets and Vitamin D capsules	Solution for infusion
Unit Dose Strength(s)/Dosage Level(s):	150 mg	500mg Calcium and 800 IU Vitamin D	4 mg single dose
Route of Administration:	IV	Oral	IV
Dosing Instructions:	60-minute infusion	Oral with water	15-minute infusion
Packaging and Labelling:	Study Treatment will be provided in labelled vials packed into in cartons containing 20 vials. Each vial and carton will be labelled as required per country requirement	Not applicable	Stocks will be labelled with study information and standard packaging.
Responsible Manufacturer:	Mereo Biopharma 3 Ltd, 1 Cavendish Place, London, W1G 0QF	Provided by Investigational sites	Provided by Mereo Biopharma 3 Ltd, 1 Cavendish Place, London, W1G 0QF

8.1.1. Zoledronic acid therapy

Following the end of setrusumab therapy all participants will have the option to receive a dose of zoledronic acid at 12 and 18 months. This will be prescribed at the discretion of the treating physician and in line with local guidelines.

8.2. Method of Treatment Assignment

All participants will be centrally randomised using an Interactive Web Response System (IWRS) in a 1:1:1:1 ratio to receive either 20 mg/kg, 8 mg/kg, 2 mg/kg or open-label 20 mg/kg. Subject to informed consent being given by the participant, all participants assigned to placebo prior to protocol amendment 4.0 will be reassigned to begin 12 months of open-label 20 mg/kg setrusumab treatment. ICON Biostatistics will produce a randomisation list that links participant numbers to randomisation numbers. These randomisation numbers will be linked to different treatment regimens and the randomisation scheme will be stratified according to the Sillence Clinical Classification of OI type into 2 groups (Type I or III/IV).

Following confirmation from the investigator, the pharmacist will contact the IWRS and be issued with a treatment regimen. Should the participant be allocated to a setrusumab regimen, then the pharmacist will input the patient's weight into the IWRS and receive a calculated dose per participant.

Before the study is initiated, the web address for the IWRS and the log in information & directions will be provided to each site.

Study treatment will be dispensed and dosed at the study visits summarised in the Schedule of Activities.

8.3. Blinding

With the exception of the open-label treatment arm, investigators and participants will remain blinded to each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party (pharmacist) will be responsible for the reconstitution and dispensation of all study treatment. A separate unblinded Clinical Research Associate (CRA) will monitor the pharmacy.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the site(s) to verify that randomisation/dispensing has been performed accurately.

The IWRS will be programmed with blind-breaking instructions. The study blind may be broken if, in the opinion of the investigator, it is in the participant's best interest to know the study treatment assignment. Mereo must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition (eg, antidote is available). In this case, Mereo must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

8.4. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment

On written confirmation by the investigators, the pharmacist will contact the IWRS, enter the participant number and weight. The IWRS will inform the pharmacist of the treatment allocation

and dose required for the participant, based on their weight. The IWRS will provide the number of vials required to reconstitute and mix the appropriate dose for the participant. The pharmacist will select and record the vials used to reconstitute and mix the dose in the IWRS.

Further details of the preparation and administration of the study treatment, please refer to the Study Treatment Administration Guide and the MBPS205 Pharmacy Manual.

Only participants enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the handling, disposition and accountability of study treatment are provided in the MBPS205 Pharmacy Manual.

8.5. Treatment Compliance

The per protocol dosage, timing and mode of administration of study medication may not be changed. Any departures from the intended regimen must be recorded in the eCRF and notified to the sponsor.

8.6. Concomitant Therapy

Concomitant Vitamin D and Calcium Therapy

Vitamin D levels should be 50 nmol/L or higher during the study. If less than 50 nmol/L at screening the participant should be treated as per the local guidelines and retested during the study to maintain vitamin D levels above 50 nmol/L. Calcium levels should be in the normal range for study entry. For the duration of the study participants can, if required, receive a daily dose of 500 mg calcium and/or 800 I.U. vitamin D as background treatment, but if the participant already receives a higher dose, they can stay on the dose they receive. Calcium tablets should not be taken 2 hours prior to DXA lumbar scan.

The following classes of medication listed below are not permitted to be taken during the conduct of the study starting from screening (for details of screening criteria concerning medications, see Section 7.2):

1. Bisphosphonates (oral and injectable)
2. RANKL antibodies (Denosumab)
3. PTH and analogues
4. All other monoclonal antibodies
5. Medications known to affect bone physiology (e.g. aromatase inhibitors)
6. Systemic corticosteroid drugs

Physical aids and physiotherapy are explicitly allowed. Treatment with zoledronic acid during the follow-up period is explicitly allowed at Months 12 and 18 only at the discretion of the treating physician.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

All other concomitant medications are allowed, unless they are explicitly not allowed or are known to affect bone or bone metabolism.

The ICON Medical Monitor can be contacted if there are any questions regarding concomitant or prior therapy.

8.7. Treatment After the End of the Study

Participants completing the MBPS205 study will be able to discuss other potential treatments for their osteogenesis imperfecta with their investigators when they complete the 12-month follow up period at the end of MBPS205.

9. Discontinuation Criteria

9.1. Discontinuation of Study Treatment

Participants may voluntarily discontinue investigational treatment for any reason at any time. If the participant no longer wants to take part in the study, they will be asked to attend an end of treatment visit and 60-day follow-up visit and be discontinued from the study.

The investigator should discontinue investigational treatment of a given participant if, on balance, he/she believes that continuation would be detrimental to the participant's well-being. However, the participant should be followed up to the end of the study and all study procedures should be performed per protocol.

Investigational treatment must be discontinued under the following circumstances and then further steps need to be discussed with the medical monitor:

1. Anaphylactic reaction or other severe systemic reaction to study drug injection
2. Diagnosis of malignancy during study
3. Evidence of pregnancy
4. Absolute corrected QT interval (QTc) corrected using Fridericia's formula (QTcF) is >500 msec and rise from baseline, confirmed by triplicate ECGs, is ≥60 msec (Refer to Section 10.4.3)
5. Any of the following confirmed laboratory abnormalities:
   - Renal function values that require discontinuation:
     - Discontinue investigational treatment for a participant if individual serum creatinine increases ≥ 50% compared to baseline (and is considered clinically significant), or in the event of treatment-emergent proteinuria (albumin: creatinine ratio > 300 mg/g or > 30 mg/mmol; protein: creatinine ratio (PCR) ≥ 500 mg/g or > 50 mg/mmol), unless the event is not drug related, or if the risk/benefit assessment supports continuing investigational treatment.

     Note: A renal event leading to participant discontinuation should be followed up until event resolution (serum creatinine within 10% of baseline, PCR within 50% of baseline), stabilises or becomes not clinically significant, or is assessed as being chronic.

   - Liver laboratory values that require discontinuation
     - Confirmed alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal (ULN) (for more than 2 weeks)
     - Confirmed ALT or AST > 3 times the ULN and confirmed bilirubin total > 2 times ULN (unless elevated bilirubin is related to confirmed Gilbert's syndrome)

     Note: If the laboratory abnormality is considered causally related to study drug, study treatment will be permanently discontinued. In cases in which a causal relationship to study drug can be reasonably excluded, (ie, an alternative cause is evident), study treatment will be discontinued but it may be resumed when the laboratory abnormality is sufficiently normalised. A decision to resume study treatment will be made jointly by the investigator and medical monitor (medical monitor's written approval is required).

6. Withdrawal of informed consent
7. Significant non-compliance of the participant with study procedures
8. Sponsor decision

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcF after enrolment; the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Refer to the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

9.1.1. Temporary Discontinuation

Study drug dosing may be temporarily suspended in the event of:

1. Clinically important laboratory abnormalities
2. Other intercurrent illnesses or major surgery
3. Use of prohibited treatment
4. Any other protocol deviation that results in a significant risk to the participant's safety
5. Sponsor decision

After a laboratory abnormality leading to a delay of dosing normalises sufficiently, study treatment may resume at the discretion of the principal investigator in consultation with the medical monitor. Similarly, study treatment may resume after the medication leading to suspension of dosing is discontinued. A decision to discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor. The investigator may suspend study treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the participant's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation.

9.1.2. Rechallenge

Resumption of study treatment after temporary discontinuation should always be discussed with the medical monitor.

9.2. Discontinuation from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or administrative reason.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

9.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- In cases in which the participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10. Study Assessments and Procedures

Study procedures and their timing are summarised in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 480 mL over the duration of the study.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

10.1. Efficacy Assessments

10.1.1. Radiology

In order to ensure the consistent assessment of BMD and fractures, site-based radiology staff and central readers will be fully trained. Details of each radiological assessment, procedures for calibration of equipment to ensure assessment continuity and central reading procedures will be provided in the MBPS205 Imaging Charter and Training Manual and made available.

10.1.1.1. HRpQCT

HRpQCT scans, including calibration, should be performed according to MBPS205 Imaging Charter and Training Manual on distal non-dominant arms unless the arm has been supported with rods or there is significant deformity. In this case, the investigator should document that the dominant limb was selected and specify the rationale. If rodding (or other metal implant) is present in both distal tibiae, or if severe deformities do not physically allow entry of either lower limb into the HRpQCT scanner, please discuss the participant's involvement in the study with the study medical monitor prior to inclusion in the study.

HRpQCT will be used to measure the primary efficacy endpoint of trabecular volumetric BMD of the radius (see SoA).

In addition, HRpQCT will be used to examine other aspects of the tibial and radial trabecular and cortical bone volume and microarchitecture. Morphological analysis will measure or derive bone volume, trabecular number, thickness and spacing, cortical volume and thickness, structure model index, connectivity density and degree of anisotropy.

Exploratory end points will be assessed with time-lapse dynamic in vivo morphometry of HRpQCT image datasets.

Morphological analysis procedures are described in detail by (Liu et al 2010) and in the MBPS205 Imaging Charter and Manual.

Refer to Appendix 6 for Radiation Exposure.

10.1.1.2. Dual-Energy X-ray Absorptiometry

Bone mineral density will also be evaluated using DXA. T-Score will be calculated based on actual measured bone density value. Change in TBS from baseline will be assessed from DXA images using TBS (iNsight software). Lean and fat body mass will be evaluated using whole body DXA. Calcium tablets should not be taken 2 hours prior to DXA lumbar scan.

Refer to Appendix 6 for Radiation Exposure and the MBPS205 Imaging Charter and Imaging Training Manual for further details of the DXA including patient positioning.

10.1.1.3. Radiography

Vertebral radiographs will be used to assess the number of historic vertebral fractures, the percentage change in numbers of vertebral fractures from baseline at 6 and 12 months and the percentage change in vertebral height from baseline.

Genant's semi-quantitative method and 6-point quantitative morphometry will be used to evaluate vertebral fractures and vertebral height, as detailed in the Imaging Charter.

Fracture assessment, confirmed by central radiographic reading, will be carried out separately for peripheral including all major long bones, minor bone (digits, ribs) and vertebral fractures. Fractures without clinical symptoms, detected only by means of radiographic investigations will not be included in the analysis.

Date of diagnosis (defined as first occurrence of symptoms of fracture) will be adopted for all time to event analyses.

Refer to Appendix 6 for Radiation Exposure and the MBPS205 Imaging Charter and Manual for further details.

10.1.2. Bone Biopsy

Bone biopsies will be performed once at either Month 6 or Month 12 in a sub-set of participants. Informed consent will be obtained using a specific bone biopsy consent form.

Double labelling of bone, according to the procedure detailed in the MBPS205 Bone Biopsy Manual, will be carried out before the bone biopsy procedure to allow determination of the level of bone turnover, and bone formation and mineralisation rates.

All biopsies will be analysed at a central laboratory as per the MBPS205 Bone Biopsy Manual.

10.1.3. Audiometry

This procedure can be omitted if the investigative site does not have the capability to complete the audiometry assessment. Participants will be asked to remove anything which might affect the test results such as spectacles, earrings and hearing aids. The ear will be examined with an otoscope to assess the requirement for wax removal and to determine whether the eardrum has suffered any damage which may reduce the ability of sound to be transported to the cochlea. The audiometric test will be carried out using standard or automatic audiometers. The participant will be asked to indicate whether they can just hear or cannot hear a certain sound; the sound level may be increased from a very low level or reduced from a high level. Headphones will be fitted to the participant and the test performed on each ear. A threshold test will be performed first in which each ear will be subjected to sound at a frequency of 1 kHz at varying levels of intensity ranging from low to high and high to low. This will be repeated several times in order to derive an average threshold for the test. Following this pre-check, both of the participant's ears will be tested through a range of frequencies (0.5, 1, 2, 3, 4, 6 and 8 kHz) and hearing loss recorded for each frequency via a series of sound exposures. The decibel hearing loss will be recorded using the grading scores in Appendix 7.

10.1.4. Patient-Reported Quality of Life

The SF-12 is a generic, 12-item survey that measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these 8 domains and 2 summary measures of physical and mental health: The Physical Component Summary and the Mental Component Summary.

The EQ-5D-5L is a standardised measure of health status comprised of a descriptive system of 5 health-related quality of life states (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a Visual Analogue Scale (VAS) of overall health. Each dimension is rated on a 5-point response scale indicating severity of problems, where 1 is "no problems" and 5 is "extreme problems". The 5 questions are scored and together contribute to the EQ-5D index (utility) score between 0 and 1 (1 being perfect health), which will be calculated using the developers' algorithm based on country-specific reference score sets. The EQ-5D VAS is a measure of overall self-rated health status, used and analysed separately from the index score. The VAS ranges from 0 to 100, with higher scores indicative of better overall health.

The OIQoL-A is a PRO instrument for use in adults with OI Type I, III, or IV. The OIQoL-A currently measures 5 areas of quality of life related to OI (Physical Function, Pain, Hearing Loss, taking care/Concerns, Social and Family Life and Activities); data collected from the phase 2b trial will be used to validate the instrument prior to its use within the phase 3 study.

10.2. Adverse Events

The definitions of an AE or SAE/AESI can be found in Appendix 4.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE/AESI and remain responsible for following up AE that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8.7).

10.2.1. Time Period and Frequency for Collecting AE and SAE/AESI Information

All AE and SAE/AESI will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF.

All SAEs/AESIs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE/AESI in former study participants. However, if the investigator learns of any SAE/AESI, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE/AESI and the procedures for completing and transmitting SAE/AESI reports are provided in Appendix 4.

10.2.2. Method of Detecting AE and SAE/AESI

Care will be taken not to introduce bias when detecting AE and/or SAE/AESI. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

10.2.3. Follow-up of AE and SAE/AESI

After the initial AE/SAE/AESI report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs/AESIs, will be followed until resolution, stabilisation, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 9.3). Further information on follow-up procedures is given in Appendix 4.

10.2.4. Regulatory Reporting Requirements for SAE

- Prompt notification by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.2.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 70 days after the last dose.

If a pregnancy is reported, the investigator should inform the Safety Clinical Research Organisation (CRO) within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

10.3. Treatment of Overdose

For this study, any dose of setrusumab greater than 120% of the calculated dosage will be considered an overdose.

Mereo does not recommend specific treatment for an overdose.

In the event of an overdose, the pharmacist / unblinded CRA should:

1. Contact the ICON Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE/AESI and laboratory abnormalities until setrusumab can no longer be detected systemically (at least 60 days).
3. Obtain a plasma sample for PK analysis within 14 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF and source documents.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

10.4. Safety

Planned time points for all safety assessments are provided in the SoA.

10.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, Musculoskeletal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

10.4.2. Vital Signs

- Tympanic or oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the semi-Fowler's position with a manual device, unless a manual device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (after the participant has been sitting for 5 minutes, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.
- For the first 2 administrations of study drug per patient, oral or tympanic temperature, blood pressure and pulse will be monitored at the beginning of the infusion at 5, 15 and 30 minutes after the start of infusion, and at 60 minutes after the end of the infusion. For the remaining infusions, vital signs will be monitored during the infusion.

10.4.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 9.1 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- If triplicate ECGs are required (Refer to Section 9.1), 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

10.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 60 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

10.5. Pharmacokinetics

- Approximately 3 mL of whole blood to provide serum samples of approximately 1.5 mL will be collected for measurement of serum concentrations of setrusumab as specified in the SoA.
- A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor in MBPS205 Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of setrusumab. Each serum sample will be divided into 2 aliquots (1 each for setrusumab PK, and a back-up]). Samples collected for analyses of setrusumab serum concentration may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study.
- Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained. At visits during which samples for the determination of serum concentration of setrusumab will be taken, 1 blood draw of sufficient volume can be used.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Further details of sampling and processing requirements for the PK samples can be found in the MBPS205 Laboratory Manual.

10.6. Pre-Screening Genetics

A documented historical confirmed mutation in the COL1A1/COL1A2 genes can be used to satisfy the entry criteria. However, if the COL1A1/COL1A2 mutation is not confirmed, investigators will be able to pre-screen participants using a local facility for analysis or alternatively, one of the facilities listed in the MBPS205 Laboratory Manual.

In the event of a test being required, participants can be consented using the separate genotyping consent. Approximately 10 mL of blood will be required for DNA isolation. Details on processes

for collection and shipment of these samples may be found by contacting local laboratories or can be found in the MBPS205 Laboratory Manual.

In the event of DNA extraction failure, a replacement screening genetics blood sample may be requested from the participant.

The final disposition of samples will be conducted per local regulations.

10.7. Biomarkers

Collection of samples for bone biomarker research is also part of this study. 10 mL fasting blood samples will be collected from all participants in this study as specified in the SoA.

Additional, optional 10 mL blood samples for biomarker research should be collected from participants in the study at 8 days post-baseline and 14 days post-Month 9 Visit.

In the treatment period samples will be tested for PTH, P1NP, P1CP, OC, BSAP, CTX-1, NTX-1, RANKL, osteoprotegerin, TGF-β, sclerostin, Pro-C5, and C5M to evaluate their association with the observed clinical responses in bone turnover to setrusumab. In the follow-up period samples can be tested for CTX-1 and P1NP.

All samples will be processed within 3 months of the end of study.

Further details of sampling and processing requirements for the bone biomarker blood samples can be found in the Study MBPS205 Laboratory Manual.

10.8. Immunogenicity Assessments

Antibodies to setrusumab will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to setrusumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to BPS804 and/or to further characterise the immunogenicity of setrusumab.

The detection and characterisation of antibodies to setrusumab will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for setrusumab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterised and/or evaluated for their ability to neutralise the activity of the study treatment(s). Samples may be stored for a maximum of 1 year following the last participant’s last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to setrusumab.

Further details of sampling and processing requirements for the Immunogenicity blood samples can be found in the MBPS205 Laboratory Manual.

10.9. Medical Resource Utilisation and Health Economics

Medical resource utilisation and health economics data, associated with medical encounters, will be collected in the eCRF by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and medical encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient).
- Duration of hospitalisation (total days or length of stay, including duration by wards [eg, intensive care unit]).
- Number and type of diagnostic and therapeutic tests and procedures.
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).
- Use and change of use of physical aids.

11. Statistical Considerations

11.1. Sample Size Determination

The number of participants is based on power considerations for the trabecular vBMD derived from HRpQCT at Month 12. The primary analysis method for this endpoint will be on the change from baseline within each treatment group, so the primary hypothesis to be tested is

$$H_0: \mu_T \leq 0 \text{ vs. } H1: \mu_T > 0$$

where μ_T denotes the change from baseline for each dose of Setrusumab. Under the assumptions of a maximum change from baseline of [redacted], a standard deviation at both timepoints of [redacted] and a correlation between both measurements of [redacted], a sample size of 25 patients per group yields approximately 80% power for a one-sided test with significance level 0.025, if the data are analysed on the log scale using a t-test.

For a change from baseline of [redacted], with standard deviation as above the one-sided test would have a probability of 80% to yield a p-value below 5%, being considered indicative of a trend.

Following a review of the trabecular vBMD (radius) derived from HRpQCT at Month 6 of those subjects within the 20 mg/kg Setrusumab open label treatment group, a change from baseline standard deviation of [redacted] was observed. This yields to a correlation between baseline and Month 6 visits of [redacted] (much higher than the [redacted] that was originally assumed). If such a correlation is observed at Month 12, given 25 subjects per arm, the one-sided test would have a probability of 80% to yield a p-value below 5% for a change in baseline of [redacted].

As a secondary analysis, the MCPMod approach will be applied to the data in order to assess a non-flat dose-response curve and to obtain information about the underlying dose-response curve. Due to the missing placebo group, the power of this approach depends heavily on the underlying dose-response curve.

The following candidate models will be used:

- EMax (ED_{50} of 1.5 mg)
- Exponential ($\delta = 2$)

Under the assumptions of each of the two candidate models being the true dose-response curve, and in addition an Sigmoid EMax model with parameters $ED_{50} = 10$ mg and $h = 2.4$, a contrast test at a one-sided significance level of 2.5% has the following power for each of the three models:

Model	EMax	Exponential	Sigmoid EMax
Power	13.7%	73.2%	60.7%

The total sample size required is therefore determined as 100:

- 25 participants on open-label setrusumab (20 mg/kg)
- 25 participants on each of the active arms (2 mg/kg, 8 mg/kg, 20 mg/kg)

Approximately 100 participants will be randomised.

11.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Full Analysis Set (FAS)	All participants who are randomised to one of the blinded treatment arms and take at least 1 dose of study treatment. Participants will be analysed according to the randomised treatment.
Modified Full Analysis Set (mFAS)	All participants from the FAS who have sufficient cross-sectional overlap across HRpQCT scans (details to be further described in the Statistical Analysis Plan). Participants will be analysed according to the randomised treatment.
Per-protocol	All participants from the mFAS who have been treated according to the protocol and fulfill the following criteria (to be further described in the Statistical Analysis Plan [SAP]): 1. All inclusion/exclusion criteria satisfied 2. Absence of relevant protocol violations with respect to factors likely to affect the efficacy of treatment where the nature of protocol violation will be defined before breaking the blind

	3. Adequate study medication compliance which will be determined before breaking the blind.
Non-restricted FAS	All participants who are randomised and take at least 1 dose of study treatment. Participants will be analysed according to the randomised treatment. Analyses using the Non-restricted FAS will comprise of such where the two 20 mg/kg dose group are pooled (for the follow-up analysis), and those where they are not.
Safety	All participants who are administered at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received. Analyses using the Safety population will comprise of such where the two 20 mg/kg dose group are pooled (for the follow-up analysis), and those where they are not.
PK	All participants in the Safety Population who have at least 1 quantifiable setrusumab serum concentration.

11.3. Statistical Analyses

The statistical evaluation will be performed by ICON using SAS®, Version 9.3 or later and ADDPLAN DF 4.0 or later.

The main population for efficacy analysis will be the FAS. Results for the mFAS, per-protocol (PP) population and the Non-restricted FAS will be considered supportive.

Data for placebo participants and open-label BPS804 20 mg/kg subjects will be reported separately from the comparison between the randomized, blinded treatment groups. In particular for the primary analysis, the open-label BPS804 20 mg/kg participants' data will not be pooled with the blinded BPS804 20 mg/kg participants' data.

The primary analysis will be performed after all participant have completed their initial 12-month study period or have withdrawn prior to completion. Analyses for the follow-up period will be carried out separately from the primary analysis when all participants have completed the 12 months follow-up period, or have withdrawn from it.

Data will be analysed by either enumeration of participants displaying distinctive characteristics within each treatment regimen or by descriptive statistical summaries such as means, standard deviations (SD), minimum, lower quartile, median, upper quartile and maximum for continuous measures. Continuous measures will be log transformed where appropriate. Categorical variables will be presented by the number of observations and absolute and relative (%) frequency. Time to event variables will be analysed using Kaplan-Meier methods, and quartiles for the median time to event will be presented together with their 95% confidence intervals (CIs).

For efficacy data summary statistics (N, mean, SD, median, minimum and maximum for continuous data, and N [%] for categorical data) will be presented at each visit.

Similarly, changes from baseline (or percentage change from baseline if appropriate) will be summarised in a similar manner.

ANCOVA dealing with nested observations within a patient (e.g., vertebral assessments) will consider this relationship in the modelling. Patient will be modelled as a random factor.

Unless stated otherwise the baseline value for a variable will be the latest value taken prior to first dose of study medication.

Data in summary tables will generally be presented on an Observed Cases basis.

Unless stated otherwise, all statistical tests will be 2-sided and conducted at the 5% level, and all quoted CIs will be 2-sided 95% CIs.

Analysis of the technical performance of the HRpQCT endpoints will be conducted to demonstrate reliability in accordance with standard metrological standards. Details of the analysis and methods are provided in a separate statistical validation analysis plan.

A primary efficacy analysis and unblinding will be performed when all data up to and including Month 12 has been collected in the blinded treatment arms. A Clinical Study Report (CSR) will be prepared based upon the results of this analysis. The data collected during the 12-month follow-up period will be analysed separately and published in the CSR addendum.

The SAP will be developed and finalised before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

11.3.1. Efficacy Analyses

Analyses for the primary efficacy endpoints and selected secondary endpoints will be analysed on the FAS, mFAS, the Non-restricted FAS and the PP samples, while analyses for the remaining secondary efficacy endpoints will be analysed on the FAS sample only. The mFAS will be used for analysis of HRpQCT endpoints only. General methods as described above will be applied to the efficacy endpoints; specific analyses are described below.

Endpoint	Statistical Analysis Methods
Primary	The HRpQCT results for the Trabecular vBMD (radius) will be log transformed and an ANCOVA model will be used to calculate Least Square Means (LSMeans) for the change from baseline, using baseline values as a covariate and treatment group and stratum as a factor. LSMeans for each treatment group will be calculated and tested against the null hypothesis of 0 in an a priori hierarchical approach, starting with the highest dose. Differences between LSMeans will also be displayed but will be analysed in an exploratory fashion only. The type I error rate will be 5% two-sided. P-values above 5% but below 10% (two-sided) will be considered as indicative for a trend. For supportive evidence, this analysis will be repeated on the mFAS, Non-restricted FAS in both versions and the PP population. Further,

Endpoint	Statistical Analysis Methods
	the following analyses will be performed, again on the FAS, mFAS, the Non-restricted FAS in both versions and the PP population: The LSMeans will further be analysed using the MCPMod methodology, using the following candidate models: • EMax (ED_{50} of 1.5 mg) • Exponential ($\delta = 2$) • Sigmoid EMax model with parameters ED50 = 10 mg and h = 2.4 Parameter estimates and predicted values for each dose will be calculated for all models. These analyses will be done primarily on the trabecular vBMD (radius). It will be repeated for the bone strength on FEA for supportive evidence. LSMeans and LSMean differences between treatment groups will be back-transformed to their original scale for descriptive purposes. After substracting the geometric mean of the log baseline values, the back-transformed LSMeans will correspond to the percentage change from baseline, while the back-transformed LSMeans differences will correspond to the ratio of percentage changes from baseline.

Secondary	• Tr. vBMD (tibia): An ANCOVA will be calculated on log transformed data as described above on the FAS, mFAS, the PP population, the FAS and the Non-Restricted FAS in both versions
	• DXA BMD: Changes will be compared treatment groups using an ANCOVA as described above on the percent change from baseline and on the T-scores for the following variables on the FAS, the PP population, the FAS and the Non-Restricted FAS in both versions:
	  o Lumbar BMD
	  o Whole body BMD
	  o Proximal femur BMD
	• Vertebral assessments:
	  o Vertebral fractures assessed by Genant's semi-quantitative method:
	  ▪ 2x2 table analysis for occurrence of new and new or worsening fractures (yes/no)
	  ▪ Poisson regression for number of new and new or worsening fractures, if appropriate

Endpoint	Statistical Analysis Methods
	▪ Shift tables to investigate the change in grade for existing fractures ▪ An ANCOVA with baseline value as covariate and treatment group and stratum as factors to investigate the percent change from baseline in numbers of vertebral fractures ▪ An ANCOVA with baseline value as covariate and treatment group and stratum as factors to investigate the total sum of vertebral gradings o Vertebral height derived from 6-point quantitative morphometry: The maximum change from baseline in the H_A/H_P and the H_M/H_P ratio for fractured vertebrae will be analysed using ANCOVA • Change in bone histomorphometry • HRpQCT parameters: o Total vBMD o Cortical vBMD o BV/TV o Met/Inn o TbTh o TbN o Inhomogeneity o Cortical thickness o Cortical porosity (tibia and radius) • Body composition: Comparisons between treatment groups will be performed using an ANCOVA as described above o Body height o Body weight o BMI o Lean body mass o Fat body mass • Change from baseline to each visit for bone turnover markers and metabolic biomarkers • Fracture rate: Chi square tests will be calculated to assess differences across treatment groups on the following on the FAS, the PP population, the FAS and the Non-Restricted FAS in both versions: o Total fracture rate o Peripheral fracture rate

Endpoint	Statistical Analysis Methods
	○ Vertebral fracture rate ○ Long-bone fracture rate • The time to first fracture will also be analysed for each fracture category for the FAS, the PP population, the FAS and the Non-Restricted FAS in both versions • PROs and QoL (FAS and Non-restricted FAS in both versions): ○ SF-12 ○ EQ-5D-5L ○ OIQoL-A
Exploratory	Will include change in TBS, and will be described in the SAP finalised before database lock

11.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	**Adverse Events** AEs will be coded using the most recent version available of the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be by system organ class and preferred term. TEAEs are defined as any AE occurring or worsening on or after the first dose of study medication. If a participant experiences the same preferred term multiple times then the event will be counted only once and by the greatest severity. The frequency and incidence of TEAEs will be presented by system organ class and preferred term for each treatment regimen (number and percentage of participants experiencing at least 1 AE per preferred term as well as the number of observed events per preferred term). These tables will be presented on both the pooled and the non-pooled version of the Safety population. Remaining safety tables will be on the pooled version of the Safety population only. Separate tables will be presented by severity and by relationship. All AEs will be presented in full in a comprehensive listing including participant number, treatment regimen, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop and duration. Details of SAEs/AESIs and AEs leading to withdrawal will be listed separately.
Secondary	All secondary safety analyses will be on the pooled version of the Safety population only. **Infusion Site reactions** Infusion site reactions will be tabulated and summarised by treatment regimen.

Endpoint	Statistical Analysis Methods
	Vital Signs Vital signs will be summarised as actual values and change from baseline by treatment regimen and visit. **Physical Examination** Physical examination results will be listed by participant and body system. **ECG** The overall ECG interpretation will be summarised by presenting the number and percentage of participants with "Normal" "Abnormal, not clinically significant" and "Abnormal, clinically significant". ECG parameter values (e.g., QTcF) will be summarised as actual values and change from baseline by treatment regimen and visit. **Clinical Laboratory** Descriptive statistics will be presented for quantitative laboratory parameters for each treatment regimen and time point. Similarly, changes from baseline will be summarised. Values outside the normal range will be categorised as H (above the normal range) or L (below the normal range) based on the laboratory's reference range and these will be flagged in the listings of individual participant data.
Tertiary / Exploratory	Will be described in the SAP finalised before database lock

11.3.3. Other Analyses

Exploratory endpoint variables will be analysed according to their scale using general methods as described above.

PK, PD, and biomarker exploratory analyses will be described in the SAP finalised before database lock. The population PK analysis and PD analyses will be presented separately from the main CSR.

11.3.4. Follow-Up Period Analyses

Variables will be analysed according to their scale using general methods as described above. Results will be presented overall and by initial treatment assignment. In addition, subgroup analyses will be performed for HRpQCT, DXA, vertebral radiograph, CTX-1, and P1NP based on the administration of zoledronic acid during the follow-up period (none; at Month 12; at Month 18). Also, the frequency of administration of zoledronic acid during the follow-up period will be related both to the site and to the 12 months outcome for both primary efficacy endpoints.

11.3.5. Interim Analyses

There is no formal interim analysis planned.

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13. Appendices

Appendix 1: Abbreviations and Trademarks

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BMD	Bone Mineral Density
BMI	Body Mass Index
BSAP	Bone-Specific Alkaline Phosphatase
BV/TV	Bone Volume Fraction
CFR	Code of Federal Regulations
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical Research Assistant
CRO	Clinical Research Organisation
C5M	Neo-Epitope of MMP-2,9 mediated degradation of Type V Collagen
CSR	Clinical Study Report
CT	Computed Tomography
CTX-1	Carboxy-terminal Telo-peptide
DMC	Data Monitoring Committee
DXA	Dual-energy X-ray Absorptiometry
EC_{50}	Half Maximal Efficacy Concentration
ED_{50}	Median Effective Dose
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOT	End of Treatment
EQ-5D-5L	EuroQol 5-dimension 5-level descriptive system
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEA	Finite Element Analysis
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice

HRpQCT	High Resolution Peripheral Quantitative Computed Tomography
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalised Ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
IV	Intravenous
LSMeans	Least Square Means
mAb	Mono-clonal Antibody
MCP-Mod	Multiple Comparison Procedure Modelling
MedDRA	Medical Dictionary for Regulatory Activities
Met/Inn	Peripheral to Medullary Trabecular Bone Density Ratio
mFAS	Modified Full Analysis Set
MMP	Matrix Metalloproteinase
NOAEL	No Observed Adverse Effect Level
NTX-1	Amino-terminal Telo-peptide
OC	Osteocalcin
OI	Osteogenesis Imperfecta
OIQoL-A	Osteogenesis Imperfecta specific Quality of Life Questionnaire for Adults
P1CP	Carboxy-terminal Propeptide of Type 1 Procollagen
P1NP	Amino-terminal Propeptide of Type 1 Procollagen
PCR	Protein: Creatinine Ratio
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-Protocol
PRO	Patient-Reported Outcome
Pro-C5	C-terminal Pro-Peptide of Type V collagen
PTH	Parathyroid Hormone
QCT	Quantitative Computed Tomography
QoL	Quality of Life
QT_C	Corrected QT Interval
QT_CF	QT_C by Fridericia's correction Formula

RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-12	Short Form 12 Health Survey
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SOST	Gene Coding for Sclerostin
SUSAR	Suspected Unexpected Serious Adverse Reaction
TbN	Trabecular Number
TbTh	Trabecular Thickness
TBS	Trabecular Bone Score
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TGF-β	Transforming Growth Factor Beta
Tr. vBMD	Trabecular Volumetric Bone Mineral Density
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
vBMD	Volumetric Bone Mineral Density
WOCBP	Women of Childbearing Potential

Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by a central laboratory unless otherwise stated.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 7 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Haematology</td><td colspan="2">Platelet Count
Red Blood Cell Count
Haemoglobin
Haematocrit</td><td colspan="2">White Blood Cell count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="3">Clinical Chemistry[1]</td><td>Blood Urea Nitrogen</td><td>Potassium
Chloride,
Bicarbonate/Carbon dioxide</td><td>AST
ALT
Alkaline phosphatase</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Thyroid stimulating hormone</td><td>Total Protein</td></tr>
<tr><td>Glucose (non-fasting)</td><td>Calcium
Vitamin D</td><td>Lipase</td><td>Prothrombin Time/ international normalised ratio</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• Specific gravity
• pH, glucose, protein, blood, ketones by dipstick
• Microscopic examination (if blood or protein is abnormal)
• Albumin creatinine ratio and protein creatinine ratio to be tested at site (if albumin or protein is abnormal)</td></tr>
<tr><td>Other screening Tests</td><td colspan="4">• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)
• Serum or urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)[2]</td></tr>
</table>

	• The estimated glomerular filtration rate (eGFR) will be calculated based on Cockcroft-Gault formula: **eGFR = ((140 - Age) / (SerumCreat)) * (Weight/72)** • All study-required laboratory assessments will be performed by a central laboratory, with the exception of COL1A1/COL1A2 genotyping. The results of each test must be entered into the eCRF.
NOTES: [1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 9.1. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalised ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis). [2] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.	

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted by Mereo and ICON in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines
  - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- In case of substantial amendment approval from the Competent Authority (or relevant regulatory agencies) will be sought by Mereo prior to implementation.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health

Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committees Structure

A Data Monitoring Committee (DMC) will be established to review the efficacy and safety results. The DMC will have access to unblinded data. Based on the data the DMC will submit its recommendations in written form to the sponsor who is responsible for responding to the recommendations of the DMC and to take appropriate action. The investigators will only be informed by the sponsor in case of stopping the trial. The DMC may choose to request additional evaluations at any time if they feel this is warranted from the standpoint of safety.

The DMC will act according to its own written standard operating procedure (SOP) described in a charter and will prepare written minutes of its meetings.

Publication Policy

The sponsor shall retain the ownership of all data. When the study is complete the sponsor shall arrange the analysis and tabulation of data. A CSR shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory authorities. All proposed publications based on this study must be participant to the sponsor's approval requirements.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of

multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

At the end of the study, investigators will be informed of the outcome of the study including the treatment allocation as soon as the results are available and can be reported. These may be shared with participants in the study.

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalisation of the study report, the results of this trial will be submitted for publication and/or posted in a publicly accessible database of clinical trial results.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 2 years after the last approval of a marketing application in an ICH region unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Manual and Monitoring Plan.

Study and Site Closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease (new or exacerbated) whether or not considered related to the medicinal product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AE. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

Definition of AESI

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g. regulators) might also be warranted (CIOMS VI and ICH E2F)

AESIs for setrusumab

Some AEs, despite their severity or outcome, will be expedited due to the relevance for participant safety or study treatment safety profile. These events should be reported to the Sponsor/designee within 24 hours. This is to enable follow-up to be performed on all these reported adverse events that have not been reported as serious adverse events (SAEs). The AESIs for setrusumab are:

- Fractures
- Cardiovascular events

Cardiovascular events that are considered to be clinically significant by the PI and/ or medical team will also be submitted to the independent DMC for CV adjudication.

Recording AE and SAE/AESI

AE and SAE/AESI Recording

- When an AE/SAE/AESI occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/AESI information in the SAE/AESI report form and the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Safety CRO in lieu of completion of the SAE/AESI report form.
- There may be instances when copies of medical records for certain cases are requested by the Safety CRO. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Safety CRO.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AESI.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE/AESI reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE/AESI.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE/AESI, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/AESI and has provided an assessment of causality.
- There may be situations in which an SAE/AESI has occurred and the investigator has minimal information to include in the initial report to the Safety CRO. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE/AESI data to the Safety CRO.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE/AESI follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE/AESI

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Safety CRO to elucidate the nature and/or causality of the AE or SAE/AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide the Safety CRO with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the SAE/AESI report form and completed eCRF.
- The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of receipt of the information.

SAE Reporting to the Safety CRO via SAE/AESI Report Form

- The primary mechanism for reporting SAE/AESI to the Safety CRO will be the SAE/AESI report form.
- The site will submit the SAE/AESI data on the SAE/AESI report form as soon as it becomes available.
- Facsimile transmission of the SAE/AESI report form is the preferred method to transmit this information to the Safety CRO Drug Safety team. The following contacts may be used:

Fax Number: 001-877-464-7787

In case of issues with fax, Email: safetyreporting@syneoshealth.com

- Contacts for SAE/AESI reporting can be found in above or in the MBPS205 Investigator Site File.

Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the Following Categories Are not Considered WOCBP

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
2. Premenarchal
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Contraception Guidance

Males Participants

- Male participants with female partners of childbearing potential do not need to use contraception during the treatment period. Setrusumab is non-genotoxic and, teratogenicity or feto-toxicity is not expected at sub-therapeutic levels*. In that situation no male contraception is required with WOCBP (Clinical Trial Facilitation Group Guidelines)

*The female exposure from vaginal transference of a monoclonal antibody (mAb) is from a male partner is very limited. Semen levels are 1-2% of plasma and that vaginal absorption is assumed maximum 10% (in cyno its only 1%). Therefore the systemic levels in a female partner after a single 6 mL semen exposure are 250,000 -500,000 x less than the levels in the male

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • oral • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomised partner *(A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Female Participants

Female participants of reproductive potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table above.

Pregnancy Testing

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.

Additional pregnancy testing should be performed at regular intervals as per SoA during the treatment period and at 60 days after the last dose of study treatment.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Pregnancy testing, with a sensitivity of 5 mIU/mL will be performed and assayed in the central laboratory.

Collection of Pregnancy Information

Male Participants With Partners of Reproductive Potential Who Become Pregnant

Investigator will attempt to collect pregnancy information on any female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Safety CRO within 24 hours of learning of the partner's pregnancy.

Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Safety CRO.

Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants Who Become Pregnant

Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to the Safety CRO within 24 hours of learning of a participant's pregnancy.

Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to the Safety CRO. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to the Safety CRO as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will be withdrawn from the study.

Appendix 6: Radiation Exposure

Assessment	Radiation dose per visit (mSv)	Visits at which performed	Total radiation dose (mSv)
DXA scan, lumbar, whole body, proximal femur	0.004-0.0081	Baseline, Month 6, 12/EOT, M18 & M24	0.020-0.0405
HRpQCT	0.006	Baseline, (Month 3 for open-label arm), Month 6, Month 12/EOT, M18 & M24	0.030-0.036
Lateral vertebral radiograph	0.6	Baseline, Month 6, Month 12/EOT, M18 & M24	3.0
		Total	3.035-3.0585

Abbreviations: DXA = Dual-energy x-ray absorptiometry; HRpQCT = high resolution peripheral quantitative computed tomography, EOT = End of Treatment

Typical Effective and Organ Doses for Various Diagnostic X-ray Examinations

Examination	Effective dose (mSv)	Organ dose (mGy)	Relevant organs
Dental radiography (intraoral)	0.005	0.005	Brain
Chest radiography (posterior-anterior)	0.02	0.01	Lung
X-ray mammography	0.4	3	Breast
Adult abdominal CT	8	10	Stomach

Source: Damilakis, J., Adams, J. E., Guglielmi, G., & Link, T. M. (2010). Radiation exposure in X-ray-based imaging techniques used in osteoporosis. *European radiology*, *20*(11), 2707-2714.
Abbreviations: CT = Computed Tomography

Appendix 7: Audiometry Scale

Grade on audiometry (db loss)	Score
<21	undetectable hearing loss
21-35	mild
36-60	moderate
>60	severe

Appendix 8: MBPS205 Study Oversight

Function	Name	Contact Details
Sponsor Signatory	[redacted]	Mereo BioPharma 3 Ltd. 1 Cavendish Place London W1G 0QF United Kingdom (UK)
Sponsor Clinical Operations Oversight	[redacted]	
Clinical Research Organisation	ICON Clinical Research Ltd.	South County Business Park, Leopardstown, Dublin 18, Ireland
Safety Clinical Research Organisation	Syneos Health	3201 Beechleaf Court, Suite 600, Raleigh, NC 27604-1547
Biostatistician	[redacted]	3rd Floor, Marlow International, Marlow, Buckinghamshire, SL7 1YL, UK Tel No.: [redacted]
Chief Coordinating Investigator	[redacted]	6410 Rockledge Drive, Suite 403, Bethesda, MD 20817, United States of America
Coordinating Investigator for Americas	[redacted]	Shriner's Hospital for Children, 1003 Decarie Blvd, Montreal, H4A 0A9, Quebec, Canada
Coordinating Investigator for Europe	[redacted]	Oxford University of Hospitals Trust, Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX3 7HE UK

Appendix 9: Summary of Versions and Changes

Summary of Versions

Protocol	Version	Date	Summary of Change
Original	Version 1.0	10 Jan 2017	Not applicable
Amendment 1	Version 2.0	27 Jan 2017	Change to OI-PRO-A End-points, minor administrative changes
Amendment 2	Version 3.0	2 May 2017	UK Regulatory Agency request for 60-day follow-up period, clarification of schedule of activities and administrative changes
Amendment 3	Version 4.0	18 Jan 2018	Adjust primary analysis to 12 months and remove DXA vertebral fracture assessment as study endpoint.
Amendment 4	Version 5.0	18 May 2018	Placebo arm replaced by open-label treatment arm and addition of 12-month follow-up period following treatment end.
Amendment 5	Version 6.0	12 Dec 2018	Addition of optional zoledronic acid therapy during follow up period.

Protocol Amendment 6 Summary of Changes

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
Tr. vBMD (tibia & radius) on HRpQCT and bone strength on FEA at 3 & 6 months in the open-label treatment arm.	Tr. vBMD (tibia & radius) on HRpQCT and bone strength on FEA at 3, 6 & 12 months in the open-label treatment arm.	Synopsis: Objectives & Endpoints	Clarification that open-label data will be assessed up to Month 12

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
MBPS205 Study Schematic: Post Study options: All consenting patients transfer to the MBPS206 Study.	MBPS205 Study Schematic *Removed.*	Synopsis: MBPS205 Study Schematic	Removal of reference to MBPS206 study in study schematic.
For a change from baseline of [redacted] which can be considered to be a clinically relevant change, with standard deviation as above the one-sided test would have a probability of 80% to yield a p-value below 5%, being considered indicative of a trend.	For a change from baseline of [redacted], with standard deviation as above the one-sided test would have a probability of 80% to yield a p-value below 5%, being considered indicative of a trend.	Synopsis: Number of Participants	Removal of reference to clinically significant change related to initial sample size calculation.
Not applicable	Following a review of the trabecular vBMD (radius) derived from HRpQCT at Month 6 of those subjects within the 20 mg/kg Setrusumab open label treatment group, a change from baseline standard deviation of [redacted] was observed. This yields to a correlation between baseline and Month 6 visits of [redacted] (much higher than the [redacted] that was originally assumed). If such a correlation is observed at Month 12, given 25 subjects per arm, the one-sided test would have a probability of 80% to yield a p-value below 5% for a change in baseline of [redacted]	Synopsis: Number of participants	Addition of further details of statistical calculations for study based on the initial results from the open-label treatment arm results at 6 months of treatment.

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
Participants will be qualified during a 28-day screening period, followed by 12 months of study treatment. At the end of treatment in MBPS205, participants will continue into the follow-up period for 12 months after which participants will be offered the option to continue into the MBPS206 Study, in which treatment with setrusumab will be offered at the dose selected in MBPS205.	Participants will be qualified during a 28-day screening period, followed by 12 months of study treatment. At the end of treatment in MBPS205, participants will continue into the follow-up period for 12 months.	Protocol Synopsis: Treatment Groups and Duration	Removal of reference to participants being offered the option to continue into the MBPS206 study.
Data for placebo participants and open-label BPS804 20 mg/kg participants will be reported separately from the comparison between the randomized, blinded treatment groups. In particular the open-label BPS804 20 mg/kg participants' data will not be pooled with the blinded BPS804 20 mg/kg participants' data.	Data for placebo participants and open-label BPS804 20 mg/kg participants will be reported separately from the comparison between the randomized, blinded treatment groups. In particular for the primary analysis, the open-label BPS804 20 mg/kg participants' data will not be pooled with the blinded BPS804 20 mg/kg participants' data.	Protocol Synopsis: General Statistical Methods	Additional clarification for the primary analysis the BPS804 open-label 20 mg/kg data will not be pooled with the blinded BPS804 20 mg/kg data.
The LSMeans will further be analysed using the MCPMod methodology, using the following candidate models: • EMax (ED_{50} of 1.5 mg) • Exponential ($\delta = 2$)	The LSMeans will further be analysed using the MCPMod methodology, using the following candidate models: • EMax (ED_{50} of 1.5 mg) • Exponential ($\delta = 2$) • Sigmoid EMax model with parameters ED50 = 10 mg and h = 2.4	Protocol Synopsis: Efficacy Analysis	Correction to include reference in efficacy section as well as the patient population section.

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
Bone Biopsy: Month 6 Sub-set of participants.	Bone Biopsy: Month 6 Month 12 Sub-set of participants. Completed once either at M6 or M12.	Schedule of Activities	Addition of option to have bone biopsy at M12 visit.
Month 24 (Can also be MBPS206 baseline visit)	Month 24	Schedule of Activities	Removal of reference to the MBPS206 study in schedule of activities.
MBPS205 Study Schematic: Post Study options: All consenting patients transfer to the MBPS206 Study.	MBPS205 Study Schematic *Removed.*	Protocol Figure 1: MBPS205 Study Schematic	Removal of reference to MBPS206 study in study schematic.

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
Since there are no approved pharmacological therapies for OI, patients participating in this study have the possibility to receive a potentially beneficial treatment, at a potentially therapeutic dose for a period of time considered long enough to achieve a benefit. It is expected that at least one of the doses of setrusumab will be sub-therapeutic; therefore patients randomised to this dose are not expected to receive any therapeutic benefit from participation. However, no proven therapy will be withheld during the study and all patients will have the possibility to continue on to study MBPS206, in which all participants will receive active drug. Therefore, all participants in this study will ultimately have the opportunity to benefit from treatment, either during the study itself or in the follow on studies.	Since there are no approved pharmacological therapies for OI, patients participating in this study have the possibility to receive a potentially beneficial treatment, at a potentially therapeutic dose for a period of time considered long enough to achieve a benefit. It is expected that at least one of the doses of setrusumab will be sub-therapeutic; therefore patients randomised to this dose are not expected to receive any therapeutic benefit from participation. However, no proven therapy will be withheld during the study until the final analysis is performed when all subjects in the blinded treatment arms have completed 12 months of treatment with setrusumab. Data from this study will provide confirmation about whether setrusumab is efficacious for the treatment in adult osteogenesis imperfecta.	Section 4.3: Benefit/Risk Assessment	Adjustment to benefit risk assessment section to remove reference to the possibility of treatment in MBPS206 study.
Tr. vBMD (tibia & radius) on HRpQCT and bone strength on FEA at 3 & 6 months in the open-label treatment arm.	Tr. vBMD (tibia & radius) on HRpQCT and bone strength on FEA at 3, 6 & 12 months in the open-label treatment arm.	Section 5: Objectives & Endpoints	Clarification that open-label data will be assessed up to Month 12

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
Participants completing the MBPS205 study will be able to discuss other potential treatments with their investigators or be offered the option to continue into the MBPS206 Study, in which treatment with setrusumab will be offered. Participation in MBPS206 will be subject to meeting any inclusion/exclusion criteria and restrictions on concomitant medication for this study. All Participants will be offered participation in MBPS206 at the end of MBPS205. In the event that a participant does not wish to participate in MBPS206, they will be able to discuss alternative treatment options or approaches with their investigator.	Participants completing the MBPS205 study will be able to discuss other potential treatments for their osteogenesis imperfecta with their investigators when they complete the 12-month follow up period at the end of MBPS205.	Section 8.7: Treatment After the End of the Study.	Section updated to remove reference to the option to join the MBPS206 study.
Bone biopsies will be performed at Month 6 in a sub-set of participants. Informed consent will be obtained using a specific bone biopsy consent form.	Bone biopsies will be performed once at either Month 6 or Month 12 in a sub-set of participants. Informed consent will be obtained using a specific bone biopsy consent form.	Section 10.1.2: Bone Biopsy	Adjustment to bone biopsy timing to allow collection at Month 12 visit as well as Month 6 visit.

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
In the treatment period samples will be tested for PTH, P1NP, P1CP, OC, BSAP, CTX-1, NTX-1, RANKL, osteoprotegerin, TGF-β, sclerostin, Pro-C5, and C5M to evaluate their association with the observed clinical responses in bone turnover to setrusumab. In the follow-up period samples will be tested for CTX-1 and P1NP.	In the treatment period samples will be tested for PTH, P1NP, P1CP, OC, BSAP, CTX-1, NTX-1, RANKL, osteoprotegerin, TGF-β, sclerostin, Pro-C5, and C5M to evaluate their association with the observed clinical responses in bone turnover to setrusumab. In the follow-up period samples can be tested for CTX-1 and P1NP.	Section 10.7: Biomarkers	Adjustment to bone biomarkers collected in follow up period should be completed if possible.
For a change from baseline of [redacted], which can be considered to be a clinically relevant change, with standard deviation as above the one-sided test would have a probability of 80% to yield a p-value below 5%, being considered indicative of a trend.	For a change from baseline of [redacted], with standard deviation as above the one-sided test would have a probability of 80% to yield a p-value below 5%, being considered indicative of a trend.	Section 11.1 Sample Size Determination	Removal of reference to participants being offered the option to continue into the MBPS206 study.

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
Not applicable	Following a review of the trabecular vBMD (radius) derived from HRpQCT at Month 6 of those subjects within the 20 mg/kg Setrusumab open label treatment group, a change from baseline standard deviation of [redacted] was observed. This yields to a correlation between baseline and Month 6 visits of [redacted] (much higher than the [redacted] that was originally assumed). If such a correlation is observed at Month 12, given 25 subjects per arm, the one-sided test would have a probability of 80% to yield a p-value below 5% for a change in baseline of [redacted].	Section 11.1: Sample Size Determination	Additional clarification for the primary analysis the BPS804 open-label 20 mg/kg data will not be pooled with the blinded BPS804 20 mg/kg data.
Not applicable	Modified Full Analysis Set (mFAS) All participants from the FAS who have sufficient cross-sectional overlap across HRpQCT scans (details to be further described in the Statistical Analysis Plan). Participants will be analysed according to the randomised treatment.	Section 11.2: Population for Analyses	Inclusion of modified full analysis set (mFAS) to ensure sufficient cross-sectional overlap in HRpQCT scans.

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
All participants from the FAS who have been treated according to the protocol and fulfill the following criteria (to be further described in the Statistical Analysis Plan [SAP]): 1. All inclusion/exclusion criteria satisfied 2. Absence of relevant protocol violations with respect to factors likely to affect the efficacy of treatment where the nature of protocol violation will be defined before breaking the blind 3. Adequate study medication compliance which will be determined before breaking the blind.	All participants from the mFAS who have been treated according to the protocol and fulfill the following criteria (to be further described in the Statistical Analysis Plan [SAP]): 1. All inclusion/exclusion criteria satisfied 2. Absence of relevant protocol violations with respect to factors likely to affect the efficacy of treatment where the nature of protocol violation will be defined before breaking the blind 3. Adequate study medication compliance which will be determined before breaking the blind.	Section 11.2: Population for Analyses	Inclusion of mFAS definition within per-protocol analysis population.
Non-restricted FAS: All participants who are randomised and take at least 1 dose of study treatment. Participants will be analysed according to the randomised treatment. Analyses using the Non-restricted FAS will comprise of such where the two 20 mg/kg dose group are pooled, and those where they are not.	Non-restricted FAS: All participants who are randomised and take at least 1 dose of study treatment. Participants will be analysed according to the randomised treatment. Analyses using the Non-restricted FAS will comprise of such where the two 20 mg/kg dose group are pooled (for the follow-up analysis), and those where they are not.	Section 11.2: Population for Analyses	Additional clarification the pooled analysis will take place as part of the follow-up analysis.

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
Safety: All participants who are administered at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received. Analyses using the Safety population will comprise of such where the two 20 mg/kg dose group are pooled, and those where they are not.	Safety: All participants who are administered at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received. Analyses using the Safety population will comprise of such where the two 20 mg/kg dose group are pooled (for the follow-up analysis), and those where they are not.	Section 11.2: Population for Analyses	Additional clarification the pooled analysis will take place as part of the follow-up analysis.
The main population for efficacy analysis will be the FAS. Results for the per-protocol (PP) population and the Non-restricted FAS will be considered supportive.	The main population for efficacy analysis will be the FAS. Results for the mFAS, per-protocol (PP) population and the Non-restricted FAS will be considered supportive.	Section 11.3: Statistical Analyses	Inclusion of mFAS analysis population.
Data for placebo participants and open-label BPS804 20 mg/kg subjects will be reported separately from the comparison between the randomized, blinded treatment groups. In particular, the open-label BPS804 20 mg/kg participants' data will not be pooled with the blinded BPS804 20 mg/kg participants' data.	Data for placebo participants and open-label BPS804 20 mg/kg subjects will be reported separately from the comparison between the randomized, blinded treatment groups. In particular for the primary analysis, the open-label BPS804 20 mg/kg participants' data will not be pooled with the blinded BPS804 20 mg/kg participants' data.	Section 11.3: Statistical Analyses	Additional clarification for the primary analysis the BPS804 open-label 20 mg/kg data will not be pooled with the blinded BPS804 20 mg/kg data.

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
Analyses for the primary efficacy endpoints and selected secondary endpoints will be analysed on the FAS, the Non-restricted FAS and the PP samples, while analyses for the remaining secondary efficacy endpoints will be analysed on the FAS sample only. General methods as described above will be applied to the efficacy endpoints; specific analyses are described below.	Analyses for the primary efficacy endpoints and selected secondary endpoints will be analysed on the FAS, mFAS, the Non-restricted FAS and the PP samples, while analyses for the remaining secondary efficacy endpoints will be analysed on the FAS sample only. The mFAS will be used for analysis of HRpQCT endpoints only. General methods as described above will be applied to the efficacy endpoints; specific analyses are described below.	Section 11.3.1: Efficacy Analyses	Inclusion of mFAS analysis population within efficacy analysis section.
The LSMeans will further be analysed using the MCPMod methodology, using the following candidate models: • EMax (ED_{50} of 1.5 mg) • Exponential ($\delta = 2$)	The LSMeans will further be analysed using the MCPMod methodology, using the following candidate models: • EMax (ED_{50} of 1.5 mg) • Exponential ($\delta = 2$) • Sigmoid EMax model with parameters ED50 = 10 mg and h = 2.4	Section 11.3.1: Efficacy Analyses	Correction to include reference in efficacy section as well as the patient population section.
Sponsor Medical Expert & Sponsor Signatory: [redacted]	Removed	Appendix 8: MBPS205 Study Oversight	Removal of [redacted] from study oversight section.

Original	Protocol Amendment 6 Change	Sections Applied	Rationale
Biostatistician: [redacted] 3rd Floor, Marlow International, Marlow, Buckinghamshire, UK Tel No.: [redacted]	Biostatistician: [redacted] 3rd Floor, Marlow International, Marlow, Buckinghamshire, SL7 1YL, UK Tel No.: [redacted]	Appendix 8: MBPS205 Study Oversight	Update to Study Statistician's name and contact details.

Appendix 10: Sponsor Electronic Signature

Signature Page for MBPS205 - Protocol v7.0

Reason for signing: Approved	Name: [redacted] Role: A[redacted] Date of signature: 19-Jul-2019 11:58:50 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: R[redacted]ad of Clinical Operations Date of signature: 19-Jul-2019 12:10:29 GMT+0000

Signature Page for VV-TMF-00266 v7.0