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

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	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	←==========→					

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

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.

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.

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.

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

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.

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

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.

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.

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

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	

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

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)

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.

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.

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

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.

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

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

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

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.