A Phase 2b, Multicenter, Long-term Extension Study of Setrusumab in Adults with Type I, III, or IV Osteogenesis Imperfecta

Protocol Number: UX143-CL203

Original Protocol: 01 December 2021

Product name (INN):	Setrusumab
Indication:	Osteogenesis imperfecta
IND Number:	113385
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA 94949 USA
Sponsor's Responsible Medical Monitor:	PPD, MD, MS PPD, Global Clinical Development Telephone: PPD
Coordinating Investigator:	To be determined

This study will be performed in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements and guidelines.

Due to the early termination of the study, no SAP was finalized

2. SYNOPSIS

Sponsor: Ultragenyx Pharmaceutical Inc. (Ultragenyx)

Product Name (International Nonproprietary Name [INN]): Setrusumab

Title: A Phase 2b, Multicenter, Long-term Extension Study of Setrusumab in Adults with Type I, III, or IV Osteogenesis Imperfecta

Development Phase: Phase 2b

Introduction

Setrusumab is a fully human anti-sclerostin monoclonal antibody that is being developed for the treatment of osteogenesis imperfecta (OI).

The purpose of this study is to investigate 1) safety and disease progression after discontinuation of setrusumab, 2) the safety and efficacy of 12 months of retreatment with setrusumab, and 3) the safety and efficacy of CCI dosing beyond 12 months of retreatment with setrusumab in adults with OI who previously participated in ASTEROID.

Objectives and Endpoints

Study objectives and endpoints are defined for each study period. The primary and secondary endpoints will be evaluated for the Retreatment Period and are shown in Table 1. All objectives and endpoints for the Observation, Retreatment, and Extension Periods are shown in Section 6.

Table 1: Study Objectives and Endpoints for the Retreatment Period

OBJECTIVES	ENDPOINTS
Primary	
Evaluate BMD after 12 months of retreatment with monthly setrusumab in adults with OI	Percentage change from Retreatment Baseline in lumbar spine BMD measured by DXA after 12 months of setrusumab
Secondary	
Evaluate BMD during 12 months of retreatment with monthly setrusumab in adults with OI	Percentage change from Retreatment Baseline in total hip BMD measured by DXA at Month 12 of the Retreatment Period
Evaluate fractures after 12 months of retreatment with monthly setrusumab in adults with OI	Annualized new fracture rate as confirmed by radiograph during the Retreatment Period
Tertiary	
CCI	

CCI

BMD, bone mineral density; CCI

DXA, dual-energy X-ray absorptiometry; CCI

Study Design

UX143-CL203 is a Phase 2b, multicenter, long-term extension study in adults with OI who participated in the Phase 2b, double-blind, dose-finding ASTEROID study (also referred to as MBPS205) (Figure 1). Briefly, in ASTEROID, subjects were treated with 12 months of setrusumab (either 2, 8, or 20 mg/kg once a month [QM]), followed by a 12-month Follow-up Period in which subjects discontinued setrusumab and had the option to receive zoledronic acid at Month 12, 18, or both. Subjects who participated in ASTEROID are eligible to participate in UX143-CL203. As the ASTEROID study completed prior to the initiation of UX143-CL203, an Off-study Period will occur for all subjects who enroll in UX143-CL203; the duration of this Off-study Period varies from subject to subject depending on completion of ASTEROID and enrollment in UX143-CL203.

UX143-CL203 comprises Observation, Retreatment, and Extension Periods. There is no intervention during the Observation Period; subjects are followed to evaluate disease progression and the long-term effects of setrusumab discontinuation. During the Observation Period, a retrospective chart review captures data that occurred during each subjects' Off-study Period. This chart review includes collection of dual-energy X-ray absorptiometry (DXA) and fracture events. After screening and enrollment, the first assessments occur during the Observation Period at the First Visit. The First Visit occurs at a CCI interval relative to the subject's ASTEROID enrollment. Following the First Visit, subjects are assessed CCI [redacted] for up to 18 months or until setrusumab becomes available for Retreatment. No minimum duration is necessary for the Observation Period and the duration of the Observation Period may vary from subject to subject depending on when they enrolled and when setrusumab is available for the Retreatment Period. Once setrusumab is available, each subject undergoes a Retreatment Screening Visit to confirm eligibility prior to restarting setrusumab, and then begins the Retreatment Period. The Retreatment Screening Visit occurs during the Observation Period, 1 to 4 weeks prior to the Retreatment Baseline Visit in the Retreatment Period. As noted in Section 8.2, subjects who are receiving bisphosphonates during the Observation Period must discontinue bisphosphonate use at least 3 months prior to the Retreatment Screening Visit.

During the Retreatment Screening Visit, subjects undergo screening to confirm eligibility for retreatment with setrusumab, including an assessment of serum calcium and 25-OH-vitamin D (Section 8.2 and Section 8.5). If a CCI Visit occurred within 4 weeks prior to the Retreatment Baseline, then safety laboratory tests do not need to be recollected at the Retreatment Screening Visit, except for the chemistry panel, which is collected at both the Retreatment Screening Visit and Retreatment Baseline.

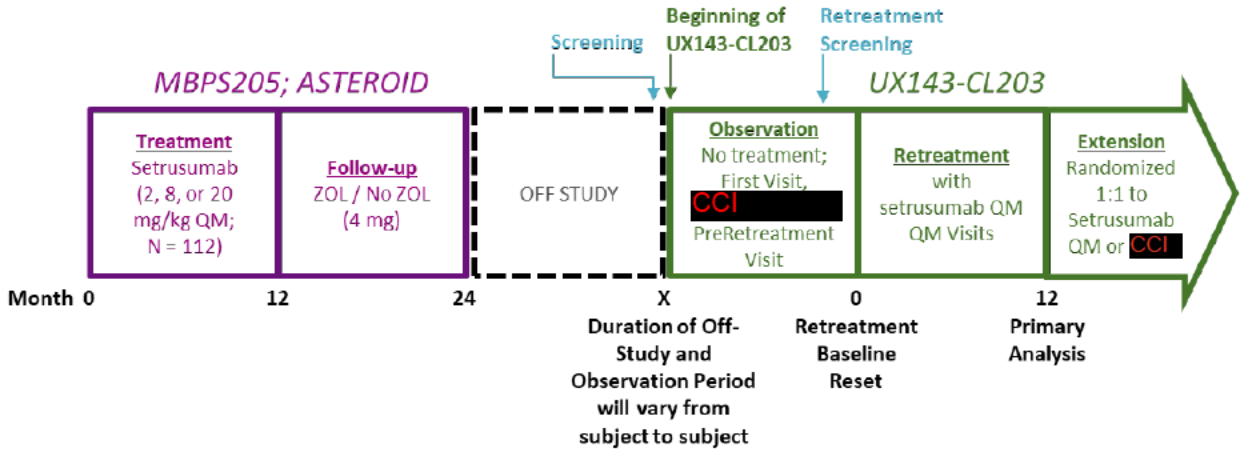
The dosing strategy in the Retreatment and Extension Periods will be based on the pharmacokinetic (PK) and serum bone turnover markers from the Phase 2b ASTEROID study and the Phase 2 Period of the UX143-CL301 study (Section 7.1.4). The selected dose will be in the range of 20 to 40 mg/kg CCI [redacted]

During the single-arm Retreatment Period, subjects receive open-label setrusumab QM for 12 months. During the Retreatment Period, subjects are assessed for safety and efficacy of setrusumab retreatment, CCI [redacted]

CCI [redacted] he primary analysis occurs at the end of the Retreatment Period.

Following the Retreatment Period, subjects enter an Extension Period, in which they are randomized 1:1 to either continue treatment with open-label setrusumab QM or transition to open-label setrusumab CCI [redacted] for at least 12 months or until setrusumab is commercially available. For the Extension Period dosing groups, randomization will be stratified by OI type (I vs III/IV).

Figure 1: UX143-CL203 Study Schema



CCI [redacted] QM, once a month; ZOL, zoledronic acid

Note: A retrospective chart review will occur during Screening to capture data that occurred during each subjects' Off-study Period

Number of Sites: Approximately 24 sites

Number of Subjects: Up to 112 subjects will be enrolled; only those who participated in ASTEROID.

Population

Subjects who participated in ASTEROID were ages 19 to 74 years at the time of enrollment. Inclusion Criteria for Enrollment into UX143-CL203:

1. Males or females who participated in the Phase 2b ASTEROID study
2. Females of childbearing potential must consent to use highly effective contraception (Appendix 2) during the Observation, Retreatment, and Extension Periods through 2 months after the last dose of setrusumab and agree not to become pregnant. Provide informed consent after the nature of the study has been explained, and prior to any research-related procedures

Exclusion Criteria for Enrollment into UX143-CL203:

1. Known hypersensitivity to setrusumab or its excipients that, in the judgment of the Investigator, places the subject at increased risk for adverse effects.
2. Presence or history of any condition that, in the view of the Investigator, would interfere with participation, pose undue risk, or would confound interpretation of results.
3. Pregnant or breastfeeding or planning to become pregnant (self or partner) at any time during the study
4. Willing to discontinue bisphosphonate use at least 3 months prior to the Retreatment Screening Visit (if applicable).Once enrolled in UX143-CL203, individuals who meet any of the following exclusion criteria will not be eligible to participate in the Retreatment Period:
5. Concurrent participation in any study that is examining the safety and efficacy of any investigational product or investigational medical device that alters bone health during the Retreatment and Extension Periods, per discretion of the Investigator in consultation with the Medical Monitor. Presence or history of any condition that, in the view of the Investigator, would interfere with participation, pose undue risk, or would confound interpretation of results.
7. Calcium levels outside the normal range. If the subject's calcium level is not within the normal range, decision to retest should be made in conjunction with the Medical Monitor.
8. Glomerular filtration rate (GFR) ≤ 29 mL/min. If the subject's GFR is ≤ 29 mL/min, decision to retest should be made in conjunction with the Medical Monitor.
9. History of skeletal malignancies or bone metastases at any time
10. History of neural foraminal stenosis (except if due to scoliosis)
11. History of myocardial infarction, angina pectoris, ischemic stroke or transient ischemic attack
    a. Investigators should consider whether the potential benefits of treatment outweigh the potential risks in patients with other cardiovascular risk factors such as hypertension, hyperlipidemia, familial hyperlipidemia, family history of premature ischemic cardiovascular disease, smoking, diabetes mellitus, and metabolic syndrome. Suggested criteria and references for evaluation of risk factors will be provided in the Study Reference Manual.
12. 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 eg, Stage IV/V renal disease
13. A history of rickets or osteomalacia or any skeletal condition (other than OI) leading to long-bone deformities and/or increased risk of fractures
14. 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

15. 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
16. Current/previously reported allergy to the study drug or any of its excipients or the class of drug under investigation
17. History of external radiation

Study Interventions

Table 2: Study Interventions

Intervention	**Setrusumab**
Dose Formulation	CCI mg lyophilized powder for solution
Unit Dose Strength(s)/Dosage Level(s)	20 to 40 mg/kg QM CCI
Route of Administration	60-minute IV infusion
Use	Experimental

[a] The dosing strategy in the Retreatment and Extension Periods will be based on the pharmacokinetic (PK) and serum bone turnover marker data from the Phase 2b ASTEROID study and the Phase 2 Period of the UX143-CL301 study. The selected dose will be in the range of 20 to 40 mg/kg CCI

IV, intravenous; CCI ; QM, once a month.

Duration of Subject Participation

Screening may take up to 1 month. The Observation Period is expected to take up to 18 months. The Retreatment Period is 12 months. The Extension Period continues for at least 12 months or until setrusumab is commercially available in a subject's given region.

Assessments

Assessments and associated timing are provided in Table 3

Table 3: Schedule of Events

Timing of Visit	Screening	Observation Period[a]			Retx Period (Month)[a]												Ext Per[a]	EOS/ ET[d]
	-4 to -1 wks prior First Visit	First Visit[b]	CCI Visits, CCI between the First Visit & Retx Period	Retx Scrn Visit, -4 to -1 wks prior to Retx BL[c]	0 (Retx BL)	1	2	3	4	5	6	7	8	9	10	11	12		
Informed Consent	X																		
Inclusion/Exclusion	X			X															
Medical History[e]	X																		
Urine Pregnancy Test	X			X															
Drug Administration[f]					X	X	X	X	X	X	X	X	X	X	X	X	X	QM CCI	
Adverse Events[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	QM	X
Complete Physical Exam		X		X													X	M24	X
Targeted Physical Exam			X		X	X	X	X	X	X	X	X	X	X	X	X		QM	
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	QM	X
Chemistry[h] (Appendix 1)	CCI																		
Urinalysis (Appendix 1)																			
Hematology (Appendix 1)																			
25-OH-vitamin D																			
12-lead ECG																			
Focused Neurological Exam																			
Audiometry																			
Dental Health																			
DXA[i]		X	X		X						X						X	CCI	
Vertebral Radiograph		X			X												X	M24	
Skeletal Survey		X			X												X		
Fracture Assessment & Radiograph (if needed)[j]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fracture Event Diary		CCI and at spontaneous report of fracture			CCI and at spontaneous report of fracture														
CCI																			

Timing of Visit	Screening	Observation Period[a]			Retx Period (Month)[a]												Ext Per[a]	EOS/ ET[d]
	-4 to -1 wks prior First Visit	First Visit[b]	CCI Visits, CCI between the First Visit & Retx Period	Retx Scrn Visit, -4 to -1 wks prior to Retx BL[c]	0 (Retx BL)	1	2	3	4	5	6	7	8	9	10	11	12	
CCI																		

[a] For each visit, all assessments must occur within ± 4 days of the scheduled visit; during the Retreatment Period and Extension Period, after the initial dose of setrusumab, the timing of all scheduled visits occur monthly based on the initial dose of setrusumab.

[b] The First Visit occurs at a CCI interval relative to the subject's ASTEROID enrollment.

[c] Prior to the Retreatment Baseline Visit, all subjects must undergo the Retreatment Screening Visit, undergoing screening for retreatment with setrusumab and safety laboratory tests to ensure subject safety prior to retreatment with setrusumab (Section 8.2 and Section 8.5). If a CCI Visit occurred within 4 weeks prior to the Retreatment Baseline, then safety laboratory tests do not need to be recollected at the Retreatment Screening Visit, except for the chemistry panel, which is collected at both the Retreatment Screening Visit and Retreatment Baseline.

[d] A safety follow-up will occur with subjects 2 months after their last dose of setrusumab.

[e] Medical history includes a chart review, including collection of DXA and fracture events.

[f] For visits in which setrusumab is administered, blood and urine should be collected prior to drug administration, with the exception of blood collection for PK assessments occurring at the EOI as noted in Table 4.

[g] AEs may be reported at any time during the study (ie, not just at scheduled clinic visits). AE collection for the Off-study Period between ASTEROID and UX143-CL203 (collected via chart review) as well as the Observation Period will be limited to AESIs.

[h] Samples are to be collected after ≥ 4 hours of fasting. When applicable, samples should be collected prior to study drug administration.

[i] CCI

[j] Radiographs may be performed to confirm a reported fracture event.

[k]

Note: Visits that do not require DXA or radiograph may be performed at home with the use of a home health nurse, instead of in the clinic.

CCI

Table 4: Detailed Sample Collection Schedule

Visit	Time Point Relative to Drug Administration	CCI
Observation Period	CCI	
Retreatment Period		
Extension Period		

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition or Explanation
ADA	antidrug antibodies
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMD	bone mineral density
CCI	[redacted]
BUN	blood urea nitrogen
COL1A1	collagen type 1 alpha 1
COL1A2	collagen type 1 alpha 2
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation and Coordination Group
CCI	[redacted]
DMC	Data Monitoring Committee
DSPV	Drug Safety and Pharmacovigilance
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
EMA	European Medicines Agency
EOI	end of injection
CCI	CCI [redacted]
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
CCI	[redacted]
IB	Investigator's Brochure
ICF	informed consent form

Abbreviation	Definition or Explanation
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG2	immunoglobulin G subclass 2
IND	Investigational New Drug
INN	international nonproprietary name
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
CCI	CCI
NOAEL	no-observed-adverse-effect-level
CCI	
OI	osteogenesis imperfecta
CCI	
CCI	
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QM	once a month
CCI	
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
CCI	
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

Definition of Terms

Investigational Product (IP) is defined as, “A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use” (from International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Harmonised Tripartite Guideline E6: Guideline for Good Clinical Practice (GCP)).

The term “study drug” may also be used in place of “investigational product (IP)” in the protocol.

5. INTRODUCTION

Setrusumab is a fully human anti-sclerostin monoclonal antibody that is being developed for the treatment of osteogenesis imperfecta (OI).

The purpose of this study is to investigate 1) safety and disease progression after discontinuation of setrusumab, 2) the safety and efficacy of 12 months of retreatment with setrusumab in adults with OI who previously participated in the Phase 2b study (ASTEROID; MBPS205), and 3) the safety and efficacy of CCI dosing beyond 12 months of retreatment with setrusumab in adults with OI who previously participated in ASTEROID.

5.1. Overview of Osteogenesis Imperfecta

OI comprises a heterogenous group of serious and debilitating genetic disorders characterized by low bone mass and bone fragility, resulting in multiple fractures and skeletal deformities. The estimated incidence of OI is 1 in 10,000 to 20,000 births (Marini et al., 2017; Lindahl et al., 2015). The initial diagnosis of OI, usually in early childhood, is typically based on clinical features and radiographic findings, and can be confirmed by collagen or DNA testing. About 85% of OI cases are caused by autosomal dominant mutations in collagen type 1 alpha 1 or 2 (COL1A1 or COL1A2), the genes that encode Type I collagen (Biggin and Munns, 2014). These mutations result in a reduced amount of normal collagen or structural modifications that impact trabecular and cortical bone architecture. A small proportion of OI cases are caused by other genes involved in collagen biosynthesis or osteoblast differentiation and bone mineralization (Marom et al., 2020).

Bone fragility is the hallmark of OI, resulting in recurrent nontraumatic fractures, skeletal deformities, and growth retardation (Tournis and Dede, 2018). Fractures can occur from birth, and continue at a high rate throughout childhood, typically involving the long bones, vertebrae, and ribs. Although the incidence of fractures is highest in the first two decades of life, adults remain at elevated risk of fractures that can impact activities of daily living and quality of life (Wekre et al., 2011; Hald et al., 2017).

Most experts classify OI caused by mutations in COL1A1 or COL1A2 as Types I to IV based on clinical presentation, radiographic features, and patterns of inheritance (Sillence et al., 1979) (Table 5). The clinical phenotype of OI can vary widely from mild to severe, depending on the specific mutations in COL1A1 or COL1A2 (Biggin and Munns, 2014). OI Type I is caused by a reduced amount of normal collagen in the bone, while Types III and IV are caused by structural defects in collagen (Marini et al., 2017). With the discovery of other genetic causes of OI, additional numerical designations have been adopted to classify newer OI types. The OI types described in this protocol include Types I, III and IV.

Table 5: OI Subtypes

OI Subtype	Phenotypic Characteristics
Type I	Blue sclerae, near-normal stature, multiple fractures from childhood and late-onset hearing loss
Type II	Perinatally lethal OI
Type III	Progressively deforming OI
Type IV	White sclerae, deforming fractures from infancy, short stature, bone deformity and dentinogenesis imperfecta; more severe than Type I but less severe than Types II and III

OI, osteogenesis imperfecta

No treatments for OI have been approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA). Current treatment approaches are primarily focused on symptomatic relief, address comorbidities, and can vary depending on patient age and disease severity. A multidisciplinary treatment approach is typically employed, including pharmacological treatment, physical therapy, occupational therapy, orthopedic interventions, and follow-up by other subspecialists (Marom et al., 2020). Patients may need to undergo 1 or more surgeries to correct skeletal deformities and to prevent and/or heal fractures (Hidalgo Perea and Green, 2021). Although not approved for the treatment of OI, children with OI who fracture frequently are often treated with intravenous (IV) bisphosphonates, typically starting at very young age upon diagnosis (Nijhuis et al., 2019). While bisphosphonates do not directly alter the defect in bone quality (Arshad and Bishop, 2021), their antiresorptive action is known to improve bone mass and microarchitecture in patients with OI (Rauch et al., 2002). Bisphosphonates are not typically used to treat adults with OI, as their impact on bone mineral density (BMD) is greatly reduced upon cessation of growth. Discontinuation of bisphosphonates is associated with only modest decreases in dual-energy X-ray absorptiometry (DXA) BMD (Rauch et al., 2006). Fracture risk reduction with bisphosphonates has not been definitively demonstrated in either adults or children with OI (Dwan et al., 2016).

Osteoanabolic therapies may be beneficial in pediatric and adult patients by stimulating bone formation and increasing bone mass. The effects of the osteoanabolic agent teriparatide were examined in a placebo-controlled study in adult subjects with Types I, III, and IV OI (Orwoll et al., 2014). Although significant gains in DXA BMD were observed after 18 months of teriparatide at the spine and hip in subjects with Type I OI; these effects were not observed in the Type III/IV subjects.

Given the elevated risk of fractures in adults with OI, and the associated disease burden and negative impact on daily living, there is a high unmet medical need for a safe and effective treatment that reduces the incidence of fractures and prevents the long-term consequences of OI.

5.2. Overview of Setrusumab Development

A brief overview of existing information on setrusumab is provided below; a comprehensive review of available data, including potential risks and expected benefits of setrusumab is contained in the Investigator's Brochure.

Setrusumab is a fully human anti-sclerostin monoclonal antibody that belongs to the immunoglobulin G subclass 2 (IgG2) lambda isotype subclass. It has an affinity of [redacted] pM for human sclerostin.

Setrusumab has been administered in 5 clinical studies including a Phase 1 study and a Phase 2a study in healthy postmenopausal women (CBPS804A2101, CBPS804A2203), 2 Phase 2 studies (CBPS804A2201 in adults with moderate OI and CBPS804A2202 in adults with hypophosphatasia [HPP]), and a Phase 2b study (ASTEROID; MBPS205) in adults with OI Types I, III, or IV.

In the first-in-human study with setrusumab, CBPS804A2101, healthy post-menopausal women with low BMD experienced increases in serological biomarkers of bone anabolism and lumbar spine BMD. This was further demonstrated in the Phase 2 study, CBPS804A2201, in adult patients with OI where setrusumab treatment led to significant increases in bone formation

biomarkers and lumbar spine BMD, indicating enhanced skeletal remodeling and bone formation. These findings were further corroborated by data from ASTEROID in adults with OI Types I, III, or IV. In ASTEROID, setrusumab treatment demonstrated notable improvements in DXA BMD and bone strength indices at the peripheral bone sites, and increased serum biomarkers of bone formation, with an acceptable safety profile. These effects were consistent across OI types.

5.3. Rationale for Setrusumab in Osteogenesis Imperfecta

Setrusumab is being investigated for the treatment of OI based on 1) the serious unmet need for a treatment for OI, 2) the mechanism of action for setrusumab that addresses the mechanism of disease for OI, and 3) previous clinical experience with setrusumab suggesting a positive benefit-risk profile in patients with OI, supporting further development.

As described in Section 5.1, there are no FDA- or EMA-approved therapies for OI. Current treatment consists of a multidisciplinary approach focusing on symptomatic relief, including pharmacological intervention, physical therapy, occupational therapy, orthopedic interventions, and follow-up by other subspecialists. Despite these approaches, patients with OI have bone fragility and remain at elevated risk of fractures, substantially impacting their daily living and quality of life.

Low bone mass and the resultant bone fragility in OI can be attributed to an imbalance in bone resorption versus bone formation. Although bisphosphonates are frequently used off-label in pediatric patients with OI, inhibition of bone resorption with bisphosphonate treatment may not be adequate to restore skeletal health in OI. Osteoanabolic therapies may be beneficial in pediatric and adult patients by stimulating bone formation and increasing bone mass. One of these potential approaches is through inhibition with Sclerostin.

Sclerostin, a small protein produced by osteocytes, inhibits canonical Wnt signaling, and thereby suppresses osteoblast differentiation and bone formation (Poole et al., 2005). Sclerostin levels have been found to be absent or low in several rare, genetic skeletal disorders that present with high BMD and low fracture risk, such as sclerosteosis and van Buchem disease. This has led to the concept that inhibiting sclerostin and thereby increasing bone formation may be useful for the treatment of disorders such as OI that are characterized by bone fragility and increased risk of fractures (Olvera et al., 2018). Anti-sclerostin antibodies have been shown to stimulate osteoblast bone formation and improve trabecular and cortical bone mass in multiple mouse models of OI, with effects that were generally similar across growing and skeletally mature mice. In a murine model of Type III OI (oim/oim), anti-sclerostin antibody therapy was also shown to reduce the number of fractures (Roschger et al., 2014). The anti-sclerostin antibody, romosozumab is approved for use in women with post-menopausal osteoporosis, in whom the increases in bone mass corresponded to significant reductions in fracture risk (Cosman et al., 2016).

As described in Section 5.2, across 5 Phase 1 or 2 studies, setrusumab increased serological markers of bone anabolism and lumbar spine BMD in healthy post-menopausal women with low BMD; and increased markers of bone formation, bone strength indices at peripheral bone sites, and lumbar spine BMD in patients with OI. Setrusumab also demonstrated an acceptable safety profile in these studies. Available nonclinical data with setrusumab support further evaluation and development of setrusumab for treatment of adults with OI and is provided in the Investigator's Brochure (IB).

5.4. Potential Benefits and Risks

5.4.1. Potential Benefits of Setrusumab

CCI

[redacted]

5.4.2. Potential Risks

CCI

[redacted]

CCI

[redacted]

To date in clinical trials, setrusumab has demonstrated an acceptable safety profile.

5.4.3. Benefit Risk Conclusion

Taking into account measures to minimize risk to subjects in this study (Section 5.5), the potential risks identified in association with setrusumab are justified by the anticipated benefits that may be afforded to subjects with OI.

5.5. Risk Minimization

This study has been carefully designed to minimize potential risks to subjects.

The study includes measures to monitor patients with an aim to minimize potential risks of setrusumab based on safety data from previous clinical studies with setrusumab as well as product class information from other anti-sclerostin antibodies.

The following potential risks will require reporting to permit processing as AESI for the study (refer to Appendix 4 for details on safety reporting).

[redacted]

Measures to minimize risk and monitor for AESIs are listed below.

[redacted]

Additional measures to monitor for other potential risks are listed below.

- CCI [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]

In addition to the above, the incidence, seriousness, severity, duration, and outcome of all potential risks will be regularly monitored throughout the study and follow up will be performed to obtain complete information on all reported events to enable a thorough medical assessment.

6. OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are defined for each study period. Objectives and endpoints for the Observation, Retreatment, and Extension Periods are shown in Table 6, Table 7, and Table 8 respectively.

Table 6: Study Objectives and Endpoints for the Observation Period

OBJECTIVES	ENDPOINTS
Primary (please see Table 7 Study Objectives and Endpoints for the Retreatment Period)	
Not applicable	Not applicable
Secondary	
Not applicable	Not applicable
Tertiary	
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CCI [redacted]

BMD, bone mineral density; CCI [redacted]

DXA, dual-energy X-ray absorptiometry; CCI [redacted]

Table 7: Study Objectives and Endpoints for the Retreatment Period

OBJECTIVES	ENDPOINTS
Primary	
Evaluate BMD after 12 months of retreatment with monthly setrusumab in adults with OI	Percentage change from Retreatment Baseline in lumbar spine BMD measured by DXA after 12 months of setrusumab
Secondary	
Evaluate BMD during 12 months of retreatment with monthly setrusumab in adults with OI	Percentage change from Retreatment Baseline in total hip BMD measured by DXA at Month 12 of the Retreatment Period
Evaluate fractures after 12 months of retreatment with monthly setrusumab in adults with OI	Annualized new fracture rate as confirmed by radiograph during the Retreatment Period
Tertiary	
CCI	

CCI

BMD, bone mineral density; CCI

DXA, dual-energy X-ray absorptiometry; CCI

Table 8: Study Objectives and Endpoints for the Extension Period

OBJECTIVES	ENDPOINTS
Primary (please see Table 7 Study Objectives and Endpoints for the Retreatment Period)	
Not applicable	Not applicable
Secondary	
Not applicable	Not applicable
Tertiary	
CCI	

CCI

BMD, bone mineral density; CCI

DXA, dual-energy X-ray absorptiometry CCI

7. INVESTIGATIONAL PLAN

7.1. Study Design

UX143-CL203 is a Phase 2b, multicenter, long-term extension study in adults with OI who participated in the Phase 2b, double-blind, dose-finding ASTEROID study (also referred to as MBPS205) (Figure 1). Briefly, in ASTEROID, subjects were treated with 12 months of setrusumab (either 2, 8, or 20 mg/kg once a month [QM]), followed by a 12-month Follow-up Period in which subjects discontinued setrusumab and had the option to receive zoledronic acid at Month 12, 18, or both. Subjects who participated in ASTEROID are eligible to participate in UX143-CL203. As the ASTEROID study completed prior to the initiation of UX143-CL203, an Off-study Period will occur for all subjects who enroll in UX143-CL203; the duration of this Off-study Period varies from subject to subject depending on completion of ASTEROID and enrollment in UX143-CL203.

UX143-CL203 comprises Observation, Retreatment, and Extension Periods. There is no intervention during the Observation Period; subjects are followed to evaluate disease progression and the long-term effects of setrusumab discontinuation. During the Observation Period, a retrospective chart review captures data that occurred during each subjects' Off-study Period. This chart review includes collection of DXA and fracture events. After screening and enrollment, the first assessments occur during the Observation Period at the First Visit. The First Visit occurs at a CCI interval relative to the subject's ASTEROID enrollment. Following the First Visit, subjects are assessed CCI [redacted] for up to 18 months or until setrusumab becomes available for Retreatment. No minimum duration is necessary for the Observation Period and the duration of the Observation Period may vary from subject to subject depending on when they enrolled and when setrusumab is available for the Retreatment Period. Once setrusumab is available, each subject undergoes a Retreatment Screening Visit to confirm eligibility prior to restarting setrusumab, and then begins the Retreatment Period. The Retreatment Screening Visit occurs during the Observation Period, 1 to 4 weeks prior to the Retreatment Baseline Visit in the Retreatment Period. As noted in Section 8.2, subjects who are receiving bisphosphonates during the Observation Period must discontinue bisphosphonate use at least 3 months prior to the Retreatment Screening Visit.

During the Retreatment Screening Visit subjects undergo screening to confirm eligibility for retreatment with setrusumab, including an assessment of serum calcium and 25-OH-vitamin D (Section 8.2 and Section 8.5). If a CCI Visit occurred within 4 weeks prior to the Retreatment Baseline, then safety laboratory tests do not need to be recollected at the Retreatment Screening Visit, except for the chemistry panel, which is collected at both the Retreatment Screening Visit and Retreatment Baseline.

The dosing strategy in the Retreatment and Extension Periods will be based on the pharmacokinetic (PK) and serum bone turnover markers from the Phase 2b ASTEROID study and the Phase 2 Period of the UX143-CL301 study. The selected dose will be in the range of 20 to 40 mg/kg CCI [redacted]

During the single-arm Retreatment Period, subjects receive open-label setrusumab QM for 12 months. During the Retreatment Period, subjects are assessed for safety and efficacy of

setrusumab retreatment.CCI [redacted] The primary analysis occurs at the end of the Retreatment Period.

Following the Retreatment Period, subjects enter an Extension Period, in which they are randomized 1:1 to either continue treatment with open-label setrusumab QM or transition to open-label setrusumab CCI [redacted] for at least 12 months or until setrusumab is commercially available. For the Extension Period dosing groups, randomization will be stratified by OI type (I vs III/IV).

7.1.1. Number of Sites

Approximately 24 sites

7.1.2. Number of Subjects

Up to 112 subjects will be enrolled; only those who participated in ASTEROID.

7.1.3. Rationale for Study Design

The purpose of this study is to further investigate the safety and efficacy of setrusumab in adults with OI. The Phase 2b study (ASTEROID; MBPS205) demonstrated clinically meaningful, dose-dependent increases in BMD over the course of 12 months of setrusumab, with discontinuation of therapy resulting in partial loss of BMD gains over the next 12 months. The proposed study will re-recruit these subjects to monitor the long-term effects off-setrusumab and to evaluate the effect of setrusumab retreatment. The potential inclusion of up to 112 subjects treated with open-label setrusumab for up to 2 years will augment the current safety and efficacy database. These results will help inform longer-term treatment strategies in adults with OI, a chronic disease for which no therapy is currently approved globally. Additionally, retreating these adults with OI will provide insight into the effects of stopping and restarting treatment with setrusumab, potentially with and without interim bisphosphonate use, and help characterize long-term safety with setrusumab treatment.

The proposed study is divided into multiple parts which each have their own goal. During the Observation Period, data will be collected to evaluate setrusumab off-treatment effects. Additional data will be collected from the Off-Study Period via chart review to provide additional information on post-setrusumab effects that occurred prior to enrollment into the Observation Period. The Observation Period visits will occur at CCI [redacted] intervals relative to the Phase 2b study. The effects of initial setrusumab dose-level and zoledronic acid administration post-setrusumab will be further elucidated, with specific evaluation of changes in BMD and fracture rate over time. Together, data collected from the Off-Study and Observation Periods provide a long-term view of the effects of setrusumab discontinuation in adult OI.

The Retreatment Period will evaluate the efficacy and safety of 12 doses of open-label setrusumab QM. Retreatment may provide additional insights into the effects of setrusumab in subjects that previously received setrusumab. The potential impact of how subjects were treated in the original Phase 2b study (initial setrusumab dose-level and/or zoledronic acid

administration) will be further elucidated. Open-label use of monthly setrusumab is warranted based on the Phase 2b data that demonstrated the relative safety and efficacy of monthly dosing in these patients.

The Extension Period will extend setrusumab administration beyond 12 months to determine the longer-term safety and efficacy of retreatment in adults with OI. The Extension Period will also explore dosing strategies, QM or CCI helping to optimize the treatment regimen for longer-term treatment with setrusumab. Demonstration of continued improvements in DXA BMD or other endpoints beyond 12 months may justify extended use of setrusumab in adult OI.

7.1.4 Dose Rationale

The dosing strategy in the Retreatment and Extension Periods will be based on the PK and serum bone turnover marker data from the Phase 2b ASTEROID study (completed) and data from the ongoing Phase 2/3 UX143-CL301 study (ages 5 to < 26 years). In the ASTEROID study, a setrusumab dose of 20 mg/kg QM increased DXA BMD, biomarkers of bone formation, and bone strength indices in adult patients with OI with an acceptable safety profile. An effect of body weight on setrusumab PK was observed, with setrusumab exposures decreasing as body weight decreased.

The dosing strategy for the Retreatment Period will also take into account data from the Phase 2 Period of the UX143-CL301 study (a seamless Phase 2/3 study with setrusumab in subjects with OI ages 5 to < 26 years). The Phase 2 Period of the UX143-CL301 study will evaluate the PK/pharmacodynamics (PD) of setrusumab at 2 dose levels, 20 and 40 mg/kg. PK/PD data from the Phase 2 Period of UX143-CL301 will be incorporated into a population PK/PD model developed using data from previous setrusumab studies, including ASTEROID, to inform the dose for the Phase 3 Period of UX143-CL301, as well as the dose for this study (UX143-CL203).

CCI [redacted]

7.2. Duration

7.2.1. Duration of Subject Participation

Screening may take up to 1 month. The Observation Period is expected to take up to 18 months. The Retreatment Period is 12 months. The Extension Period continues until setrusumab is commercially available in a subject's given region.

7.2.2. End of Study Definition

The end of the study is defined as the date of safety follow-up for the last subject in the study.

7.3. Changes to the Protocol due to Covid-19

Changes to the protocol or Investigational Plan to minimize or eliminate immediate hazards or to protect the life and well-being of research subjects and/or study staff may be implemented without Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval or before filing an amendment to the competent authority but are required to be reported afterward. Investigators should contact Ultragenyx or Designee to determine an appropriate course of action, which may include but is not limited to remote visits, home health visits, and out of window visits or assessments. Any changes to the protocol or investigational plan must be documented. The Investigator will work with Ultragenyx or Designee and IRB/IEC to prioritize reporting of protocol deviations that impact safety of trial subjects.

8. POPULATION

Prospective protocol deviations (ie, protocol waivers or exemptions) are not permitted.

8.1. Inclusion Criteria

Subjects who participated in ASTEROID were ages 19 to 74 years at the time of enrollment. Eligible individuals must meet all of the following criteria:

1. Males or females who participated in the Phase 2b ASTEROID study
2. Females of childbearing potential must consent to use highly effective contraception (Appendix 2) during the Observation, Retreatment, and Extension Periods through 2 months after the last dose of setrusumab and agree not to become pregnant. Provide informed consent after the nature of the study has been explained, and prior to any research-related procedures

8.2. Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to enroll in UX143-CL203:

1. Known hypersensitivity to setrusumab or its excipients that, in the judgment of the Investigator, places the subject at increased risk for adverse effects.
2. Presence or history of any condition that, in the view of the Investigator, would interfere with participation, pose undue risk, or would confound interpretation of results.
3. Pregnant or breastfeeding or planning to become pregnant (self or partner) at any time during the study
4. Willing to discontinue bisphosphonate use at least 3 months prior to the Retreatment Screening Visit (if applicable).Once enrolled in UX143-CL203, individuals who meet any of the following exclusion criteria will not be eligible to participate in the Retreatment Period:
5. Concurrent participation in any study that is examining the safety and efficacy of any investigational product or investigational medical device that alters bone health during the Retreatment and Extension Periods, per discretion of the Investigator in consultation with the Medical Monitor.
6. Presence or history of any condition that, in the view of the Investigator, would interfere with participation, pose undue risk, or would confound interpretation of results.
7. Calcium levels outside the normal range. If the subject's calcium level is not within the normal range, decision to retest should be made in conjunction with the Medical Monitor.
8. GFR $\leq$ 29 mL/min. If the subject's GFR is $\leq$ 29 mL/min, decision to retest should be made in conjunction with the Medical Monitor.
9. History of skeletal malignancies or bone metastases at any time
10. History of neural foraminal stenosis (except if due to scoliosis)

11. History of myocardial infarction, angina pectoris, ischemic stroke or transient ischemic attack
    a. Investigators should consider whether the potential benefits of treatment outweigh the potential risks in patients with other cardiovascular risk factors such as hypertension, hyperlipidemia, familial hyperlipidemia, family history of premature ischemic cardiovascular disease, smoking, diabetes mellitus, and metabolic syndrome. Suggested criteria and references for evaluation of risk factors will be provided in the Study Reference Manual.
12. 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 eg, Stage IV/V renal disease
13. A history of rickets or osteomalacia or any skeletal condition (other than OI) leading to long-bone deformities and/or increased risk of fractures
14. 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
15. 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
16. Current/previously reported allergy to the study drug or any of its excipients or the class of drug under investigation
17. History of external radiation

8.3. Subject Discontinuation and Stopping Rule Criteria

8.3.1. Discontinuation of Intervention

If a subject is withdrawn from treatment due to safety reasons or if a subject has an ongoing SAE or AESI considered related to study drug at the end of participation, the subject should be followed until the event resolves, or the subject's condition has stabilized.

8.3.2. Discontinuation from 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, behavioral, or compliance reasons. Ultragenyx must be notified of all subject withdrawals as soon as possible. Ultragenyx also reserves the right to discontinue participation of an Investigator due to poor enrollment or noncompliance, as applicable.

In the event a subject discontinues treatment, he or she will remain in the study for safety monitoring purposes, unless continued participation in the study poses a risk to the subject as determined by the Investigator and/or Medical Monitor.

If a subject discontinues from the study prematurely, reasonable efforts should be made to perform the early termination (ET) Visit procedures within 2 weeks of discontinuation. A safety follow-up will be performed 2 months after the subject's last treatment. In the event a subject has an ET, all efforts will be made to monitor the subject through the end of the study.

8.3.3. Study Stopping Criteria

If, at any time during the study, any of the criteria listed below are reported in subjects treated with setrusumab, DMC will be notified to review if any alteration of study procedures is warranted:

- Two or more subjects with any serious TEAE with a severity ≥ Grade 3 (according to the Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) that is assessed as related to study drug or study procedures by the Investigator or Ultragenyx
- One or more subjects with a hypersensitivity reaction that is considered Grade 4 or higher and assessed as related to study drug by the Investigator or Ultragenyx

8.4. Informed Consent

Informed consent must be obtained from the patient at the Screening visit, prior to entry into the Observation period and prior to performing any study-related procedures. In the event that a subject is rescreened, a new informed consent form (ICF) must be signed unless it has been < 30 days since the previous ICF signature was obtained.

8.5. Screening Requirements

There are 2 screening visits: the Screening Visit to determine eligibility for entry into the Observation Period of the study and the Retreatment Screening Visit to confirm eligibility to enter the Retreatment Period of the study in order to receive retreatment with setrusumab. All screening evaluations specified in Table 3 must be completed and reviewed to confirm eligibility for study entry (initial Screening Visit into the Observational /period) and Retreatment Period entry (Retreatment Screening Visit). The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

At the Screening Visit, informed consent will be obtained, general medical information (ie, demographics, general medical history, and concomitant medications) will be collected.

During the Retreatment Screening Visit subjects are rescreened and safety laboratory tests are run to ensure subject safety prior to retreatment with setrusumab (Section 8.2). Calcium levels assessed at the Retreatment Screening Visit must be in the normal range prior to the Retreatment Visit. While receiving treatment with setrusumab, subjects can receive a daily dose of CCI mg calcium as background treatment or maintain a higher dose if they are already receiving a higher dose. If the subject's calcium level is not within the normal range, decision to retest should be made in conjunction with the Medical Monitor. 25-OH-vitamin D should be ≥ CCI nmol/L prior to setrusumab retreatment. If the subject's 25-OH-vitamin D is < CCI nmol/L at the Retreatment Screening Visit, the subject should be treated as per the local guidelines and retested during the study to maintain levels above CCI nmol/L.

9. INTERVENTION(S)

Table 9: Study Interventions

Intervention	Setrusumab
Dose Formulation	CCI mg lyophilized powder for solution
Unit Dose Strength(s)/Dosage Level(s)	20 to 40 mg/kg QM CCI
Route of Administration	60-minute IV infusion
Use	Experimental

[a] The dosing strategy in the Retreatment and Extension Periods will be based on the pharmacokinetic (PK) and serum bone turnover data from the Phase 2b ASTEROID study and the Phase 2 Period of the UX143-CL301 study. The selected dose will be in the range of 20 to 40 mg/kg CCI

IV, intravenous; CCI QM, once a month.

9.1. Investigational Product: Setrusumab

Setrusumab is supplied as a CCI mg powder in a vial for solution for infusion. The vial is filled with excess setrusumab (ie, CCI mg) to ensure that the full dose is removed from the vial once reconstituted. Setrusumab is manufactured, packaged and labelled according to current Good Manufacturing Practices.

Additional information on physical and chemical properties of setrusumab are provided in the IB.**Preparation and Administration**

For detailed preparation and administration information refer to Pharmacy Manual.

Setrusumab CCI mg powder for solution for infusion needs to be reconstituted with sterile water for injection CCI and diluted in C% dextrose in a CCI mL IV bag to be administered over CCI CCI Setrusumab will be administered at scheduled study visits as outlined in the Schedule of Events (Table 3).

9.1.2. Clinical Observation and Supportive Care

Subjects will be monitored for any infusion reactions that may occur during or immediately following drug administration. Infusion-related reactions are an AESI (Section 10.6.1) and will be reported accordingly (Table 11). For the first 2 administrations of study drug per patient, oral or tympanic temperature, blood pressure, respiratory rate and pulse will be monitored at the beginning of the infusion at CCI after the end of the infusion. For the remaining infusions, vital signs will be monitored during the infusion.

9.2. Prior and Concomitant Therapy

Subjects may receive concomitant medications as required, with the exception of those identified in Section 9.3 as prohibited. Concomitant medications will be recorded as described in Section 10.6.7.

Study site personnel should indicate on relevant laboratory request documents if the subject is taking high dose biotin supplements (found in multivitamins, biotin supplements, and some supplements to support hair, skin and nail growth) due to potential risk of assay interference (eg, troponin) (FDA, 2019).

9.3. Restricted or Prohibited Medications, Devices, and Procedures

Certain medications and procedures are prohibited per the exclusion criteria in Section 8.2, including:

- Concurrent participation in any study that is examining the safety and efficacy of any investigational product or investigational medical device that alters bone health during the Retreatment and Extension Periods, per discretion of the Investigator in consultation with the Medical Monitor
- Willing to discontinue bisphosphonate use at least 3 months prior to the Retreatment Screening Visit (if applicable).

9.4. Treatment Compliance

Study drug will be administered at the study site via a single IV infusion by qualified personnel. The dose, start time, stop time, and volume of infusion will be recorded in the subject's case report form (CRF).

9.5. Treatment Assignment

9.5.1. Treatment Assignment

This is an open-label study. No study drug is provided during the Observation Period. During the Retreatment Period, all subjects will receive the same dose of setrusumab administered QM. During the Extension Period, subjects will be randomized 1:1 to either continue treatment with open-label setrusumab QM or transition to open-label setrusumab CCI. For the Extension Period dosing groups, randomization will be stratified by OI type (I vs III/IV). Randomization will be completed using interactive response technology (IRT).

10. ASSESSMENTS

Assessments, including sample collection, and associated timing are provided in Table 3 and Table 4. Protocol waivers or exemptions are not allowed.

Data will continue to be collected for all endpoints on all subjects, including those who have discontinued study treatment but remain in the study. Site Investigators will be trained about the importance of subject retention and steps to prevent missing data. Reasons for missed assessments will be collected.

The completeness of the data affects the integrity and accuracy of the study analyses. Therefore, every effort will be made to ensure complete, accurate and timely data collection, and to avoid missing data.

10.1. Skeletal Assessments

10.1.1. Dual-energy X-ray Absorptiometry

Bone mineral density of the lumbar spine, total hip, femoral neck, distal 1/3 radius, and whole body minus head will be evaluated by DXA at time points specified in Table 3. CCI [redacted] As noted in Section 10.6.2, DXA scans will also be collected retrospectively as a part of medical history. Calcium tablets should not be taken 2 hours prior to a DXA lumbar scan. Additional details regarding DXA are provided in the Study Imaging Manual.

10.1.2. Radiography

A skeletal survey and vertebral radiographs will be performed at time points specified in Table 3. Additional radiographs may be performed to confirm a reported fracture event. As noted in Section 10.6.2, radiographs for fracture events occurring prior to study entry will be collected via chart review as a part of medical history.

Radiographs of the left hand will be analyzed and evaluated for bone age and metacarpal thickness. Lateral spine radiographs will be assessed for morphometric vertebral fractures based on vertebral height using the semi-quantitative Genant method and 6-point quantitative morphometric method; Spine Deformity Index, kyphosis, and lordosis will be evaluated. Anterior-posterior spine radiographs will be used to evaluate the degree of scoliosis. Fracture healing will also be assessed.

Fractures reported via diary (Section 10.2.4) may be radiographed at the next scheduled visit (unless radiographs are obtained prior to the visit). An effort will be made to secure radiographs taken between study visits at other institutions.

All radiographs will be assessed for the presence of fractures by central readers, who are blind to the subject's treatment and trained for consistent evaluation. Additional details regarding radiography are in the Study Imaging Manual.

10.1.3. CCI

[redacted]

10.2. Patient-reported Assessments

10.2.1. CCI

CCI

[redacted]

10.2.2. CCI

CCI

[redacted]

10.2.3. CCI

CCI

[redacted]

10.2.4. Fracture Event Diary

Subjects will be prompted report any new suspected fractures and asked to provide details about a fracture event including number, location, and date of suspected fracture(s) at time points specified in Table 3. Subjects will be asked about the impact of the fracture on physical function for up to 8 weeks from the report of a fracture event. When a new fracture event is reported in the diary, the study site will be notified and will follow up with the subject to collect additional details. Radiographs will be collected at the next scheduled visit to confirm the fracture.
If radiographs were taken outside of study site, the site will attempt to collect these radiographs.
Questions regarding baseline level of function will be administered at the beginning of the study to further assess the impact of fracture.

10.3. CCI

[redacted]

10.4. CCI

CCI [redacted]

[redacted]

10.5. CCI

CCI [redacted]

10.6. Safety Assessments

During the Observation Period, safety will be evaluated by the incidence and severity of AESI as well as the relationship of AESI to prior setrusumab. Incidence and severity of AESI as well as relationship of AESI to prior setrusumab treatment will also be collected via chart review for the Off-study Period between ASTEROID and the UX143-CL203 study. During the Retreatment and Extension Periods, safety will be evaluated by the incidence, severity, and relationship to setrusumab of TEAEs, AESIs, and treatment-emergent SAEs. Safety will also be assessed by changes from the First Visit during the Observation Period and the Retreatment Screening Visit

prior to entering the Retreatment Period to scheduled time points in vital signs, physical examination, focused neurological examination, audiometry, dental health evaluations, clinical laboratory evaluations, and ECGs. Safety will also be evaluated by the development of anti-setrusumab antibodies and pregnancy testing.

Safety definitions and instructions for assessing severity and causality are presented in Appendix 3.

Refer to Appendix 4 for instructions how to elicit, record, and report including collection period timeframes and timelines for AEs, SAEs, AESIs, pregnancies, other safety information and any urgent safety measures taken to protect the safety or welfare of subjects.

10.6.1. Adverse Events of Special Interest

AESIs for this study include the potential risks of ischemic cardiovascular events, infusion reactions and hypersensitivity, and neurologic sequelae associated with bone overgrowth. Medical Dictionary for Regulatory Activities (MedDRA) search strategies will be specified for AESIs in the Statistical Analysis Plan, and include standardized MedDRA queries, if available.

AESI will be collected from the time the subject signs the ICF and through the safety follow-up period and should be reported within 24 hours of site Investigator, designee or site personnel's knowledge of the event as outlined in Table 11.

10.6.2. General Medical History

General medical history will be collected during screening (Table 3). General medical information includes subject demographics and a history of major medical illnesses, diagnoses, and surgeries. Medical history also includes a chart review, including the collection of DXA and fracture events.

10.6.3. Vital Signs

Vital signs to be measured include seated systolic blood pressure and diastolic blood pressure, heart rate, respiration rate, and temperature. Vital signs will be measured after the subject has rested for at least 5 minutes, and prior to any other study assessments and drug administration.

10.6.4. Electrocardiograms

Single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and (QTc) intervals. ECGs will be performed at timepoints indicated in the Schedule of Events (Table 3).

While conduction intervals provided by the ECG machine may be used, final interpretation of ECGs, including any rhythm abnormalities, will be made by an independent central vendor to ensure reliability and reproducibility. Any abnormalities will be recorded.

10.6.5. Safety Laboratory Tests

Blood and urine samples will be collected prior to administration of study drug, as specified in Table 3 and Table 4, and analyzed by a central laboratory. Fasting is required for visits that coincide with blood sample collection for [redacted] (Table 3 and Table 4).

Study site personnel should indicate on relevant laboratory request documents if the subject is taking high dose biotin supplements (found in multivitamins, biotin supplements, and some supplements to support hair, skin and nail growth) due to potential risk of assay interference (eg, troponin) (FDA, 2019).

The safety laboratory evaluations to be performed in this study are listed in Appendix 1.

For any subject who experiences an SAE or other AE of concern, the Investigator (and/or Medical Monitor) may at his/her discretion perform additional laboratory tests for subject safety.

10.6.6. Pregnancy Testing

Female subjects of childbearing potential will have urine pregnancy tests at visits indicated in Table 3. Females not of childbearing potential are not required to undergo pregnancy testing. Refer to Appendix 2 for childbearing potential definitions.

Female subjects with a positive pregnancy test at Screening will not be enrolled in the study.

Additional pregnancy tests will be performed at any visit in which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result or can be performed if pregnancy test by urine is not feasible. For visits in which setrusumab is administered, blood and urine should be collected prior to drug administration.

Refer to Appendix 4 for pregnancy reporting requirements.

10.6.7. Concomitant Medications

Medications (investigational, prescription, over the counter, and herbal supplements) and nutritional supplements taken during the 30 days prior to Screening will be reviewed and recorded at the Screening visit. Use of any concomitant medications during the study should be recorded on the CRF. All concomitant medications will be coded according to the WHODrug Dictionary.

Site personnel should record date the medication was taken, the name of the medication, medication dosage, formulation, route of administration and the reason the medication was taken.

10.6.8. CCI

CCI [redacted]

10.7. Physical and Neurologic Assessments

10.7.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological systems.

A targeted 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.

Weight will also be measured and recorded during both complete and targeted physical exams.

10.7.2. Focused Neurological Examinations

A focused neurologic examination, including an assessment of spinal and cranial nerves, will be conducted by a clinician with appropriate training at timepoints indicated in the Schedule of Events (Table 3). Any abnormalities will be recorded.

10.7.3. Audiometry

A hearing test will be performed at time points specified in Table 3. Additional details regarding audiometry assessment are available in the Study Reference Manual.

10.7.4. Dental Health Assessment

A dental health assessment will be performed at time points specified in Table 3. Dental health assessment includes assessing for any potential confounding effects of prior bisphosphonate exposure or risk factors for osteonecrosis of the jaw.

10.8. Appropriateness of Measurements

The efficacy endpoints to be evaluated in this study examine treatment effects on skeletal health. Fractures are a hallmark of OI, and reduction of fracture incidence is an important treatment goal. Therefore, assessments include radiographic evaluation of fracture incidence and assessment of BMD to determine whether potential increases in BMD with treatment correspond with a reduction in fracture incidence. Bone formation and resorption markers will also be assessed as indicators of treatment effect on bone health. Patient/caregiver- and clinician-reported outcomes have been included to further inform treatment benefits on key disease manifestations and symptoms as perceived by the patient or their caregiver/clinician.

The safety parameters to be evaluated in this study include standard safety assessments such as recording medical history, AEs, SAEs, physical examination, vital signs, serum chemistry, concomitant medication, and other clinical and laboratory procedures. Additionally, subjects will be monitored for AESIs, CCI [redacted] these AESIs were defined based on safety data from prior clinical studies of setrusumab and product class information from other anti-sclerostin antibodies.

11. STATISTICAL CONSIDERATIONS

A full description of the analysis details will be provided in the Statistical Analysis Plan (SAP).

11.1. Sample Size Determination

As only subjects who participated in the ASTEROID study are eligible, the sample size for this study is limited to the number of subjects who participated in ASTEROID and not driven by hypothesis testing. Assuming CCI% recruitment failure rate from the ASTEROID study and CCI% dropout rate by Month 12 of the Retreatment Period, there will be around CCI subjects with data at Month 12. For the primary endpoint of percentage change from Retreatment Baseline in lumbar spine BMD measured by DXA at Month 12 of the Retreatment Period, assuming the percentage change from Month 0 of the Retreatment Period (Retreatment Baseline) in lumbar spine BMD at Month 12 of CCI, a sample size of around CCI subjects will provide greater than CCI% power to detect the change from baseline at 1-sided significance level of CCI. For the secondary endpoint of percentage change from Retreatment Baseline in total hip BMD at Month 12 of the Retreatment Period, assuming the percentage change from Month 0 of the Retreatment Period (Retreatment Baseline) in total hip BMD at Month 12 of CCI, a sample size of around CCI subjects will provide greater than CCI% power to detect the change from baseline at 1-sided significance level of CCI.

Analysis Sets

For the purposes of analysis, the analysis sets are defined in the SAP.

11.2. Planned Methods of Analysis

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

11.2.1. General Principles

A general description of the statistical methods to be used to analyze the study endpoints is outlined below. The analyses planned in this protocol will be expanded in the SAP to include detailed description of the analyses.

The statistical analyses will be reported using summary tables, figures, and data listings. Descriptive statistics for continuous variables will include number of patients (n), mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. Frequency and percentage will be calculated for categorical variables.

11.2.2. Efficacy Analyses

11.2.2.1. Primary and Secondary Efficacy Endpoints

The primary endpoint, percentage change from Retreatment Baseline in lumbar spine BMD measured by DXA at Month 12 of the Retreatment Period will be analyzed using a mixed-effects model for repeated measures that includes visit as a categorical variable and adjusted for baseline measurement. Other covariates may be considered. Model-based estimates of the percentage changes from baseline and corresponding CCI% confidence intervals will be provided along with p-values.

The secondary endpoint, percentage change from Retreatment Baseline in total hip BMD measured by DXA at Month 12 of the Retreatment Period, will be analyzed similarly to lumbar spine BMD as described above.

The other secondary endpoint, number of fractures (total and by fracture type) and proportion of subjects who experience a fracture, as confirmed by radiograph during the Retreatment Period, will be summarized descriptively. The annualized new fracture rate during Retreatment Period will be compared with the annualized fracture rate during the Observational Period and\or Off-study Period using a generalized linear mixed effect model.

11.2.2.2. Tertiary Efficacy Endpoints

CCI [redacted]

11.3. Safety Analyses

Safety variables including all SAEs, TEAEs, AESIs, safety laboratory assessments, anti-setrusumab antibodies, vital signs, ECGs, physical examination, focused neurological examination, audiometry, and dental health assessments will be summarized descriptively and listed by subject.

All AEs will be coded according to the MedDRA Version 24.0 or above. The frequency and severity of all TEAEs, SAEs, AESIs and clinically relevant laboratory and ECG abnormalities reported as AEs will be reported by System Organ Class, Preferred Term, by severity, and by relationship to study drug, if applicable. All non-serious AEs reported with onset after the first dose of study drug (ie, TEAEs) will be included in the analysis. All SAEs will also be reported by relationship to study drug as reported by Investigator, seriousness criteria, timing, duration, and outcome. For all TEAEs; SAEs; AESIs; and treatment-related TEAEs, SAEs, and AESIs; the percentage of subjects who experienced at least 1 occurrence of the given event will be summarized. Data summaries and\or listings, and narratives will be provided for subjects who died, discontinued treatment or withdrew from study due to TEAE, or experienced SAEs, AESIs, and any study procedure-related AEs.

Clinical laboratory data changes from ASTEROID Baseline and Retreatment Baseline will be summarized by the type of laboratory test. Reference ranges and abnormal results (specified in the SAP) will be used in the summary of laboratory and ECG data. The frequency and percentage of subjects who experience abnormal clinical laboratory results (ie, outside of reference ranges) and/or clinically significant abnormalities (as determined by the Investigator) will be presented for each clinical laboratory measurement, including for Hy's Law analysis (alanine transaminase [ALT], aspartate aminotransferase [AST], total and direct bilirubin, alkaline phosphatase). Shift tables will be provided for changes from ASTEROID Baseline and Retreatment Baseline in selected chemistry and hematology laboratory parameters (if applicable). Listings of abnormal vital signs and physical findings will be provided (if applicable).

The SAP will provide additional details on the planned safety analyses.

11.4. Planned Analyses

The primary analysis is planned at the end of the Retreatment Period, reflecting 12 months of retreatment with setrusumab. No interim analyses are planned. The final analysis will be conducted at the end of the study.

11.5. Data Monitoring Committee

An independent DMC will be established with subject matter experts to serve in an advisory capacity to Ultragenyx.

The DMC will meet and review study data, including cardiovascular events and other AESIs, at the frequency defined and in accordance with the scope and objectives set forth in the DMC Charter. The DMC will provide advice to Ultragenyx regarding the safety of subjects, the ethics of the study and the continuing scientific validity of the study. The DMC may also make recommendations to Ultragenyx concerning continuation, termination or other modifications of

the study based on their review of data. Further details regarding the DMC can be found in the DMC charter.

Ultragenyx Data Review Board will review the DMC recommendations and determine necessary actions that will be communicated accordingly to all stakeholders, eg, Regulatory Authorities, IRB/IECs, and Investigators.

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13. GENERAL APPENDICES

APPENDIX 1. SAFETY LABORATORY ASSESSMENTS

Table 10: Specified Laboratory Assessments

Chemistry	**Hematology**	**Urinalysis**
Alanine aminotransferase (ALT)	Hematocrit	Appearance
Alkaline phosphatase	Hemoglobin	Color
Amylase	Mean corpuscular hemoglobin (MCH)	pH
Aspartate aminotransferase (AST)	MCH concentration (MCHC)	Specific gravity
Bicarbonate (Total CO2)		
Bilirubin (direct and total)	Mean corpuscular volume (MCV)	
Blood urea nitrogen (BUN)	Platelet count	Bilirubin
Calcium	Red blood cell (RBC) count	Creatinine
Chloride	Reticulocyte count	Glucose
Cholesterol (total)	White blood cell (WBC) count	Hemoglobin
Creatine kinase	WBC differential:	Ketones
Creatinine	Basophil count (absolute and %)	Nitrite
Gamma-glutamyl transpeptidase (GGT)	Eosinophil count (absolute and %)	Protein
Glucose	Lymphocyte count (absolute and %)	Urobilinogen
Lactate dehydrogenase (LDH)	Monocyte count (absolute and %)	
Lipase	Neutrophil count (absolute and %)	Pregnancy test (if applicable)
Magnesium		
Phosphorus	Complete blood count with differential (CBC/diff)	
Potassium		
Protein (albumin and total)		*Special assessment
Sodium		Serum pregnancy test if a positive urine pregnancy test
Triglycerides		

APPENDIX 2. CONTRACEPTION GUIDANCE

The guidance below applies for development products with potential or unknown reproductive toxicity (for products in clinical trials, where pre-clinical data are indicative of risk or have not yet been completed).

Female subjects of childbearing potential who are heterosexually active must consent to use a highly effective method of contraception as listed below to prevent pregnancy over the time period required for product levels to decrease to a concentration that is no longer considered relevant for human teratogenicity/fetotoxicity. This time period is generally determined by the pharmacokinetic properties of the study product and non-clinical reproductive toxicity data and is defined in the protocol or product Investigator Brochure.

Highly effective contraceptive methods are those with a failure rate of less than 1% per year when used consistently and correctly.

Female subjects of childbearing potential are defined as having reached menarche prior to or during the study. Females not of childbearing potential include those who have not experienced menarche, are postmenopausal (defined as having no menses for at least 12 months without an alternative medical cause) or are permanently sterile due to having total hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

- 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. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient and multiple measurements are needed.

Male subjects who are heterosexually active with female partners of childbearing potential must consent to use one of the highly effective methods of contraception listed below to prevent pregnancy over the period defined in the protocol or product Investigator Brochure. The time period required is generally determined by the pharmacokinetic properties of the study product and non-clinical reproductive toxicity data, plus 90 days for a full sperm cycle.

Highly effective methods of contraception (CTFG, 2020) include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (eg, oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (eg, oral, injectable, implantable)
- Intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male sterilization, also called vasectomy
- Sexual abstinence is defined as refraining from heterosexual intercourse during the entire study period associated with risk of the Investigational Product (IP), other study treatments or procedures

The reliability of sexual abstinence should be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

Abstinence is only considered a highly effective method of contraception if practiced consistently for the entire period of exposure to IP or other study treatments.

Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not acceptable methods of contraception.

Note: Barrier methods (such as a condom used with or without a spermicide or a diaphragm or cervical cap used with a spermicide) used alone are NOT highly effective contraception methods.

Additional Requirement: If IP is an advanced therapy medicinal product (eg, gene therapy), a condom with spermicide is also required to be used by all sexually active males in the study in order to prevent potential transmission of the vector via seminal fluid.

APPENDIX 3. SAFETY DEFINITIONS AND ASSESSMENTS

Adverse Event (AE)

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a pre-existing condition is considered an AE.

Any abnormal laboratory test results (hematology, clinical chemistry, or urine) or other safety assessments (eg, vital sign measurements), including those that worsen from Screening/baseline that are felt to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs.

Treatment-emergent AE (TEAE)

A TEAE is defined as any AE not present prior to the initiation of the drug treatment or any AE already present that worsens in either intensity or frequency following exposure to the drug treatment.

Serious Adverse Event (SAE)

An SAE is an AE that meets any of the following criteria in the view of either the Investigator or Ultragenyx:

- Death
- Life-threatening

A life-threatening AE is an event that places the patient or subject at immediate risk of death. It does not include events that if it had occurred in a more serious or severe form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

- Inpatient hospitalization or prolongation of existing hospitalization

Hospitalization is defined by Ultragenyx as a full admission to hospital for a period of 24 hours or longer for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization. Examples of visits to a hospital facility that do not meet the serious criteria for hospitalization include:

  - *Emergency room visits (that do not result in a full hospital admission)*
  - *Preplanned or elective procedures prior to study enrollment (e.g., outpatient surgery)*
  - *Protocol procedures*

Hospitalization signifies that the subject 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. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

AEs requiring hospitalization should be considered SAEs. Hospitalization planned prior to study enrollment (eg, for elective surgery or routine clinical procedures) that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to seriousness criteria described above.

- Disability/Incapacity

An AE is disabling or incapacitating if it results in substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

    - Congenital anomaly/birth defect not present at screening

- Important Medical Events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the criteria listed in the definition. Examples of such events are:

Intensive treatment in an emergency room or at home for allergic bronchospasm

Blood dyscrasias that do not result in inpatient hospitalization

Development of drug dependency or drug abuse

Adverse Events of Special Interest (AESI)

An AESI is one of scientific or medical interest specific to the product (or product class) or program requiring further investigation and ongoing monitoring to better characterize them. Such events can be serious or non-serious and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.

Participation-emergent Adverse Events

These events may be related to study participation or biological specimen collection and will be reported by the investigator and noted as such in the case report form (CRF) as related to study intervention.

Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. All cases of overdose (with or without associated AEs) will be documented in the CRF. **Assessment of Severity**

The severity or intensity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of all AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, published on 27 November 2017.

If an AE cannot be graded using the CTCAE criteria, it should be graded using the following definitions:

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

Note: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Assessment of Causality

The Investigator will make a causality assessment about the relationship of each AE to study drug. Treatment-related conditions must be distinguished from disease-related conditions.

The Investigator should determine the causality (relation to the study drug) based on his/her clinical experience and on the information given in the Investigator’s Brochure. The causal relationship of all AEs to the study drug will be judged as either related (which includes possibly, probably or definitely related) or not related (which includes unlikely or doubtfully related).

To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

- A **related** causal relationship means that there is at least a reasonable possibility that the event is caused by the study drug or the research procedures. There may be a reasonable possibility of a causal relationship between study drug/Investigational Product (IP) and the AE when the event:

Follows a reasonable temporal sequence post IP administration

The event is known to be or could be a response to the IP, based upon pre-clinical or clinical data with the product or similar products

The event could not be explained by the subject's primary disease including progression/expression of the disease state, other concurrent or underlying illness, and/or prior/concomitant therapies

Positive dechallenge: the event resolves or improves after discontinuation of IP (when this information is available)

Positive rechallenge: the event reappears or worsens when dosing with IP is resumed after an interruption (when this information is available)

- **Not related** means there is unlikely to be a reasonable possibility of a causal relationship between the event and study drug/IP or the research procedures, and/or that there is a clear causal relationship between other conditions and the AE. There is not likely to be a reasonable possibility of a causal relationship between study drug/IP and the AE when:

The event does not follow a reasonable temporal sequence post IP administration

There are no data with the IP or similar products, suggesting the event occurs or may occur with the IP

There is a more likely alternative etiology, such as subject's underlying primary disease including disease progression or expression, other concurrent or underlying illness, or prior/concomitant therapies

Negative dechallenge: the event does not improve after discontinuation of IP (when this information is available)

Negative rechallenge: the event does not worsen after interruption of IP when dosing is resumed after an interruption (when this information is available)

Note: The Investigator's assessment of causality for individual AEs is part of the study documentation process and will be recorded in the patient's medical record, CRF, and SAE form, if applicable. AEs recorded without the Investigator's assessment of the relationship to study drug will be followed up until causality is assigned.

Suspected Unexpected Serious Adverse Reaction (SUSAR) means an SAE that occurs in a clinical trial subject, which is assessed by the Investigator or Ultragenyx as being serious and unexpected based on Reference Study Information (e.g., Investigators Brochure), and as having a reasonable possibility of a causal relationship with the study drug/IP.

Urgent Safety Measure means any measure taken to protect the subjects of a clinical trial against an immediate hazard to their health or safety.

APPENDIX 4. ADVERSE EVENT COLLECTION, ELICITING, RECORDING AND REPORTING

Collection Period & Reporting Timeframe: Adverse Event & Other Safety Information Reporting

Table 11: Collection Period and Reporting Timeframes for Adverse Event and Other Safety Information Reporting

Event Type	Collection Period	Reporting Timeframe	Report to:
Serious Adverse Event (SAE)	**Start:** From the time the subject signs the ICF **End:** Two months after the final administration of study drug	Report all SAEs within 24 hours of site Investigator, designee or site personnel's knowledge of the event.	Electronic Data Capture (primary) Ultragenyx (back-up if Electronic Data Capture is down or not available) email: ultragenyx@primevigilance.com Fax: 1 (415) 930-4033
Adverse Event (AE)	**Start:** From the time the subject signs the ICF **End:** Two months after the final administration of study drug	Report all non-serious AEs within a target of 3 business days of site Investigator, designee or site personnel's knowledge of the event.	Electronic Data Capture
Treatment-emergent adverse events (TEAEs)	**Start:** From the time the subject signs the ICF **End:** Two months after the final administration of study drug	Report all non-serious TEAEs within a target of 3 business days of site Investigator, designee or site personnel's knowledge of the event.	Electronic Data Capture
Pregnancy (includes Partner pregnancy)	**Start:** From the time the subject signs the ICF **End:** Two months after the final administration of study drug	Report all pregnancies within 24 hours of site Investigator, designee or site personnel's knowledge of the event	Electronic Data Capture (primary) Ultragenyx (back-up if Electronic Data Capture is down or not available) email: ultragenyx@primevigilance.com Fax: 1 (415) 930-4033
Adverse Events of Special Interest (AESI)	**Start:** From the time the subject signs the ICF **End:** Two months after the final administration of study drug	Report all AESI within 24 hours of site Investigator, designee or site personnel's knowledge of the event.	Electronic Data Capture (primary) Ultragenyx (back-up if Electronic Data Capture is down or not available) email: ultragenyx@primevigilance.com Fax: 1 (415) 930-4033

Table 12: Safety Contact Information

Global Drug Safety & Pharmacovigilance Serious Adverse Events, Adverse Events of Special Interest, and Pregnancy Reporting	Medical Monitor
Email: ultragenyx@primevigilance.com Fax: +1 (415) 930-4033	PPD, MD, MS PPD PPD

Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:

- "Since the last visit, has the patient experienced any health problems?"
- "Have there been any new or changed health problems since you were last here?"

Recording AEs and SAEs

All AEs (ie, any new condition or worsening in severity or frequency of a preexisting condition) experienced by the patient within the protocol defined timeframes must be promptly documented on the case report form (CRF) and SAE form if applicable. For clinically significant worsening of a preexisting condition from Baseline the changes will be documented as AEs on the CRF. Clinical significance is defined as any variation in signs, symptoms, or testing that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the assessment returns to Baseline or until the Investigator determines that follow-up is no longer medically necessary.

For IP and for non-IP studies, any AEs or SAEs considered associated with study protocol-required procedures will also be collected

The Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring documentation of the events is adequate. Details of the AEs must include severity, seriousness, relationship to study drug/IP, duration (dates of onset and resolution), and outcome.

In addition, the Investigator should report any AE or SAE they are made aware of that occurs after this time period and that is believed to have a reasonable possibility of being associated with study drug.

Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF and SAE form (if applicable) rather than individual signs and symptoms. Whenever medically appropriate, the Investigator should group signs or symptoms that constitute a single diagnosis into a unifying event term. For example, record "liver failure" rather than jaundice, asterixis, and elevated transaminases, or record "upper respiratory tract infection" rather than cough, rhinitis, and sneezing. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE on the CRF and SAE form (if applicable). If a diagnosis is subsequently established, it should be reported as follow-up information by revising the CRF and SAE form (if applicable). Vague, nonspecific AE terms such as "erythema," "rash," or "lump on head" should be avoided and more specific information

should be provided, such as “erythematous macule on right leg,” “allergic dermatitis,” or “scalp cyst.”

Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as the AE on the CRF and, if also serious, on the SAE form. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the CRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded individually on the CRF.

Abnormal Laboratory Values

Only clinically significant laboratory abnormalities in the opinion of the Investigator are to be recorded as AEs on the CRF and SAE form (if applicable). For example, abnormalities that require study drug dose modification, discontinuation of study drug, more frequent follow-up assessments, or further diagnostic investigation may be considered clinically significant by the Investigator.

If the clinical significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 × upper limit of normal associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded on the CRF and the SAE form (if applicable).

If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs on the CRF and SAE form (if applicable), unless their severity, seriousness, or etiology changes.

Reporting Serious Adverse Events

Any AE that meets SAE criteria must be reported to Ultragenyx or its designee within 24 hours of the site Investigator, designee or site personnel’s knowledge of the event. Regardless of causality, all SAEs must be reported during the time period specified. All SAEs must also be recorded in the patient’s source documentation and on the CRF. Copies of discharge summaries, consultant reports, and any other relevant documents should be provided with the SAE report when available.

If follow-up is obtained or requested by Ultragenyx and/or the Medical Monitor, the additional information should be sent within 24 hours of knowledge.

Refer to Safety Contact Information for SAE reporting.

Reporting of Pregnancy in Subject or Partner

For protocols requiring pregnancy reporting, any reported pregnancy of a subject or a subject's partner that occurs during participation in the study will be monitored for the full duration of the study and/or followed until the outcome of the pregnancy is known. In the event of a pregnancy in the partner of a subject, the Investigator should make every effort to obtain the female partner's consent for release of protected health information.

Pregnancy in a subject or subject's partner, complications of the pregnancy and the outcomes of pregnancy should be reported to the Ultragenyx or designee within 24 hours of site Investigator, designee or site personnel's knowledge of the event.

Pregnancies will be reported by completing and submitting Pregnancy Notification Form to Ultragenyx or designee.

Pregnancy outcomes will be reported by completing and submitting Pregnancy Outcome Form to Ultragenyx or designee.

The following pregnancy outcomes should always be classified as serious and reported to Ultragenyx or designee within 24 hours by completing and submitting the SAE and Pregnancy Outcome Form:

- Spontaneous abortion/Miscarriage
- Therapeutic abortion
- Ectopic pregnancy
- Fetal death/Still birth
- Molar pregnancy
- Birth defect/Congenital anomaly

Reporting Suspected Unexpected Serious Adverse Reactions

Ultragenyx or its designee will submit suspected unexpected serious adverse reactions (SUSARs) to appropriate Regulatory Authorities (including Competent Authorities in all Member States concerned), Institutional Review Boards /Independent Ethics Committees (IRBs/IECs), and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than seven calendar days of first knowledge of the event and follow-up information submitted within an additional eight days. All other SUSARs will be submitted within 15 calendar days of first knowledge of the event.

The Investigator will notify the IRBs/IECs of SUSAR, in accordance with IRB/IEC requirements and local laws and regulations.

Non-SUSARs will be maintained in the Ultragenyx global safety database and provided in annual safety reports and/or other aggregate periodic summary reports to Regulatory Authorities and IRBs/IECs per local laws and regulations.

Reporting Urgent Safety Measures

Investigators are required to report any urgent safety measures taken to protect the safety or welfare of subject to Ultragenyx or its designee within 24 hours. Ultragenyx or its designee will inform the Regulatory Authorities, IRBs/IECs, and other investigators of any events (eg, change to the safety profile of Investigational Product (IP), major safety findings) that may occur during the clinical study that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical study, as required, in accordance with applicable laws and regulations.

The Investigator will notify the IRBs/IECs of urgent safety measures, in accordance with IRB/IEC requirements and local laws and regulations.

APPENDIX 5. ETHICS AND CONDUCT

This protocol is written in accordance with the principles established by the 18th World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects and subsequent amendments and clarifications adopted by the General Assemblies (World Medical Association, 2013).

Ultragenyx and the Investigator will ensure the study described in this protocol is conducted in compliance with those principles and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable local law, eg, Food and Drug Administration (FDA) regulations, European Union (EU) regulations, and any other local ethical and regulatory requirements ("Applicable Study Conduct Obligations"). Should a conflict arise, Ultragenyx and the Investigator will follow whichever Applicable Study Conduct Obligations affords the greater protection to the subject(s).

Institutional Review Board or Independent Ethics Committee and Competent Health Authority

The Institutional Review Boards /Independent Ethics Committees (IRBs/IECs) must be a properly constituted board or committee operating in accordance with Applicable Study Conduct Obligations and should safeguard the rights, safety, and well-being of all study subjects. Before screening any subject, the IRB/IEC, and as applicable Competent Health Authority, must review and approve this protocol and if applicable, the associated assents and informed consent forms (ICFs), agreed to by the study site (ie, Institution) and by Ultragenyx. Further, IRB/IEC and Competent Health Authority approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, unless there is a need to protect subject safety. In that case and with prior IRB/IEC approval/favorable opinion, the Investigator may deviate from the protocol to eliminate an immediate hazard(s) to study subjects and will immediately notify the chair of the IRB/IEC and Ultragenyx of the amendment.

If Investigational product (IP) is provided under the protocol, IP will not be shipped to the study site until Ultragenyx or its designee has received a copy of the letter or certificate of approval/favorable opinion from the IRB/IEC, all Ultragenyx-required documents, and, where required, the Competent Health Authority authorization/approval of the protocol. If IP is not provided under the protocol, this paragraph and the section on IP accountability do not apply.

Before releasing advertisements or solicitations to the public for subject enrollment in the study, such advertisements or public solicitations must be submitted to Ultragenyx or its designee for review and approval. After receiving Ultragenyx approval for the advertisements or public solicitations, the Investigator must submit them to his/her IRB/IEC for review and approval before using them.

Subject Information and Consent

The contents of the ICF and any assents for minors, as well as the method of obtaining and documenting informed consent must comply with Applicable Study Conduct Obligations.

Ultragenyx or its designee will provide the Investigator written informed consent(s), which includes assents for minors. Any revisions to the ICF must be reviewed and approved by Ultragenyx before submission to the IRB/IEC for its approval. The study site agrees not to begin enrolling subjects until the IRB/IEC approval is complete.

Adequate consent for access to, use of, and/or processing of coded personal health information and other personally identifiable information will be obtained in accordance with the applicable laws, such as U.S. Health Insurance Portability and Accountability Act regulations, state data privacy laws, the EU General Data Protection Regulation, or other applicable national or local data usage and protection laws.

In accordance with applicable local laws and with the subject's express and optional consent, any remaining biological samples taken for the purposes of the study, as well as any voluntary samples, may be used by Ultragenyx for additional research and development in accordance with the subject's express consent. Any such consent will be optional and not a requirement to study participation.

Before conducting any study procedures, the Investigator must obtain informed consent for or from each potential subject. Part of obtaining that informed consent requires the Investigator to fully explain to each potential subject the methods, objectives, requirements, and potential risks of the study and to answer any inquiries. Further, the Investigator must explain to each potential subject that the subject is completely free to refuse to enter the study or to withdraw from the study at any time without either decision impacting his/her care. The Investigator or a qualified designee must be available to answer each subject's questions throughout the study, and all of the subject's questions must be answered to the subject's satisfaction.

Pediatric subjects or adult subjects with cognitive limitations will provide assent (if possible) and a legally authorized representative (parent or legal guardian) must provide informed consent for such subjects. If, over the course of the study, a pediatric subject becomes old enough for a subsequent assent or reaches the legal age of majority, he/she must sign the then-age-appropriate assent or consent as the case may be.

Subjects will be given a copy of the signed ICF and/or assent and will be provided any new information during the course of the study that might affect their continued participation in the study. If the protocol is amended and the ICF is revised, each subject as applicable will be required to provide informed consent again using the revised ICF. The signed ICF or assent will remain in each subject's study file and must be available to the study monitor(s) at all times.

Data Protection, Anonymization and Security

Any study data transferred to Ultragenyx will be coded and will not contain names or any other information that would make the subject identifiable.

Study information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Ultragenyx.

The subject must be informed that the Ultragenyx auditors or other authorized personnel appointed by Ultragenyx may examine his/her medical records. The same applies for appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Ultragenyx has a Standard Operating Procedure to address data breaches. Ultragenyx also requires all vendors supporting the study to comply with applicable data protection laws and to agree to data protection terms that include a data breach response plan and an obligation to collaborate with Ultragenyx. These measures exist so Ultragenyx can mitigate the breach and meet their obligations under applicable data protection laws.

Protocol Deviations

A protocol deviation is any instance of protocol noncompliance, either at study entry or during the study conduct. A major protocol deviation is defined by Ultragenyx as a having a significant impact on a clinical study data and subject rights, safety, or welfare. All other protocol deviations are considered minor protocol deviations.

Ultragenyx does not issue protocol deviation waivers. The Investigator must inform Ultragenyx of all protocol deviations in a timely manner; provided, however, that Ultragenyx be informed of all major Protocol deviations immediately of becoming aware of such deviations.

Future Use of Stored Study Samples

With the subject's consent, Ultragenyx will use remaining protocol-driven samples and/or will collect optional, non-protocol-required biologic samples to be used for additional future research. These samples will be de-identified and may be stored for up to 20 years from the end of the study, or shorter as required by local law.

Investigators and Study Administrative Structure

Prior to the Investigator beginning performance of the study, Ultragenyx must be in receipt of all essential documents, including, among others, a signed Form Food and Drug Administration (FDA) 1572 or equivalent signed by the Investigator and an appropriate Financial Disclosure Form from each.

A Coordinating Investigator will be identified for multicenter studies. The Coordinating Investigator will be selected on the basis of active participation in the study, thorough knowledge of the therapeutic area being studied, and the ability to interpret data. The Coordinating Investigator will read and sign the Clinical Study Report.

Investigational Product Accountability

The Investigator must be thoroughly familiar with the appropriate administration and potential risks of administration of the IP, as described in this protocol and the Investigator Brochure (IB), prior to initiation of the study.

IP delivered to the study site and/or Investigator must be stored in a secure limited access location at controlled temperature as described in the Investigator's Brochure and product packaging. Any such location must be available for inspection by the study monitor or auditors for inspection at any time during the study. If subjects take IP offsite, they will be given instructions on the proper storage of IP when initially dispensed and reminded of storage requirements at all subsequent visits.

An IP accountability record must be maintained for all IP received, dispensed, returned, destroyed, and/or lost during the study. This record must be kept current and made available to the study monitor or auditors for inspection. At the completion of the study, all unused IP must be returned to Ultragenyx and/or its designee, unless other instructions have been provided for final disposition of the IP.

Data Handling and Record Keeping

Case Report Forms and Source Documents

The Investigator is required to initiate and maintain, for each subject, an adequate and accurate case history that records all observations and other data related to the study for that subject. Data must be recorded on Case Report Forms (CRFs), electronic or otherwise, in accordance with the Clinical Trial Agreement executed between Ultragenyx and the study site and/or Investigator. Recorded data is subject to Ultragenyx verification. All information recorded on CRFs must be consistent with the subject's source documentation. For electronic CRFs, a validated Electronic Data Capture system will be used for entry of the data.

Data entry and data corrections will be made only by Ultragenyx-authorized users, and will be captured in an electronic audit trail. All data entered in to the CRF must be verifiable; therefore, CRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records by Ultragenyx or its designee. The Investigator must allow Ultragenyx or its designee direct access to all source documents.

Data Quality Assurance

Monitoring and auditing procedures will be implemented to ensure compliance with Applicable Study Conduct Obligations. The Ultragenyx designated representative (i.e., the site monitor) will contact the Investigator and conduct regular visits to the study site. The site monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. Instances of missing or uninterpretable data will be resolved in coordination with the Investigator.

The site monitor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The site monitor will maintain contact through frequent direct communications with the study site by e-mail, telephone, facsimile, and/or mail. The Investigator and all other personnel supporting the study (ie, Project Personnel) must agree to cooperate fully with the site monitor and will work in good faith with the site monitor to resolve all questions raised and all identified issues.

Record Retention

For study monitoring, audit, or inspection, the IRB/IEC and Ultragenyx or its designees have the right to access all CRFs, source documents, and other study documentation. The Investigator or study site will retain such documents from the start of the study to at least 25 years after the close of the study, guarantee access to these documents and cooperate with and support such audits and inspections.

Publication Policy

The Investigator and/or study site must submit any publication or presentation about the study to Ultragenyx prior to making it public in accordance with the process in the Clinical Trial Agreement executed between Ultragenyx and the study site and/or Investigator.

Registration of Study and Disclosure of Results

Ultragenyx will register the study and post results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

Budgeting and Insurance

The budget and insurance for this clinical study will be addressed in the Clinical Trial Agreement between Ultragenyx and the study site and/or Investigator executed between Ultragenyx and the study site and/or Investigator.

STATEMENT OF COMPLIANCE

Protocol Title: A Phase 2b, Multicenter, Long-term Extension Study of Setrusumab in Adults with Type I, III, or IV Osteogenesis Imperfecta**Protocol Number:** UX143-CL203 dated 01 December 2021

INVESTIGATOR SIGNATURE:

I have read the Protocol and agree to conduct the study as detailed in this protocol and in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP), and all applicable regulatory requirements and guidelines.

Investigator Signature Date

Printed Name: _____

SPONSOR SIGNATURE:

As the Sponsor representative, I confirm that Ultragenyx Pharmaceutical Inc will comply with all Sponsor obligations as detailed in this protocol and in compliance with the Declaration of Helsinki, GCP, and all applicable regulation requirements and guidelines. I will ensure that the Investigator is informed of all relevant information that becomes available during the conduct of this study.

PPD , MD Date
PPD , Global Clinical Development
Ultragenyx Pharmaceutical Inc.