An Operationally Seamless, Randomized Phase 2/3 Study Consisting of a Phase 2 Single Blind, Dose-Evaluation Phase and a Phase 3 Double-Blind, Placebo-controlled Phase to Assess the Efficacy and Safety of Setrusumab in Subjects with Osteogenesis Imperfecta

Published: 08-02-2023
Last updated: 05-10-2024

This study has been transitioned to CTIS with ID 2024-510919-29-00 check the CTIS register for the current data. OBJECTIVES - Phase 2 (not to be conducted in NL):Phase 2 Primary Objective:- Identify a setrusumab dosing strategy in subjects with OI…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON53714

Source
ToetsingOnline

Brief title
UX143-CL301 'ORBIT' (ICON 3106/0040)

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
Brittle bone syndrome; inherited (genetic) bone disorder that is present at birth

Research involving
Human

Sponsors and support

Primary sponsor: Ultragenyx Pharmaceutical Inc.
Source(s) of monetary or material Support: Ultragenyx Pharmaceutical Inc.

Intervention

Keyword: Minors and young adults with OI, Phase 2/3, Setrusumab

Outcome measures

Primary outcome

Primary Endpoint - Phase 2 (not to be conducted in NL):

- Percent change in serum P1NP from Baseline at Month 1

Primary Endpoint - Phase 3:

- Annualized rate of all radiographically-confirmed fractures, excluding morphometric vertebral fractures (footnote a) and fractures of the fingers, toes, face, and skull, during the double-blind (DB) Treatment Period.

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Footnote:

a. Morphometric vertebral fractures are identified by a change from baseline in the Genant semi-quantitative scoring based on an annual vertebral radiograph.

Secondary outcome

SECONDARY ENDPOINTS - Phase 2 (not to be conducted in NL):

(1) Serum setrusumab concentration at scheduled time points

(2a) Baseline-corrected AUEC for serum P1NP over a 1- and 2-month timeframe

(2b) Percent change from Baseline in bone turnover markers (P1NP and OCN) over time

(3a) Change from Baseline in DXA lumbar spine BMD z-scores over time

(3b) Percent change from Baseline in DXA lumbar spine BMD over time

(4) Frequency, severity, and relationship to treatment of TEAEs, SAEs, and AESIs

(5) Incidence of anti-setrusumab binding and neutralizing antibodies at scheduled time points

SECONDARY ENDPOINTS - Phase 3:

(1a) Annualized rate of all radiographically-confirmed fractures, excluding morphometric vertebral fractures (footnote a), but including fractures of the fingers, toes, face and skull, during the DB Treatment Period

(1b) Annualized rate of all radiographically-confirmed fractures during the DB Treatment Period

(2) Change from Baseline in DXA lumbar spine BMD z-score at 12 months

(3) Change from Baseline at 12 months for:

• POSNA-PODCI Sports/Physical Functioning and Pain/comfort subscale scores for subjects <= 18 years of age at screening

• SF-36 PF and BP Domain Scales for subjects >= 18 years of age at screening

(4) Frequency, severity, and relationship to treatment of TEAEs, SAEs, and AESIs

(5) Incidence of binding and neutralizing anti-setrusumab antibodies at

scheduled time points

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Abbreviations:

AUEC, area under the effect curve;

AESI, adverse event of special interest;

BMD, bone mineral density;

DB, double-blind;

DXA, dual-energy X-ray absorptiometry;

OCN, osteocalcin;

OI, osteogenesis imperfecta;

P1NP, amino-terminal propeptide of type 1 procollagen;

PD, pharmacodynamic;

PK, pharmacokinetic;

SAE, serious adverse event;

TEAE, treatment-emergent adverse event

Study description

Background summary

[Protocol Amendment 3, 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 [of the protocol], there are no FDA- or EMA-approved treatments 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. 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 (Cardinal et al., 2019). 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 [of the protocol], 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 support the evaluation of setrusumab safety and efficacy in pediatric and adult patients with OI. The underlying disease pathology of OI is similar in children and adults, though fracture rates in OI patients are highest during childhood, similar improvements in bone mass and reductions in fracture risk are expected across ages. The rationale for the use of setrusumab in children and adults with OI is to facilitate bone building and decrease the risk of fractures and

fracture-related sequelae.

[Protocol Amendment 3, 7.1.3. Rationale for Study Design, extract from 'Phase 3-specific Rationale']
Based on its mechanism of action of increasing BMD and bone formation as demonstrated in adults with OI, it is hypothesized that setrusumab treatment will reduce fractures over time in the proposed study population.

Study objective

This study has been transitioned to CTIS with ID 2024-510919-29-00 check the CTIS register for the current data.

OBJECTIVES - Phase 2 (not to be conducted in NL):

Phase 2 Primary Objective:
- Identify a setrusumab dosing strategy in subjects with OI

Phase 2 Secondary Objectives:
- Evaluate the PK of setrusumab doses in subjects with OI
- Determine the PD effects of setrusumab on bone formation and turnover markers
- Evaluate the effect of setrusumab on lumbar spine BMD (bone mineral density)
- Evaluate the safety profile of setrusumab for the treatment of subjects with OI
- Evaluate the immunogenicity of setrusumab for the treatment of subjects with OI

OBJECTIVES - Phase 3:

Phase 3 Primary Objective:
- Evaluate the effect of setrusumab vs placebo on reduction in fracture rate, excluding morphometric vertebral fractures and fractures of the fingers, toes, face, and skull

Phase 3 Secondary Objectives:
- Evaluate the effect of setrusumab vs placebo on reduction in fracture rate
- Evaluate the effect of setrusumab vs placebo on lumbar spine BMD
- Evaluate the effect of setrusumab vs placebo on functional assessments and patient-/caregiver-reported health-related quality of life, including pain
- Evaluate the effect of setrusumab vs placebo on clinical outcome assessments including subject-/caregiver-reported assessments of physical function, pain, and health-related quality of life
- Assess the safety profile of setrusumab
- Evaluate the immunogenicity of setrusumab for the treatment of subjects with

OI

Study design

UX143-CL301 is an operationally seamless Phase 2/3 study that consists of a randomized single blind, Phase 2 dose-evaluation phase and a Phase 3 double-blind (DB), placebo-controlled phase to evaluate the efficacy and safety of setrusumab in OI subjects 5 to < 26 years of age. Phase 2 and Phase 3 consist of separate and distinct subject cohorts, and data will be analyzed separately in the primary analysis for each phase (refer to protocol, Section 11).

In Phase 2, subjects will be randomized 1:1 to receive 20 or 40 mg/kg setrusumab intravenously once a month (QM); subjects and Investigators will be blinded to setrusumab dose. The Phase 2 primary analysis will evaluate pharmacokinetics (PK), pharmacodynamic (PD) and safety data from the early part of Phase 2 to determine the dosing strategy for initiation of Phase 3 and the Phase 2 open-label Treatment Extension Period. After a dosing strategy has been determined, a separate cohort of subjects will be randomized 2:1 into Phase 3 to receive setrusumab or placebo throughout the double-blind (DB), placebo-controlled period, after which subjects will transition to the open-label Treatment Extension Period. After initiation of Phase 3, the two phases will be conducted in parallel to the end of the study. An optional substudy will be conducted in approximately 10 subjects (>= 8 years) consisting of a bone biopsy following at least 12 months of setrusumab exposure to investigate the impact of setrusumab on bone histomorphology.

Intervention

Interventions (footnote a)

SETRUSUMAB

Dose Formulation: 160 mg lyophilized powder for solution
Unit Dose Strength(s)/Dosage Level(s):
- Phase 2 (not in NL): 20 mg/kg or 40 mg/kg through the Phase 2 primary analysis; 20 mg/kg (footnote b)
- Phase 3: 20 mg/kg (footnote b)
Route of Administration: IV infusion over 60 minutes (footnote c)
Use: Experimental
Frequency: Once a month (QM)

PLACEBO

Dose Formulation: Dextrose / glucose 5% solution in water
Unit Dose Strength(s)/Dosage Level(s): N/A

Route of Administration: IV infusion over 60 minutes (footnote c)
Use: Placebo comparator
Frequency: Once a month (QM)

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Footnotes:
a. During Phase 2 and Phase 3, subjects may receive supplementation with calcium and vitamin D, if needed, as directed by the treating physician.
b. 20 mg/kg is the selected dosing strategy for Phase 3 and Phase 2 open-label extension period (OLE); all Phase 2 subjects transition to 20 mg/kg after the last Phase 2 subject completes the Month 6 study visit. Dose selection took into consideration all PD, PK, safety, and available BMD data through Month 2, including the primary endpoint of percent change from Baseline in serum P1NP at Month 1.
c. The infusion rate may be adjusted to extend the infusion time (eg, based on subject*s history with any infusions), and/or the infusion interrupted or discontinued for clinical safety concerns (eg, infusion-related reaction) at any time at the discretion of the Investigator.

Study burden and risks

The potential benefits of setrusumab are based on initial efficacy results seen in clinical trials....
The potential risks of setrusumab are based on nonclinical studies and results seen in clinical trials.

The study has been carefully designed to minimize potential risks of treatment with setrusumab (details are given in the Protocol, 5.5. Risk Minimization). During the design of this clinical study, efforts were made to minimize burden on subjects during the study (details are given in the Protocol, 5.6. Measures Taken to Minimize Subject Burden).

Potential risks and benefits are detailed in the protocol:
5.4. Potential Risks and Benefits
5.4.1. Potential Benefits
5.4.2. Potential Risks
5.4.2.1 Nonclinical Summary
5.4.2.2. Potential Clinical Risks

The 'Benefit Risk Conclusion' is provided in the protocol, Section 5.4.3.:
Taking into account measures to minimize risk to subjects in this study (protocol, Section 5.5), the potential risks in association with setrusumab are justified by the anticipated benefits that may be afforded to subjects with OI.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

1. Males and females 5 to < 26 years of age at time of informed consent
2. Diagnosis of OI Type I, III, or IV as confirmed by identification of pathogenic or likely pathogenic genetic variants in COL1A1 or COL1A2. If a variant of uncertain significance is identified, then clinical presence of the expected phenotype can be used to confirm the diagnosis.
3. >= 1 fracture in the past 12 months, >= 2 fractures in the past 24 months, or >= 1 tibia, femur, or humerus fracture in the past 24 months
4. Serum 25-hydroxyvitamin D >= 20 ng/mL at the Screening Visit. If 25-hydroxyvitamin D levels are below 20 ng/mL, 25-hydroxyvitamin D testing can be repeated after a minimum of 14 days of vitamin D supplementation as directed

by the treating physician
5. Willing to not receive bisphosphonate therapy during the study
6. From the period following informed consent to 60 days after the last dose of study drug, females of childbearing potential and fertile males must consent to use highly effective contraception. If female, agree not to become pregnant. If male, agree not to father a child or donate sperm
7. Willing and able to provide informed consent for subjects >= 18 years of age, or provide assent (if possible) and have a legally authorized representative provide informed consent, after the nature of the study has been explained and prior to any research-related procedures
8. Willing to provide access to medical records for the collection of radiographic data, fracture data, growth data, and disease history
9. Must, in the opinion of the Investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule, and comply with the assessments

Exclusion criteria

1. For Phase 2 subjects only, a history of major bone surgery within the previous 6 months prior to Screening or planned major bone surgery for the first 3 months of the study
2. History of skeletal malignancies or bone metastases at any time
3. History of neural foraminal stenosis (except if due to scoliosis)
4. Clinically unstable manifestations of Chiari malformation or basilar invagination within the past 2 years. Presence of any other neurologic disease that has been clinically unstable within past 2 years requires review by the Medical Monitor.
5. History of or uncontrolled concomitant diseases such as hypo/hyperparathyroidism, Paget*s disease, abnormal thyroid function, thyroid disease or other endocrine disorders or conditions that could affect bone metabolism
6. Rickets or any skeletal condition (other than OI) leading to bone deformities and/or increased risk of fractures
7. History of stroke, myocardial infarction, TIA, or angina. 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.
8. Hypocalcemia, defined as serum calcium levels below the age-adjusted normal limits after a >= 4 hour fast
9. Estimated glomerular filtration rate < 29 mL/min/1.73 m2
10. Prior treatment with the following:
a. Teriparatide, growth hormone, or other bone anabolic or anti-resorptive medications within 6 months of the first dose of study drug (Month 0)

b. Denosumab within 24 months of the first dose of study drug (Month 0)
c. Romosozumab at any time
11. Documented alcohol and/or drug abuse within 12 months prior to dosing or evidence of such abuse, as determined by the Investigator
12. 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
13. Known hypersensitivity to setrusumab or its excipients that, in the judgment of the Investigator, places the subject at increased risk for adverse effects
14. History of external radiation therapy
15. Pregnant or breastfeeding or planning to become pregnant (self or partner) at any time during the study
16. Use of any investigational product or investigational medical device within 4 weeks or 5 half-lives of investigational drug (whichever is longer) prior to Screening, or during the study (per discretion of the Investigator in consultation with the Medical Monitor)
17. Concurrent participation in another clinical study without prior approval from the Investigator in consultation with the Medical Monitor

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-11-2023
Enrollment:	4
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	n/a
Generic name:	Setrusumab

Ethics review

Approved WMO Date:	08-02-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	18-04-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2024
Application type:	Amendment

Review commission: METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-510919-29-00
EudraCT	EUCTR2021-006597-23-NL
ClinicalTrials.gov	NCT05125809
CCMO	NL83275.041.23