Clinical trial results:
A long-term follow-up study to assess bone mineral density in subjects with uterine fibroids completing the Phase 3 studies of linzagolix, PRIMROSE 1 or PRIMROSE 2

Summary

EudraCT number	2021-000452-19
Trial protocol	HU PL LV BG RO
Global end of trial date	14 November 2022

Results information

Result version number	v1 (current)
This version publication date	18 November 2023
First version publication date	18 November 2023

Trial information

Trial identification

Sponsor protocol code	20-OBE2109-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kissei Pharmaceutical Co., Ltd.
Sponsor organisation address	3-1-3 Koishikawa, Bunkyo-ku, Tokyo, Japan, 112-0002
Public contact	Kissei Pharmaceutical Co., Ltd., Clinical Projects Management, rinsyousiken@pharm.kissei.co.jp
Scientific contact	Kissei Pharmaceutical Co., Ltd., Clinical Projects Management, rinsyousiken@pharm.kissei.co.jp

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to describe BMD changes for up to 24 months following previous treatment with placebo or linzagolix at 100 mg or 200 mg alone or with ABT for at least 20 weeks in the context of the PRIMROSE 1 and PRIMROSE 2 studies.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (adopted Version Fortaleza, Brazil October 2013) as well as with the valid national law(s) of the participating countries, with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP, the US Code of Federal Regulations or the EU Clinical Trial Directive and applicable local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Ukraine: 11
Country: Number of subjects enrolled	United States: 75
Worldwide total number of subjects	134
EEA total number of subjects	48

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	134
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 3 sites in Bulgaria, 4 sites in Czech Republic, 4 sites in Hungary, 1 site in Latvia, 6 sites in Poland, 1 site in Romania, 5 sites in Ukraine and 32 sites in the US.

Pre-assignment

Screening details:

Of the 137 screened subjects, 134 were enrolled, and 130 were included in SS. Although this study consists of 7 arms, the values of "LGX 200 mg + AB Placebo" group is not included in the below tables because it consists of only 1 subject. Therefore, the No. of "Started" subjects of Period 1 are equal to neither the No. of SS nor enrolled subjects.

Period 1

Period 1 title	For BMD and Safety Evaluation (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LGX Placebo + AB Placebo

Arm description:

Linzagolix Placebo + Add-back Placebo for 52 weeks

Arm type	Placebo
Investigational medicinal product name	Linzagolix placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Linzagolix: 0 mg

Investigational medicinal product name	E2/NETA placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ESTRADIOL HEMIHYDRATE: 0 mg
NORETHISTERONE ACETATE: 0 mg

Arm title	LGX Placebo + AB Placebo / LGX 200 mg + AB

Arm description:

Linzagolix Placebo + Add-back Placebo for 24 weeks, then Linzagolix 200 mg + Add-back for 28 weeks

Arm type	Experimental
Investigational medicinal product name	Linzagolix placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Linzagolix: 0 mg

Investigational medicinal product name	E2/NETA placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ESTRADIOL HEMIHYDRATE: 0 mg
NORETHISTERONE ACETATE: 0 mg

Investigational medicinal product name	Linzagolix
Investigational medicinal product code	
Other name	OBE2109
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Linzagolix: 100 mg X 2

Investigational medicinal product name	E2/NETA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ESTRADIOL HEMIHYDRATE: 1 mg
NORETHISTERONE ACETATE: 0.5 mg

Arm title	LGX 100 mg + AB Placebo

Arm description:

Linzagolix 100 mg + Add-back Placebo for 52 weeks

Arm type	Experimental
Investigational medicinal product name	Linzagolix
Investigational medicinal product code	
Other name	OBE2109
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Linzagolix: 100 mg

Investigational medicinal product name	E2/NETA placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ESTRADIOL HEMIHYDRATE: 0 mg
NORETHISTERONE ACETATE: 0 mg

Arm title	LGX 100 mg + AB

Arm description:

Linzagolix 100 mg + Add-back for 52 weeks

Arm type	Experimental
Investigational medicinal product name	Linzagolix
Investigational medicinal product code	
Other name	OBE2109
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details: Linzagolix: 100 mg	
Investigational medicinal product name	E2/NETA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: ESTRADIOL HEMIHYDRATE: 1 mg NORETHISTERONE ACETATE: 0.5 mg	
Arm title	LGX 200 mg + AB Placebo / LGX 200 mg + AB
Arm description: Linzagolix 200 mg + Add-back Placebo for 24 weeks, then Linzagolix 200 mg + Add-back for 28 weeks	
Arm type	Experimental
Investigational medicinal product name	Linzagolix
Investigational medicinal product code	
Other name	OBE2109
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Linzagolix: 100 mg X 2	
Investigational medicinal product name	E2/NETA placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: ESTRADIOL HEMIHYDRATE: 0 mg NORETHISTERONR ACETATE: 0 mg	
Investigational medicinal product name	E2/NETA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: ESTRADIOL HEMIHYDRATE: 1 mg NORETHISTERONE ACETATE: 0.5 mg	
Arm title	LGX 200 mg + AB
Arm description: Linzagolix 200 mg + add-back for 52 weeks	
Arm type	Experimental
Investigational medicinal product name	Linzagolix
Investigational medicinal product code	
Other name	OBE2109
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Linzagolix: 100 mg X 2	
Investigational medicinal product name	E2/NETA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule

Routes of administration	Oral use

Dosage and administration details:

ESTRADIOL HEMIHYDRATE: 1 mg
NORETHISTERONE ACETATE: 0.5 mg

Number of subjects in period 1[1]	LGX Placebo + AB Placebo	LGX Placebo + AB Placebo / LGX 200 mg + AB	LGX 100 mg + AB Placebo
Started	7	26	22
Completed	7	23	16
Not completed	0	3	6
Consent withdrawn by subject	-	-	2
Special military situation in Ukraine	-	3	1
Lost to follow-up	-	-	2
Facility closed	-	-	1

Number of subjects in period 1[1]	LGX 100 mg + AB	LGX 200 mg + AB Placebo / LGX 200 mg + AB	LGX 200 mg + AB
Started	23	30	21
Completed	21	23	19
Not completed	2	7	2
Consent withdrawn by subject	2	3	1
Special military situation in Ukraine	-	1	1
Lost to follow-up	-	2	-
Facility closed	-	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 134 subjects were enrolled in the study and 130 subjects were used in BMD and Safety evaluation, and the remaining four subjects were excluded because no DXA data were obtained during the study.
Moreover, because the LGX 200mg group was excluded from reporting group, one subject of this group is not presented in the below tables.

Baseline characteristics

Reporting groups	
Reporting group title	LGX Placebo + AB Placebo
Reporting group description:	
Linzagolix Placebo + Add-back Placebo for 52 weeks	
Reporting group title	LGX Placebo + AB Placebo / LGX 200 mg + AB
Reporting group description:	
Linzagolix Placebo + Add-back Placebo for 24 weeks, then Linzagolix 200 mg + Add-back for 28 weeks	
Reporting group title	LGX 100 mg + AB Placebo
Reporting group description:	
Linzagolix 100 mg + Add-back Placebo for 52 weeks	
Reporting group title	LGX 100 mg + AB
Reporting group description:	
Linzagolix 100 mg + Add-back for 52 weeks	
Reporting group title	LGX 200 mg + AB Placebo / LGX 200 mg + AB
Reporting group description:	
Linzagolix 200 mg + Add-back Placebo for 24 weeks, then Linzagolix 200 mg + Add-back for 28 weeks	
Reporting group title	LGX 200 mg + AB
Reporting group description:	
Linzagolix 200 mg + add-back for 52 weeks	

Reporting group values	LGX Placebo + AB Placebo	LGX Placebo + AB Placebo / LGX 200 mg + AB	LGX 100 mg + AB Placebo
Number of subjects	7	26	22
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	26	22
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	39.9	42.2	43.9
standard deviation	± 9.0	± 6.3	± 4.2
Gender categorical Units: Subjects			
Female	7	26	22
Male	0	0	0

Reporting group values	LGX 100 mg + AB	LGX 200 mg + AB Placebo / LGX 200 mg + AB	LGX 200 mg + AB

Number of subjects	23	30	21
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	23	30	21
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	43.0	41.6	44.7
standard deviation	± 5.4	± 5.7	± 5.0
Gender categorical Units: Subjects			
Female	23	30	21
Male	0	0	0

Reporting group values	Total		
Number of subjects	129		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	129		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	129		
Male	0		

End points

End points reporting groups

Reporting group title	LGX Placebo + AB Placebo
Reporting group description: Linzagolix Placebo + Add-back Placebo for 52 weeks	
Reporting group title	LGX Placebo + AB Placebo / LGX 200 mg + AB
Reporting group description: Linzagolix Placebo + Add-back Placebo for 24 weeks, then Linzagolix 200 mg + Add-back for 28 weeks	
Reporting group title	LGX 100 mg + AB Placebo
Reporting group description: Linzagolix 100 mg + Add-back Placebo for 52 weeks	
Reporting group title	LGX 100 mg + AB
Reporting group description: Linzagolix 100 mg + Add-back for 52 weeks	
Reporting group title	LGX 200 mg + AB Placebo / LGX 200 mg + AB
Reporting group description: Linzagolix 200 mg + Add-back Placebo for 24 weeks, then Linzagolix 200 mg + Add-back for 28 weeks	
Reporting group title	LGX 200 mg + AB
Reporting group description: Linzagolix 200 mg + add-back for 52 weeks	

Primary: Change in Lumbar Spine BMD at 24 Months from Post-treatment Baselinee

End point title	Change in Lumbar Spine BMD at 24 Months from Post-treatment Baselinee[1]
End point description:	
End point type	Primary
End point timeframe: 24 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point.

End point values	LGX Placebo + AB Placebo	LGX Placebo + AB Placebo / LGX 200 mg + AB	LGX 100 mg + AB Placebo	LGX 100 mg + AB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	20	15	17
Units: g/cm2				
arithmetic mean (standard deviation)	0.120 (± 1.848)	-0.375 (± 4.187)	1.477 (± 5.935)	1.507 (± 6.771)

End point values	LGX 200 mg + AB Placebo / LGX 200 mg +	LGX 200 mg + AB		

	AB			
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	18		
Units: g/cm2				
arithmetic mean (standard deviation)	3.173 (± 5.885)	-0.319 (± 4.083)		

Statistical analyses

No statistical analyses for this end point

Primary: Change in Femoral Neck BMD at 24 Months from Post-treatment Baseline

End point title	Change in Femoral Neck BMD at 24 Months from Post-treatment Baseline[2]

End point description:

End point type	Primary

End point timeframe:

24 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point.

End point values	LGX Placebo + AB Placebo	LGX Placebo + AB Placebo / LGX 200 mg + AB	LGX 100 mg + AB Placebo	LGX 100 mg + AB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	21	15	17
Units: g/cm2				
arithmetic mean (standard deviation)	3.230 (± 7.789)	-2.071 (± 10.565)	1.236 (± 6.635)	-0.113 (± 5.861)

End point values	LGX 200 mg + AB Placebo / LGX 200 mg + AB	LGX 200 mg + AB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: g/cm2				
arithmetic mean (standard deviation)	1.643 (± 4.749)	-1.259 (± 3.352)		

Statistical analyses

No statistical analyses for this end point

Primary: Change in Total Hip BMD at 24 Months from Post-treatment Baseline

End point title	Change in Total Hip BMD at 24 Months from Post-treatment Baseline[3]

End point description:

End point type	Primary

End point timeframe:

24 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point.

End point values	LGX Placebo + AB Placebo	LGX Placebo + AB Placebo / LGX 200 mg + AB	LGX 100 mg + AB Placebo	LGX 100 mg + AB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	21	15	17
Units: g/cm2				
arithmetic mean (standard deviation)	5.263 (± 5.548)	-2.633 (± 9.196)	0.431 (± 3.337)	-0.377 (± 3.842)

End point values	LGX 200 mg + AB Placebo / LGX 200 mg + AB	LGX 200 mg + AB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: g/cm2				
arithmetic mean (standard deviation)	1.559 (± 4.431)	0.697 (± 4.951)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: Up to 24 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	LGX Placebo + AB Placebo
Reporting group description: -	
Reporting group title	LGX Placebo + AB Placebo / LGX 200 mg + AB
Reporting group description: -	
Reporting group title	LGX 100 mg + AB Placebo
Reporting group description: -	
Reporting group title	LGX 100 mg + AB
Reporting group description: -	
Reporting group title	LGX 200 mg + AB Placebo / LGX 200 mg + AB
Reporting group description: -	
Reporting group title	LGX 200 mg + AB
Reporting group description: -	

Serious adverse events	LGX Placebo + AB Placebo	LGX Placebo + AB Placebo / LGX 200 mg + AB	LGX 100 mg + AB Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 26 (0.00%)	0 / 22 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	LGX 100 mg + AB	LGX 200 mg + AB Placebo / LGX 200 mg + AB	LGX 200 mg + AB
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 30 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	LGX Placebo + AB Placebo	LGX Placebo + AB Placebo / LGX 200 mg + AB	LGX 100 mg + AB Placebo
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 7 (0.00%)	0 / 26 (0.00%)	0 / 22 (0.00%)

Non-serious adverse events	LGX 100 mg + AB	LGX 200 mg + AB Placebo / LGX 200 mg + AB	LGX 200 mg + AB
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 23 (0.00%)	0 / 30 (0.00%)	0 / 21 (0.00%)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: This is a long-term follow-up study, and no procedure-related AE during the study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported