



Clinical trial results:

A randomized, double-blind, placebo-controlled, phase 2b dose-ranging study to assess the efficacy and safety of OBE2109 in subjects with endometriosis associated pain.

Summary

EudraCT number	2016-001736-35
Trial protocol	PL
Global end of trial date	04 September 2019

Results information

Result version number	v1 (current)
This version publication date	20 May 2021
First version publication date	20 May 2021

Trial information

Trial identification

Sponsor protocol code	15-OBE2109-001
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ObsEva SA
Sponsor organisation address	12, Chemin des Aulx, Plan-les-Ouates, Geneva, Switzerland, 1228
Public contact	Clinical Trials Information, ObsEva SA, clinicaltrials@obseva.ch
Scientific contact	Clinical Trials Information, ObsEva SA, clinicaltrials@obseva.ch

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	04 November 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of a range of oral doses of linzagolix versus placebo, in reducing pelvic pain in subjects with moderate to severe endometriosis pain.

To assess the safety and tolerability of linzagolix in subjects with endometriosis.

Protection of trial subjects:

This study was performed in accordance with the protocol, the Declaration of Helsinki, the ICH Harmonised Tripartite Guideline for GCP, and all applicable local regulatory requirements.

Subjects read and understood the Informed Consent Form (ICF) and voluntarily agreed to participation in this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 67
Country: Number of subjects enrolled	Ukraine: 73
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	United States: 177
Worldwide total number of subjects	328
EEA total number of subjects	67

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)	328
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 328 females were randomized at 62 sites in 4 countries: 48 sites in USA (177 subjects), 5 sites in Poland (67 subjects), 5 sites in Ukraine (73 subjects) and 4 sites in Russia (11 subjects).

Pre-assignment

Screening details:

716 subjects were screened and 328 were randomized; 327 were included in the safety set (1 not included as didn't receive study treatment). 323 subjects were included in the FAS, 5 randomized subjects were excluded: 1 as per the safety set and 4 were prematurely discontinued at one US site due to the site's serious non-compliance to the protocol.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Linzagolix 50 mg
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Arm description:

50 mg linzagolix, once daily for 12 weeks.

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

Dosage and administration details:

Study drug was taken at approximately the same time every morning (1 tablet of 50 mg). To maintain the blind, placebo tablet was also administered.

Arm title	Linzagolix 75 mg
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Arm description:

75 mg linzagolix, once daily for 12 weeks.

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

Dosage and administration details:

Study drug was taken at approximately the same time every morning (1 tablet of 75 mg). To maintain the blind, placebo tablet was also administered.

Arm title	Linzagolix 100 mg
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Arm description:

100 mg linzagolix, once daily for 12 weeks.

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

Dosage and administration details:

Study drug was taken at approximately the same time every morning (1 tablet of 100 mg). To maintain the blind, placebo tablet was also administered.

Arm title	Linzagolix 200 mg
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Arm description:

200 mg linzagolix, once daily for 12 weeks.

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

Dosage and administration details:

Two tablets of 100 mg linzagolix. Study drug was taken at approximately the same time every morning.

Arm title	Placebo
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Arm description:

Placebo, once daily for 12 weeks.

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

Dosage and administration details:

Two placebo tablets were taken at approximately the same time every morning.

Number of subjects in period 1^[1]	Linzagolix 50 mg	Linzagolix 75 mg	Linzagolix 100 mg
Started	49	114	51
Completed	45	104	45
Not completed	4	10	6
Consent withdrawn by subject	2	4	1
Adverse event, non-fatal	2	5	3
Dosing compliance issue	-	1	-
Sponsor request	-	-	1
Lost to follow-up	-	-	-
Protocol deviation	-	-	1

Number of subjects in period 1^[1]	Linzagolix 200 mg	Placebo
Started	56	53

Completed	49	45
Not completed	7	8
Consent withdrawn by subject	3	5
Adverse event, non-fatal	3	1
Dosing compliance issue	-	-
Sponsor request	-	-
Lost to follow-up	1	2
Protocol deviation	-	-

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: The number of subjects reported to be in the baseline period are as per the FAS.

328 subjects were randomized, 323 subjects were included in the FAS; 5 randomized subjects were excluded: 1 didn't receive study treatment and 4 subjects were prematurely discontinued at one US site due to the site's serious non-compliance to the protocol.

Baseline characteristics

Reporting groups

Reporting group title	Linzagolix 50 mg
Reporting group description: 50 mg linzagolix, once daily for 12 weeks.	
Reporting group title	Linzagolix 75 mg
Reporting group description: 75 mg linzagolix, once daily for 12 weeks.	
Reporting group title	Linzagolix 100 mg
Reporting group description: 100 mg linzagolix, once daily for 12 weeks.	
Reporting group title	Linzagolix 200 mg
Reporting group description: 200 mg linzagolix, once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description: Placebo, once daily for 12 weeks.	

Reporting group values	Linzagolix 50 mg	Linzagolix 75 mg	Linzagolix 100 mg
Number of subjects	49	114	51
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)	49	114	51
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	30.9	31.8	33.0
standard deviation	± 5.98	± 6.17	± 5.78
Gender categorical Units: Subjects			
Female	49	114	51
Male	0	0	0

Reporting group values	Linzagolix 200 mg	Placebo	Total
Number of subjects	56	53	323
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)	56	53	323
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	30.9	32.4	
standard deviation	± 6.03	± 5.78	-
Gender categorical			
Units: Subjects			
Female	56	53	323
Male	0	0	0

End points

End points reporting groups

Reporting group title	Linzagolix 50 mg
Reporting group description:	50 mg linzagolix, once daily for 12 weeks.
Reporting group title	Linzagolix 75 mg
Reporting group description:	75 mg linzagolix, once daily for 12 weeks.
Reporting group title	Linzagolix 100 mg
Reporting group description:	100 mg linzagolix, once daily for 12 weeks.
Reporting group title	Linzagolix 200 mg
Reporting group description:	200 mg linzagolix, once daily for 12 weeks.
Reporting group title	Placebo
Reporting group description:	Placebo, once daily for 12 weeks.

Primary: 30% or Greater Reduction from Baseline to Week 12 in Mean Overall Pelvic Pain Score (0-3 VRS)

End point title	30% or Greater Reduction from Baseline to Week 12 in Mean Overall Pelvic Pain Score (0-3 VRS)
End point description:	The primary efficacy endpoint of the study was a response at Week 12, with response defined as a reduction of 30% or greater from baseline in mean overall pelvic pain, recorded daily and assessed via electronic diary during the preceding 28 days (4-week period) on a VRS of 0 (no pain) to 3 (severe pain).
End point type	Primary
End point timeframe:	Week 12 of the treatment period

End point values	Linzagolix 50 mg	Linzagolix 75 mg	Linzagolix 100 mg	Linzagolix 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	114	51	55
Units: responder rate				
number (not applicable)	49.4	61.5	56.4	56.3

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: responder rate				
number (not applicable)	34.5			

Statistical analyses

Statistical analysis title	Statistical Analysis 50 mg
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Statistical analysis description:

Analysis of the primary endpoint was conducted via a generalized linear model for binary data with repeated (correlated) measures, using generalized estimating equations (marginal model), with the model including terms for the treatment group, 4-week period, baseline, and the interactions: treatment group x 4-week period, and baseline x 4-week period.

Comparison groups	Linzagolix 50 mg v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.155
Method	generalized linear model
Parameter estimate	Odds ratio (OR)
Point estimate	1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.791
upper limit	4.317

Statistical analysis title	Statistical Analysis 75 mg
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Statistical analysis description:

Analysis of the primary endpoint was conducted via a generalized linear model for binary data with repeated (correlated) measures, using generalized estimating equations (marginal model), with the model including terms for the treatment group, 4-week period, baseline, and the interactions: treatment group x 4-week period, and baseline x 4-week period.

Comparison groups	Linzagolix 75 mg v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	generalized linear model
Parameter estimate	Odds ratio (OR)
Point estimate	3.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.469
upper limit	6.239

Statistical analysis title	Statistical Analysis 100 mg
Statistical analysis description:	
Analysis of the primary endpoint was conducted via a generalized linear model for binary data with repeated (correlated) measures, using generalized estimating equations (marginal model), with the model including terms for the treatment group, 4-week period, baseline, and the interactions: treatment group x 4-week period, and baseline x 4-week period.	
Comparison groups	Linzagolix 100 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	generalized linear model
Parameter estimate	Odds ratio (OR)
Point estimate	2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.049
upper limit	5.741

Statistical analysis title	Statistical Analysis 200 mg
Statistical analysis description:	
Analysis of the primary endpoint was conducted via a generalized linear model for binary data with repeated (correlated) measures, using generalized estimating equations (marginal model), with the model including terms for the treatment group, 4-week period, baseline, and the interactions: treatment group x 4-week period, and baseline x 4-week period.	
Comparison groups	Linzagolix 200 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	generalized linear model
Parameter estimate	Odds ratio (OR)
Point estimate	2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.069
upper limit	5.593

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to Week 12

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Linzagolix 50 mg
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Reporting group description:

50 mg linzagolix, once daily for 12 weeks.

Reporting group title	Linzagolix 75 mg
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Reporting group description:

75 mg linzagolix, once daily for 12 weeks.

Reporting group title	Linzagolix 100 mg
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Reporting group description:

100 mg linzagolix, once daily for 12 weeks.

Reporting group title	Linzagolix 200 mg
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Reporting group description:

200 mg linzagolix, once daily for 12 weeks.

Reporting group title	Placebo
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Reporting group description:

Placebo, once daily for 12 weeks.

Serious adverse events	Linzagolix 50 mg	Linzagolix 75 mg	Linzagolix 100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 49 (2.04%)	0 / 114 (0.00%)	1 / 52 (1.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Stab wound			
subjects affected / exposed	0 / 49 (0.00%)	0 / 114 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 114 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 49 (0.00%)	0 / 114 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyelonephritis acute			
subjects affected / exposed	1 / 49 (2.04%)	0 / 114 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Linzagolix 200 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 57 (1.75%)	1 / 55 (1.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Stab wound			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 57 (1.75%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis acute			

subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Linzagolix 50 mg	Linzagolix 75 mg	Linzagolix 100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 49 (57.14%)	70 / 114 (61.40%)	34 / 52 (65.38%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 49 (2.04%)	4 / 114 (3.51%)	0 / 52 (0.00%)
occurrences (all)	1	4	0
Vascular disorders			
Hot flush			
subjects affected / exposed	7 / 49 (14.29%)	22 / 114 (19.30%)	14 / 52 (26.92%)
occurrences (all)	7	22	15
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 49 (20.41%)	23 / 114 (20.18%)	12 / 52 (23.08%)
occurrences (all)	29	37	16
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 49 (2.04%)	0 / 114 (0.00%)	3 / 52 (5.77%)
occurrences (all)	1	0	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 49 (6.12%)	3 / 114 (2.63%)	3 / 52 (5.77%)
occurrences (all)	3	6	3
Toothache			
subjects affected / exposed	0 / 49 (0.00%)	1 / 114 (0.88%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	0 / 49 (0.00%)	1 / 114 (0.88%)	2 / 52 (3.85%)
occurrences (all)	0	1	2

Psychiatric disorders Mood swings subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2	2 / 114 (1.75%) 2	2 / 52 (3.85%) 2
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 5	8 / 114 (7.02%) 8	1 / 52 (1.92%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	5 / 114 (4.39%) 5	1 / 52 (1.92%) 1
Bronchitis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 114 (0.88%) 1	1 / 52 (1.92%) 1

Non-serious adverse events	Linzagolix 200 mg	Placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	41 / 57 (71.93%)	30 / 55 (54.55%)	
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3	1 / 55 (1.82%) 1	
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	24 / 57 (42.11%) 28	6 / 55 (10.91%) 6	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	17 / 57 (29.82%) 27	14 / 55 (25.45%) 27	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2	0 / 55 (0.00%) 0	
Gastrointestinal disorders Nausea			

subjects affected / exposed occurrences (all)	7 / 57 (12.28%) 7	1 / 55 (1.82%) 1	
Toothache subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 2	3 / 55 (5.45%) 3	
Reproductive system and breast disorders Vulvovaginal dryness subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3	0 / 55 (0.00%) 0	
Psychiatric disorders Mood swings subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2	5 / 55 (9.09%) 6	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	3 / 55 (5.45%) 4	
Urinary tract infection subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 5	0 / 55 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3	0 / 55 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2016	<ul style="list-style-type: none">• Addition of an optional treatment extension phase.• Change in inclusion criterion: most recent surgical diagnosis was increased from 7 to 10 years.• Change in inclusion criterion: e-Diary completion compliance limit was reduced from 80% to 75% during the screening period.
21 April 2017	<ul style="list-style-type: none">• OATP1B1/1B3 inhibitors were prohibited during the treatment period.• The potential induction of CYP3A4 by linzagolix previously reported in Section 6.6.1 was removed.• Additional guidance was provided in the case of withdrawal from study during the first 4 weeks of treatment: Subjects should undergo the procedures required at Week 24 visit except the DXA.• Change in inclusion criterion: the lower limit of BMI ≥ 18 kg/m² was included, upper limit was removed.
03 August 2017	<ul style="list-style-type: none">• Clarification on sexual abstinence, as a birth control method (inclusion criteria for the main study and extension phase).• The washout period for the depot contraceptive, medroxyprogesterone acetate, was extended from 6 to 10 months.• Change in exclusion criterion for the extension phase: Subjects found to have had a BMD loss of $>7\%$ at any anatomic site or a Z-score ≤ -2.5 are to be excluded from the extension study.• Change in discontinuation criteria related to BMD loss: Subjects found to have a BMD loss of more than 7% at any anatomic site or a Z-score ≤ -2.5 should be discontinued from the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported