Clinical trial results:
A Phase 3, multicentre, randomized, double-blind, placebo controlled study investigating the efficacy and safety of daily oral administration of OBE2109 alone and in combination with add-back therapy for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.

Summary

EudraCT number	2016-004059-53
Trial protocol	HU LV CZ BG PL LT
Global end of trial date	09 November 2020

Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022

Trial information

Trial identification

Sponsor protocol code	16-OBE2109-009

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, Geneva, Switzerland,
Public contact	Clinical Trial Information, ObsEva SA, +41 225523840, clinicaltrials@obseva.ch
Scientific contact	Clinical Trial Information, ObsEva SA, +41 225523840, 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	16 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2020
Global end of trial reached?	Yes
Global end of trial date	09 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a prospective, randomized, parallel-group, double-blind, placebo-controlled phase 3 study investigating the efficacy and safety of linzagolix alone and in combination with add-back therapy for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. Note that add-back therapy (ABT) consists of estradiol 1 mg/norethisterone acetate 0.5 mg. The trial consists of 3 periods (24, 52 and 76 weeks) with 5 treatment groups per period.

Efficacy objective: To demonstrate the superior efficacy versus placebo of linzagolix alone and in combination with add-back therapy for the reduction of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.

Safety objectives:
- To assess the effect of linzagolix alone and in combination with add-back therapy versus placebo on bone mineral density.
- To assess the overall safety of linzagolix alone and in combination with add-back therapy in subjects with uterine fibroids.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and with Good Clinical Practice (GCP) rules and in line with local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 156
Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	Czechia: 23
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Latvia: 17
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	United States: 50
Country: Number of subjects enrolled	Romania: 37
Country: Number of subjects enrolled	Ukraine: 213

Worldwide total number of subjects	535
EEA total number of subjects	272

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)	535
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 95 clinical sites throughout the world, including centers in Bulgaria, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Ukraine, and the United States of America.

Pre-assignment

Screening details:

Number of subjects:
- 1363 screened
- 535 randomized; 21 discontinued between randomization and Day 1, main reason was subject's request; a further 3 subjects discontinued the study after Day 1 without receiving any study drug
- 501 included in Full Analysis Set (FAS)
- 511 received at least one dose of study drug (Safety Analysis Set)

Period 1

Period 1 title	Treatment period up to Week 24
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebos were used for both the test drug (linzagolix) and the add-back therapy (ABT; E2/NETA). Commercially available E2/NETA tablets were overencapsulated to maintain study blinding. Placebo was also used to maintain the blind for linzagolix dose levels. Packaging and labeling did not identify whether a package contained active medication or placebo. The randomization list was secured in a computer file with access restricted to designated personnel only.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

placebo linzagolix + placebo ABT (up to 24 weeks)

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

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Investigational medicinal product name	placebo ABT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Arm title	Linzagolix 100 mg

Arm description:

linzagolix 100 mg + placebo ABT (up to 24 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:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Investigational medicinal product name	placebo ABT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

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

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Arm title	Linzagolix 100 mg + ABT

Arm description:

linzagolix 100 mg + E2/NETA (up to 24 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:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

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

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

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

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Arm title	Linzagolix 200 mg

Arm description:	
linzagolix 200 mg + placebo ABT (up to 24 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:	
The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.	
Investigational medicinal product name	placebo ABT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.	
Arm title	Linzagolix 200 mg + ABT
Arm description:	
linzagolix 200 mg + E2/NETA (up to 24 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:	
The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.	
Investigational medicinal product name	E2/NETA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.	

Number of subjects in period 1[1]	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT
Started	102	97	101
Completed	90	80	81
Not completed	12	17	20
Adverse event, non-fatal	3	6	4
Other	-	2	3
Lost to follow-up	1	1	-

Subject's request	5	7	9
Lack of efficacy	3	1	3
Protocol deviation	-	-	1

Number of subjects in period 1[1]	Linzagolix 200 mg	Linzagolix 200 mg + ABT
Started	103	98
Completed	88	85
Not completed	15	13
Adverse event, non-fatal	8	2
Other	1	1
Lost to follow-up	-	2
Subject's request	6	7
Lack of efficacy	-	1
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 Full Analysis Set (FAS). A total of 535 subjects were randomized, 501 subjects were included in the FAS. 34 randomized subjects were excluded: 21 subjects discontinued the study between randomization and Day 1 (i.e., before receiving study drug); the main reason was subject's request; 3 subjects discontinued the study after Day 1 without receiving any study drug; 10 subjects met exclusion criteria.

Period 2

Period 2 title	Treatment period up to Week 52
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebos were used for both the test drug (linzagolix) and the add-back therapy (ABT; E2/NETA). Commercially available E2/NETA tablets were overencapsulated to maintain study blinding. Placebo was also used to maintain the blind for linzagolix dose levels. Packaging and labeling did not identify whether a package contained active medication or placebo. The randomization list was secured in a computer file with access restricted to designated personnel only.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo / linzagolix 200 mg + ABT

Arm description:

linzagolix 200 mg + E2/NETA (from 24 weeks up to 52 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:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

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

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Arm title	Linzagolix 100 mg

Arm description:

linzagolix 100 mg + placebo ABT (from 24 weeks up to 52 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:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

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

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Investigational medicinal product name	placebo ABT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Arm title	Linzagolix 100 mg + ABT

Arm description:

linzagolix 100 mg + E2/NETA (from 24 weeks up to 52 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:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

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

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

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

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Arm title	Linzagolix 200 mg / linzagolix 200 mg + ABT

Arm description:

linzagolix 200 mg + E2/NETA (from 24 weeks up to 52 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:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

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

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Arm title	Linzagolix 200 mg + ABT

Arm description:

linzagolix 200 mg + E2/NETA (from 24 weeks up to 52 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:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

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

Dosage and administration details:

The subject was to take 2 tablets of linzagolix/placebo and 1 capsule of ABT/placebo orally, ideally in the morning of each day.

Number of subjects in period 2[2]	Placebo / linzagolix 200 mg + ABT	Linzagolix 100 mg	Linzagolix 100 mg + ABT
Started	89	79	80
Completed	75	60	68
Not completed	14	19	12
No Week 52 visit	-	-	-
Adverse event, non-fatal	4	3	-
Other	1	6	3
Pregnancy	-	1	-
Lost to follow-up	-	-	1
Subject's request	8	6	5
Missing	-	1	-
Lack of efficacy	1	2	3
Protocol deviation	-	-	-

Number of subjects in period 2[2]	Linzagolix 200 mg / linzagolix 200 mg + ABT	Linzagolix 200 mg + ABT
Started	88	83
Completed	62	72
Not completed	26	11
No Week 52 visit	1	-
Adverse event, non-fatal	4	-
Other	11	6
Pregnancy	-	-
Lost to follow-up	1	-
Subject's request	8	5
Missing	-	-
Lack of efficacy	-	-
Protocol deviation	1	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Overall 424 subjects completed the study up to Week 24 (Period 1). A total of 421 subjects received study drug after Week 24 and were included in the Week 52 Safety Analysis Set. Two of these subjects were excluded from the Week 52 FAS due to exclusion criteria 19 or 20 (these subjects entered the study before discontinuation was mandatory in such cases); thus, the Week 52 FAS included 419 subjects.

Period 3

Period 3 title	Follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Treatment allocation, individual P4 and E2 levels, AH results (as of Study Day 1) and the Week 24 and Week 52 study results remained blinded up to the final Week 76 database lock for the Investigator and the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo / linzagolix 200 mg + ABT

Arm description:

Subjects who completed 52 weeks of treatment were to be followed for 24 weeks after the end of treatment (up to week 76).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Linzagolix 100 mg

Arm description:

Subjects who completed 52 weeks of treatment were to be followed for 24 weeks after the end of treatment (up to week 76).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Linzagolix 100 mg + ABT

Arm description:

Subjects who completed 52 weeks of treatment were to be followed for 24 weeks after the end of treatment (up to week 76).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Linzagolix 200 mg / linzagolix 200 mg + ABT

Arm description:

Subjects who completed 52 weeks of treatment were to be followed for 24 weeks after the end of treatment (up to week 76).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Linzagolix 200 mg + ABT

Arm description:

Subjects who completed 52 weeks of treatment were to be followed for 24 weeks after the end of treatment (up to week 76).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Placebo / linzagolix 200 mg + ABT	Linzagolix 100 mg	Linzagolix 100 mg + ABT
Started	75	60	67
Completed	68	52	57
Not completed	7	8	10
Adverse event, non-fatal	1	-	-
Other	1	-	3
Lost to follow-up	3	-	3
Subject's request	2	8	4
Lack of efficacy	-	-	-

Number of subjects in period 3	Linzagolix 200 mg / linzagolix 200 mg + ABT	Linzagolix 200 mg + ABT
Started	63	72
Completed	59	66
Not completed	4	6
Adverse event, non-fatal	1	1
Other	-	-
Lost to follow-up	-	2
Subject's request	3	2
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: placebo linzagolix + placebo ABT (up to 24 weeks)	
Reporting group title	Linzagolix 100 mg
Reporting group description: linzagolix 100 mg + placebo ABT (up to 24 weeks)	
Reporting group title	Linzagolix 100 mg + ABT
Reporting group description: linzagolix 100 mg + E2/NETA (up to 24 weeks)	
Reporting group title	Linzagolix 200 mg
Reporting group description: linzagolix 200 mg + placebo ABT (up to 24 weeks)	
Reporting group title	Linzagolix 200 mg + ABT
Reporting group description: linzagolix 200 mg + E2/NETA (up to 24 weeks)	

Reporting group values	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT
Number of subjects	102	97	101
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)	102	97	101
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	42.9	43.4	42.5
standard deviation	± 5.3	± 5.4	± 5.1
Gender categorical Units: Subjects			
Female	102	97	101
Male	0	0	0
Body Mass Index (BMI) Units: kg/m2			
arithmetic mean	26.83	27.44	27.22
standard deviation	± 5.42	± 5.67	± 5.82
Baseline menstrual blood loss (MBL) Units: mL			
arithmetic mean	216.83	244.52	192.82

standard deviation	± 129.14	± 162.82	± 92.79

Reporting group values	Linzagolix 200 mg	Linzagolix 200 mg + ABT	Total
Number of subjects	103	98	501
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)	103	98	501
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	42.7	43.1	
standard deviation	± 5.8	± 4.8	-
Gender categorical Units: Subjects			
Female	103	98	501
Male	0	0	0
Body Mass Index (BMI) Units: kg/m2			
arithmetic mean	26.82	26.80	
standard deviation	± 5.55	± 5.47	-
Baseline menstrual blood loss (MBL) Units: mL			
arithmetic mean	216.81	212.67	
standard deviation	± 136.97	± 142.76	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: placebo linzagolix + placebo ABT (up to 24 weeks)	
Reporting group title	Linzagolix 100 mg
Reporting group description: linzagolix 100 mg + placebo ABT (up to 24 weeks)	
Reporting group title	Linzagolix 100 mg + ABT
Reporting group description: linzagolix 100 mg + E2/NETA (up to 24 weeks)	
Reporting group title	Linzagolix 200 mg
Reporting group description: linzagolix 200 mg + placebo ABT (up to 24 weeks)	
Reporting group title	Linzagolix 200 mg + ABT
Reporting group description: linzagolix 200 mg + E2/NETA (up to 24 weeks)	
Reporting group title	Placebo / linzagolix 200 mg + ABT
Reporting group description: linzagolix 200 mg + E2/NETA (from 24 weeks up to 52 weeks)	
Reporting group title	Linzagolix 100 mg
Reporting group description: linzagolix 100 mg + placebo ABT (from 24 weeks up to 52 weeks)	
Reporting group title	Linzagolix 100 mg + ABT
Reporting group description: linzagolix 100 mg + E2/NETA (from 24 weeks up to 52 weeks)	
Reporting group title	Linzagolix 200 mg / linzagolix 200 mg + ABT
Reporting group description: linzagolix 200 mg + E2/NETA (from 24 weeks up to 52 weeks)	
Reporting group title	Linzagolix 200 mg + ABT
Reporting group description: linzagolix 200 mg + E2/NETA (from 24 weeks up to 52 weeks)	
Reporting group title	Placebo / linzagolix 200 mg + ABT
Reporting group description: Subjects who completed 52 weeks of treatment were to be followed for 24 weeks after the end of treatment (up to week 76).	
Reporting group title	Linzagolix 100 mg
Reporting group description: Subjects who completed 52 weeks of treatment were to be followed for 24 weeks after the end of treatment (up to week 76).	
Reporting group title	Linzagolix 100 mg + ABT
Reporting group description: Subjects who completed 52 weeks of treatment were to be followed for 24 weeks after the end of treatment (up to week 76).	
Reporting group title	Linzagolix 200 mg / linzagolix 200 mg + ABT
Reporting group description: Subjects who completed 52 weeks of treatment were to be followed for 24 weeks after the end of treatment (up to week 76).	
Reporting group title	Linzagolix 200 mg + ABT
Reporting group description: Subjects who completed 52 weeks of treatment were to be followed for 24 weeks after the end of	

treatment (up to week 76).

Primary: Reduced menstrual blood loss at Week 24	
End point title	Reduced menstrual blood loss at Week 24
End point description: Reduced menstrual blood loss (MBL) is defined as MBL ≤ 80 mL and ≥ 50% reduction from baseline.	
End point type	Primary
End point timeframe: Week 24	

End point values	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	97	101	103
Units: Proportion				
number (confidence interval 95%)	29.4 (20.8 to 39.3)	56.7 (46.3 to 66.7)	77.2 (67.8 to 85.0)	77.7 (68.4 to 85.3)

End point values	Linzagolix 200 mg + ABT			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: Proportion				
number (confidence interval 95%)	93.9 (87.1 to 97.7)			

Statistical analyses

Statistical analysis title	Number of responders at Week 24
Statistical analysis description: Cochran-Mantel-Haenszel test with race as stratification factor.	
Comparison groups	Placebo v Linzagolix 100 mg
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.74
upper limit	5.64

Notes:

[1] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Number of responders at Week 24
Statistical analysis description:	
Cochran-Mantel-Haenszel test with race as stratification factor.	
Comparison groups	Placebo v Linzagolix 100 mg + ABT
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	9.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.97
upper limit	18.99

Notes:

[2] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Number of responders at Week 24
Statistical analysis description:	
Cochran-Mantel-Haenszel test with race as stratification factor.	
Comparison groups	Placebo v Linzagolix 200 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	7.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.29
upper limit	14.75

Notes:

[3] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Number of responders at Week 24
Statistical analysis description:	
Cochran-Mantel-Haenszel test with race as stratification factor.	
Comparison groups	Placebo v Linzagolix 200 mg + ABT

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	35.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.06
upper limit	87.68

Notes:

[4] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Secondary: Time to reduced menstrual blood loss up to Week 24

End point title	Time to reduced menstrual blood loss up to Week 24

End point description:

End point type	Secondary

End point timeframe:

From Baseline up to Week 24

End point values	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30[5]	97	101	103
Units: days				
median (confidence interval 95%)	0 (0 to 0)	138.0 (112.0 to 148.0)	3.0 (2.0 to 14.0)	3.0 (1.0 to 7.0)

Notes:

[5] - not estimable

End point values	Linzagolix 200 mg + ABT			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: days				
median (confidence interval 95%)	1.0 (1.0 to 3.0)			

Statistical analyses

Statistical analysis title	Time to reduced MBL up to Week 24
Comparison groups	Linzagolix 100 mg v Placebo

Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001 [7]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.55
upper limit	3.77

Notes:

[6] - Kaplan-Meier analysis:
Estimated hazard ratios and 95% CIs obtained from stratified Cox model with treatment group as main effect and race as stratification factor.

[7] - P-value obtained from a 2-sided stratified log-rank test for each linzagolix group versus placebo comparison using race as stratification factor.
Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Time to reduced MBL up to Week 24
Comparison groups	Placebo v Linzagolix 100 mg + ABT
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.001 [9]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	5.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.68
upper limit	8.66

Notes:

[8] - Kaplan-Meier analysis:
Estimated hazard ratios and 95% CIs obtained from stratified Cox model with treatment group as main effect and race as stratification factor.

[9] - P-value obtained from a 2-sided stratified log-rank test for each linzagolix group versus placebo comparison using race as stratification factor.
Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Time to reduced MBL up to Week 24
Comparison groups	Placebo v Linzagolix 200 mg
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.001 [11]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	5.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.58
upper limit	8.37

Notes:

[10] - Kaplan-Meier analysis:
Estimated hazard ratios and 95% CIs obtained from stratified Cox model with treatment group as main effect and race as stratification factor.
[11] - P-value obtained from a 2-sided stratified log-rank test for each linzagolix group versus placebo comparison using race as stratification factor.
Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Time to reduced MBL up to Week 24
Comparison groups	Placebo v Linzagolix 200 mg + ABT
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.001 [13]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	8.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.65
upper limit	13.25

Notes:

[12] - Kaplan-Meier analysis:
Estimated hazard ratios and 95% CIs obtained from stratified Cox model with treatment group as main effect and race as stratification factor.
[13] - P-value obtained from a 2-sided stratified log-rank test for each linzagolix group versus placebo comparison using race as stratification factor.
Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Secondary: Amenorrhea at Week 24

End point title	Amenorrhea at Week 24

End point description:

Amenorrhea is defined as having no data from the alkaline hematin method from the central laboratory or volume below the lower limit of quantification over at least a 35-day interval and without showing bleeding after this interval.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	97	101	103
Units: proportion				
number (confidence interval 95%)	11.8 (6.2 to 19.6)	34.0 (24.7 to 44.3)	63.4 (53.2 to 72.7)	70.9 (61.1 to 79.4)

End point values	Linzagolix 200 mg + ABT			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: proportion				
number (confidence interval 95%)	80.6 (71.4 to 87.9)			

Statistical analyses

Statistical analysis title	Amenorrhea at Week 24
Statistical analysis description: Cochran-Mantel-Haenszel test with race as stratification factor.	
Comparison groups	Placebo v Linzagolix 100 mg
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.84
upper limit	7.94

Notes:
[14] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Amenorrhea at Week 24
Statistical analysis description: Cochran-Mantel-Haenszel test with race as stratification factor.	
Comparison groups	Placebo v Linzagolix 100 mg + ABT
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	14.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.76
upper limit	29.71

Notes:
[15] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Amenorrhea at Week 24
Statistical analysis description: Cochran-Mantel-Haenszel test with race as stratification factor.	
Comparison groups	Placebo v Linzagolix 200 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	17.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.38
upper limit	35.66

Notes:
[16] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Amenorrhea at Week 24
Statistical analysis description: Cochran-Mantel-Haenszel test with race as stratification factor.	
Comparison groups	Placebo v Linzagolix 200 mg + ABT
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [17]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	31.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.27
upper limit	69.02

Notes:
[17] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Secondary: Time to amenorrhea up to Week 24	
End point title	Time to amenorrhea up to Week 24
End point description: Kaplan-Meier estimates of the first quartile (95% CI) for time to amenorrhea are shown.	
End point type	Secondary
End point timeframe: From Baseline up to Week 24	

End point values	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102[18]	97	101	103
Units: days				
number (confidence interval 95%)	0 (0 to 0)	104.0 (55.0 to 128.0)	6.0 (4.0 to 17.0)	3.0 (1.0 to 5.0)

Notes:

[18] - Not estimable

End point values	Linzagolix 200 mg + ABT			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: days				
number (confidence interval 95%)	2.0 (1.0 to 4.0)			

Statistical analyses

Statistical analysis title	Time to amenorrhea up to Week 24

Statistical analysis description:

Estimated hazard ratios and 95% CIs obtained from stratified Cox model with treatment group as main effect and race as stratification factor.

Comparison groups	Placebo v Linzagolix 100 mg
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.001 [20]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	3.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.79
upper limit	6.73

Notes:

[19] - p-value obtained from a 2-sided stratified log-rank test for each treatment group versus placebo comparison using race as stratification factor.
[20] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Time to amenorrhea up to Week 24

Statistical analysis description:

Estimated hazard ratios and 95% CIs obtained from stratified Cox model with treatment group as main effect and race as stratification factor.

Comparison groups	Placebo v Linzagolix 100 mg + ABT

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.001 [22]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.8
upper limit	16.53

Notes:

[21] - p-value obtained from a 2-sided stratified log-rank test for each treatment group versus placebo comparison using race as stratification factor.
[22] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Time to amenorrhea up to Week 24

Statistical analysis description:

Estimated hazard ratios and 95% CIs obtained from stratified Cox model with treatment group as main effect and race as stratification factor.

Comparison groups	Placebo v Linzagolix 200 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.001 [24]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	11.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.44
upper limit	21.96

Notes:

[23] - p-value obtained from a 2-sided stratified log-rank test for each treatment group versus placebo comparison using race as stratification factor.
[24] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Time to amenorrhea up to Week 24

Statistical analysis description:

Estimated hazard ratios and 95% CIs obtained from stratified Cox model with treatment group as main effect and race as stratification factor.

Comparison groups	Linzagolix 200 mg + ABT v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	< 0.001 [26]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	14.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	7.76
upper limit	26.32

Notes:

[25] - p-value obtained from a 2-sided stratified log-rank test for each treatment group versus placebo comparison using race as stratification factor.
[26] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Secondary: Number of days of uterine bleeding up to Week 24

End point title	Number of days of uterine bleeding up to Week 24

End point description:

Number of days of uterine bleeding for the last 28-day interval prior to Week 24 - Zero-inflated negative binomial model.

End point type	Secondary

End point timeframe:

Number of days of uterine bleeding for each 28-day interval up to week 24.

End point values	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	94	97	98
Units: percentage				
number (not applicable)				
0 days	18.0	52.1	76.3	79.6
1-5 days	54.0	36.2	9.3	9.2
>5 days	28.0	11.7	14.4	11.2

End point values	Linzagolix 200 mg + ABT			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: percentage				
number (not applicable)				
0 days	85.4			
1-5 days	8.3			
>5 days	6.3			

Statistical analyses

Statistical analysis title	Number of days of uterine bleeding

Statistical analysis description:

Zero-inflated negative binomial model:
The zero-inflation probability model includes treatment group as main effect.
The regression model for the mean includes treatment group as main effect and baseline value and race

as covariates. LSMeans are computed for the regression model only and not for the zero-inflation probability model.
The overall mean is calculated as (1 – Probability) * LSMean.

Comparison groups	Placebo v Linzagolix 100 mg
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [27]
Method	Regression, Logistic

Notes:

[27] - Testing joint null hypothesis of no treatment effect in zero-inflation probability model and the regression model for the mean.
Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Number of days of uterine bleeding

Statistical analysis description:

Zero-inflated negative binomial model:
The zero-inflation probability model includes treatment group as main effect.
The regression model for the mean includes treatment group as main effect and baseline value and race as covariates. LSMeans are computed for the regression model only and not for the zero-inflation probability model.
The overall mean is calculated as (1 – Probability) * LSMean.

Comparison groups	Placebo v Linzagolix 100 mg + ABT
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [28]
Method	Regression, Logistic

Notes:

[28] - Testing joint null hypothesis of no treatment effect in zero-inflation probability model and the regression model for the mean.
Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Number of days of uterine bleeding

Statistical analysis description:

Zero-inflated negative binomial model:
The zero-inflation probability model includes treatment group as main effect.
The regression model for the mean includes treatment group as main effect and baseline value and race as covariates. LSMeans are computed for the regression model only and not for the zero-inflation probability model.
The overall mean is calculated as (1 – Probability) * LSMean.

Comparison groups	Placebo v Linzagolix 200 mg
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [29]
Method	Regression, Logistic

Notes:

[29] - Testing joint null hypothesis of no treatment effect in zero-inflation probability model and the regression model for the mean.
Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Number of days of uterine bleeding

Statistical analysis description:

Zero-inflated negative binomial model:
The zero-inflation probability model includes treatment group as main effect.
The regression model for the mean includes treatment group as main effect and baseline value and race as covariates. LSMeans are computed for the regression model only and not for the zero-inflation probability model.

The overall mean is calculated as (1 – Probability) * LSMean.

Comparison groups	Placebo v Linzagolix 200 mg + ABT
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [30]
Method	Regression, Logistic

Notes:

[30] - Testing joint null hypothesis of no treatment effect in zero-inflation probability model and the regression model for the mean.
Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Secondary: Hemoglobin levels at Week 24 in anemic subjects

End point title	Hemoglobin levels at Week 24 in anemic subjects

End point description:

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	61	59	57
Units: g/dL				
least squares mean (confidence interval 95%)	10.56 (10.05 to 11.07)	11.49 (10.99 to 11.99)	12.16 (11.65 to 12.68)	12.28 (11.79 to 12.77)

End point values	Linzagolix 200 mg + ABT			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: g/dL				
least squares mean (confidence interval 95%)	12.44 (11.95 to 12.93)			

Statistical analyses

Statistical analysis title	Hemoglobin level at Week 24 in anemic subjects

Statistical analysis description:

Analysis using mixed model repeated measures with actual value as response variable, baseline hemoglobin value, treatment, visit and race as covariates and including treatment, baseline value and race by visit interactions.

Comparison groups	Placebo v Linzagolix 100 mg

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [31]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.45

Notes:

[31] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Hemoglobin level at Week 24 in anemi...

Statistical analysis description:

Analysis using mixed model repeated measures with actual value as response variable, baseline hemoglobin value, treatment, visit and race as covariates and including treatment, baseline value and race by visit interactions.

Comparison groups	Placebo v Linzagolix 100 mg + ABT
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [32]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	2.13

Notes:

[32] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Hemoglobin level at Week 24 in anemi...

Statistical analysis description:

Analysis using mixed model repeated measures with actual value as response variable, baseline hemoglobin value, treatment, visit and race as covariates and including treatment, baseline value and race by visit interactions.

Comparison groups	Placebo v Linzagolix 200 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [33]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	2.24

Notes:

[33] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Statistical analysis title	Hemoglobin level at Week 24 in anemi...

Statistical analysis description:

Analysis using mixed model repeated measures with actual value as response variable, baseline hemoglobin value, treatment, visit and race as covariates and including treatment, baseline value and race by visit interactions.

Comparison groups	Placebo v Linzagolix 200 mg + ABT
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [34]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.36
upper limit	2.39

Notes:

[34] - Each active treatment group is compared versus placebo at the 0.0125 level of significance.

Other pre-specified: Change from Baseline in bone mineral density at the lumbar spine at Week 24

End point title	Change from Baseline in bone mineral density at the lumbar spine at Week 24

End point description:

End point type	Other pre-specified

End point timeframe:

Week 24

End point values	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	71	72	75
Units: %CfB				
geometric mean (confidence interval 95%)	0.538 (-0.001 to 1.076)	-2.068 (-2.630 to -1.506)	-0.998 (-1.570 to -0.425)	-4.032 (-4.680 to -3.385)

End point values	Linzagolix 200 mg + ABT			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: %CfB				
geometric mean (confidence interval 95%)	-1.350 (-1.956 to -0.745)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in bone mineral density at the lumbar spine at Week 52

End point title	Change from Baseline in bone mineral density at the lumbar spine at Week 52

End point description:

End point type	Other pre-specified

End point timeframe:

Week 52

End point values	Placebo / linzagolix 200 mg + ABT	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg / linzagolix 200 mg + ABT
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	55	54	53
Units: %CfB				
geometric mean (confidence interval 95%)	-0.536 (-1.251 to 0.179)	-2.401 (-3.142 to -1.660)	-1.479 (-2.016 to -0.942)	-3.062 (-3.823 to -2.300)

End point values	Linzagolix 200 mg + ABT			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: %CfB				
geometric mean (confidence interval 95%)	-2.026 (-2.808 to -1.244)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in bone mineral density at the lumbar

spine at Week 76

End point title	Change from Baseline in bone mineral density at the lumbar spine at Week 76

End point description:

End point type	Other pre-specified

End point timeframe:

Week 76

End point values	Placebo / linzagolix 200 mg + ABT	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg / linzagolix 200 mg + ABT
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	40	41	47
Units: %CfB				
geometric mean (confidence interval 95%)	0.297 (-0.494 to 1.088)	-2.282 (-3.076 to -1.489)	-0.664 (-1.436 to 0.109)	-1.508 (-2.454 to -0.563)

End point values	Linzagolix 200 mg + ABT			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: %CfB				
geometric mean (confidence interval 95%)	-1.133 (-2.033 to -0.234)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Screening up to Week 76.

Adverse event reporting additional description:

Data on adverse events were to be obtained at scheduled or unscheduled study visits, based on information spontaneously provided by the subject and/or through questioning of the subject. Only treatment-emergent adverse events are reported here.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo 24w
Reporting group description: -	
Reporting group title	Linzagolix 100 mg 24w
Reporting group description: -	
Reporting group title	Linzagolix 100 mg + ABT 24w
Reporting group description: -	
Reporting group title	Linzagolix 200 mg 24w
Reporting group description: -	
Reporting group title	Linzagolix 200 mg + ABT 24w
Reporting group description: -	
Reporting group title	Placebo / linzagolix 200 mg + ABT 52w
Reporting group description: -	
Reporting group title	Linzagolix 100 mg 52w
Reporting group description: -	
Reporting group title	Linzagolix 100 mg + ABT 52w
Reporting group description: -	
Reporting group title	Linzagolix 200 mg / linzagolix 200 mg + ABT 52w
Reporting group description: -	
Reporting group title	Linzagolix 200 mg + ABT 52w
Reporting group description: -	
Reporting group title	Placebo / linzagolix 200 mg + ABT 76w
Reporting group description: -	
Reporting group title	Linzagolix 100 mg 76w
Reporting group description: -	
Reporting group title	Linzagolix 100 mg + ABT 76w
Reporting group description: -	
Reporting group title	Linzagolix 200 mg / linzagolix 200 mg + ABT 76w
Reporting group description: -	
Reporting group title	Linzagolix 200 mg + ABT 76w

Reporting group description: -

Serious adverse events	Placebo 24w	Linzagolix 100 mg 24w	Linzagolix 100 mg + ABT 24w
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 105 (1.90%)	1 / 99 (1.01%)	5 / 102 (4.90%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholesteatoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Ovarian epithelial cancer			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Injury, poisoning and procedural complications			
Intervertebral disc injury			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 105 (0.95%)	0 / 99 (0.00%)	0 / 102 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 105 (0.00%)	1 / 99 (1.01%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Vaginal haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Menometrorrhagia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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

Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 105 (0.00%)	0 / 99 (0.00%)	0 / 102 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 105 (0.95%)	0 / 99 (0.00%)	0 / 102 (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 24w	Linzagolix 200 mg + ABT 24w	Placebo / linzagolix 200 mg + ABT 52w
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 104 (0.96%)	1 / 101 (0.99%)	3 / 89 (3.37%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	1 / 104 (0.96%)	0 / 101 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Cholesteatoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Ovarian epithelial cancer			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Injury, poisoning and procedural complications			
Intervertebral disc injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Menorrhagia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Menometrorrhagia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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

Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 104 (0.00%)	1 / 101 (0.99%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 104 (0.00%)	0 / 101 (0.00%)	0 / 89 (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

Serious adverse events	Linzagolix 100 mg 52w	Linzagolix 100 mg + ABT 52w	Linzagolix 200 mg / linzagolix 200 mg + ABT 52w
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 79 (1.27%)	2 / 81 (2.47%)	2 / 87 (2.30%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Uterine leiomyoma			

subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Cholesteatoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 79 (0.00%)	1 / 81 (1.23%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 81 (1.23%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Ovarian epithelial cancer			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Injury, poisoning and procedural complications			
Intervertebral disc injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Deep vein thrombosis			

subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Menorrhagia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Vaginal haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menometrorrhagia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	1 / 87 (1.15%)
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			
Emphysema			

subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 81 (0.00%)	0 / 87 (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
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 79 (0.00%)	0 / 81 (0.00%)	0 / 87 (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

Serious adverse events	Linzagolix 200 mg + ABT 52w	Placebo / linzagolix 200 mg + ABT 76w	Linzagolix 100 mg 76w
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 84 (1.19%)	2 / 75 (2.67%)	1 / 60 (1.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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

Cholesteatoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Ovarian epithelial cancer			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Injury, poisoning and procedural complications			
Intervertebral disc injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 75 (1.33%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 75 (1.33%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Menometrorrhagia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	1 / 84 (1.19%)	0 / 75 (0.00%)	0 / 60 (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
Skin and subcutaneous tissue disorders			
Dermatitis			

subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 75 (0.00%)	0 / 60 (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

Serious adverse events	Linzagolix 100 mg + ABT 76w	Linzagolix 200 mg / linzagolix 200 mg + ABT 76w	Linzagolix 200 mg + ABT 76w
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 68 (0.00%)	2 / 63 (3.17%)	2 / 73 (2.74%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Cholesteatoma			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 68 (0.00%)	1 / 63 (1.59%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian epithelial cancer			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Intervertebral disc injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	1 / 63 (1.59%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Vaginal haemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Menometrorrhagia			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Skin and subcutaneous tissue disorders			
Dermatitis			

subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	0 / 63 (0.00%)	0 / 73 (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

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

Non-serious adverse events	Placebo 24w	Linzagolix 100 mg 24w	Linzagolix 100 mg + ABT 24w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 105 (20.95%)	39 / 99 (39.39%)	23 / 102 (22.55%)
Vascular disorders			
Hot flush			
subjects affected / exposed	4 / 105 (3.81%)	14 / 99 (14.14%)	8 / 102 (7.84%)
occurrences (all)	4	16	8
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 105 (5.71%)	4 / 99 (4.04%)	5 / 102 (4.90%)
occurrences (all)	8	4	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 105 (10.48%)	19 / 99 (19.19%)	10 / 102 (9.80%)
occurrences (all)	12	20	10
Skin and subcutaneous tissue disorders			
Hyperhidrosis			

subjects affected / exposed	1 / 105 (0.95%)	2 / 99 (2.02%)	0 / 102 (0.00%)
occurrences (all)	1	2	0

Non-serious adverse events	Linzagolix 200 mg 24w	Linzagolix 200 mg + ABT 24w	Placebo / linzagolix 200 mg + ABT 52w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 104 (55.77%)	29 / 101 (28.71%)	11 / 89 (12.36%)
Vascular disorders			
Hot flush			
subjects affected / exposed	33 / 104 (31.73%)	13 / 101 (12.87%)	3 / 89 (3.37%)
occurrences (all)	36	14	3
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 104 (13.46%)	7 / 101 (6.93%)	0 / 89 (0.00%)
occurrences (all)	23	17	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 104 (3.85%)	9 / 101 (8.91%)	6 / 89 (6.74%)
occurrences (all)	4	9	6
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	7 / 104 (6.73%)	0 / 101 (0.00%)	2 / 89 (2.25%)
occurrences (all)	7	0	2

Non-serious adverse events	Linzagolix 100 mg 52w	Linzagolix 100 mg + ABT 52w	Linzagolix 200 mg / linzagolix 200 mg + ABT 52w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 79 (6.33%)	5 / 81 (6.17%)	3 / 87 (3.45%)
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 79 (2.53%)	1 / 81 (1.23%)	1 / 87 (1.15%)
occurrences (all)	2	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 79 (1.27%)	2 / 81 (2.47%)	1 / 87 (1.15%)
occurrences (all)	1	4	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 79 (2.53%)	2 / 81 (2.47%)	1 / 87 (1.15%)
occurrences (all)	3	2	1

Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0	0 / 81 (0.00%) 0	0 / 87 (0.00%) 0

Non-serious adverse events	Linzagolix 200 mg + ABT 52w	Placebo / linzagolix 200 mg + ABT 76w	Linzagolix 100 mg 76w
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 84 (5.95%)	2 / 75 (2.67%)	4 / 60 (6.67%)
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	3 / 84 (3.57%) 4	0 / 75 (0.00%) 0	0 / 60 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 22	0 / 75 (0.00%) 0	0 / 60 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	2 / 75 (2.67%) 2	4 / 60 (6.67%) 4
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	0 / 75 (0.00%) 0	0 / 60 (0.00%) 0

Non-serious adverse events	Linzagolix 100 mg + ABT 76w	Linzagolix 200 mg / linzagolix 200 mg + ABT 76w	Linzagolix 200 mg + ABT 76w
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 68 (5.88%)	0 / 63 (0.00%)	3 / 73 (4.11%)
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	0 / 63 (0.00%) 0	0 / 73 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	0 / 63 (0.00%) 0	0 / 73 (0.00%) 0
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4	0 / 63 (0.00%) 0	3 / 73 (4.11%) 3
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	0 / 63 (0.00%) 0	0 / 73 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2017	• Changes and clarifications to screening and in- and exclusion criteria • PK - related: new data; OATP1B1/1B3 inhibitors were prohibited during the treatment period • Modification of the ABT dose for the linzagolix 100 mg group • Modification of the subject withdrawal section with respect to BMD measurements (DXA scan) at the time of withdrawal
18 December 2017	• Change in treatment discontinuation criteria related to BMD result and hepatic parameters measured at Day 1 and during treatment. • Clarification and addition of secondary efficacy objectives (incidence and time to amenorrhea, impact of submucosal fibroids on the primary endpoint). • Removal of the substrates of CYP2C8 and of OAT3 as prohibited medicines. • Addition of temperature storage requirements for the IMP. • Modification of statistical sections for consistency with the Statistical Analysis Plan. • Addition of a section presenting the definition and reporting procedures for protocol deviations.
28 May 2018	• Modification of myoma size inclusion criterion. • Addition of ECG monitoring. • Clarification: inclusion criterion on the menstrual cycle duration. • Addition of an ultrasound prior to washout for patients with an IUD (confirmation of fibroid size criterion). • Addition of the instruction that subjects who did not bleed for 50 days during screening were to be considered screen failures. • Removal of OATP1B1/1B3 inhibitors from the list of prohibited medicines.
04 October 2019	• Modification of the wording, ordering and ranking of secondary endpoints. • Clarification of the rules for discontinuation of study treatment in relation to elevated liver function tests, BMD decrease and endometrial biopsies and safety follow-up. • Specification of criteria for referring subjects to a with respect to QTc prolongation.
27 November 2019	• Clarification of the definition of baseline. • Clarification of the timing of the Week 52 visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported