Clinical trial results:
LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Summary

EudraCT number	2016-005113-50
Trial protocol	HU CZ BE PL
Global end of trial date	10 July 2019

Results information

Result version number	v1 (current)
This version publication date	28 June 2020
First version publication date	28 June 2020

Trial information

Trial identification

Sponsor protocol code	MVT-601-3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03103087
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Myovant Sciences GmbH
Sponsor organisation address	Viaduktstrasse 8, Basel, Switzerland, 4051
Public contact	Clinical Trials at Myovant, Myovant Sciences GmbH, +1 650 238 0250, clinicaltrials@myovant.com
Scientific contact	Senior VP of Clinical Development, Myovant Sciences GmbH, +1 650 238 0250, LIBERTY@myovant.com

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	31 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2019
Global end of trial reached?	Yes
Global end of trial date	10 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the benefit of relugolix 40 milligrams (mg) once daily co-administered with estradiol (E2) 1.0 mg and norethindrone acetate (NETA) 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 January 2017
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: 17
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Hungary: 22
Country: Number of subjects enrolled	United States: 284
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Chile: 24
Country: Number of subjects enrolled	South Africa: 17
Worldwide total number of subjects	382
EEA total number of subjects	52

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	382
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 99 study centers throughout the world, including centers in the United States, Belgium, Brazil, Chile, Czech Republic, Hungary, Poland, and South Africa.

Pre-assignment

Screening details:

A total of 382 premenopausal women aged 18 to 50 years old (inclusive) with heavy menstrual bleeding (≥ 160 millilitres [mL] during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method) associated with uterine fibroids were randomized. One participant was randomized in error before eligibility confirmed.

Period 1

Period 1 title	Treatment (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
Arm title	Relugolix plus E2/NETA (Group A)

Arm description:

Relugolix co-administered with E2/NETA for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Relugolix
Investigational medicinal product code	
Other name	TAK-385, MVT-601
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Relugolix (40 mg) tablet administered orally for 24 weeks.

Investigational medicinal product name	Estradiol/Norethindrone Acetate
Investigational medicinal product code	
Other name	E2/NETA, low-dose hormonal add-back
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

E2 (1.0 mg)/NETA (0.5 mg) co-formulated capsule administered orally once daily for 24 weeks.

Arm title	Relugolix plus Delayed E2/NETA (Group B)

Arm description:

Relugolix co-administered with E2/NETA placebo for 12 weeks, followed by relugolix co-administered with E2/NETA for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Relugolix
Investigational medicinal product code	
Other name	TAK-385, MVT-601
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Relugolix (40 mg) tablet administered orally for 24 weeks.

Investigational medicinal product name	Estradiol/Norethindrone Acetate
Investigational medicinal product code	
Other name	E2/NETA, low-dose hormonal add-back
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

E2 (1.0 mg)/NETA (0.5 mg) a co-formulated capsule administered orally once daily for the last 12 weeks of treatment.

Investigational medicinal product name	Estradiol/Norethindrone Acetate Placebo
Investigational medicinal product code	
Other name	E2/NETA, low-dose hormonal add-back placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

E2 (0 mg)/NETA (0 mg) placebo capsule administered orally once daily for the first 12 weeks of treatment.

Arm title	Placebo (Group C)

Arm description:

Relugolix placebo co-administered with E2/NETA placebo for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Relugolix Placebo
Investigational medicinal product code	
Other name	TAK-385 Placebo, MVT-601 Placebo
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Relugolix (0 mg) placebo tablet administered orally once daily for 24 weeks.

Investigational medicinal product name	Estradiol/Norethindrone Acetate Placebo
Investigational medicinal product code	
Other name	E2/NETA, low-dose hormonal add-back placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

E2 (0 mg)/NETA (0 mg) placebo capsule administered orally once daily for 24 weeks.

Number of subjects in period 1	Relugolix plus E2/NETA (Group A)	Relugolix plus Delayed E2/NETA (Group B)	Placebo (Group C)
Started	126	127	129
Received at Least 1 Dose of Study Drug	125	127	129
Safety Population	126	126	129
Completed	102	98	102
Not completed	24	29	27
Consent withdrawn by subject	13	6	6
Did not receive any study drug	1	-	-
Adverse event, non-fatal	2	15	6
Other	1	3	5

Pregnancy	-	-	1
Lost to follow-up	4	2	7
Lack of efficacy	2	1	1
Protocol deviation	1	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Relugolix plus E2/NETA (Group A)
Reporting group description:	
Relugolix co-administered with E2/NETA for 24 weeks.	
Reporting group title	Relugolix plus Delayed E2/NETA (Group B)
Reporting group description:	
Relugolix co-administered with E2/NETA placebo for 12 weeks, followed by relugolix co-administered with E2/NETA for 12 weeks.	
Reporting group title	Placebo (Group C)
Reporting group description:	
Relugolix placebo co-administered with E2/NETA placebo for 24 weeks.	

Reporting group values	Relugolix plus E2/NETA (Group A)	Relugolix plus Delayed E2/NETA (Group B)	Placebo (Group C)
Number of subjects	126	127	129
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)	126	127	129
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	42.5	42.1	41.8
standard deviation	± 5.37	± 5.25	± 5.26
Gender categorical Units: Subjects			
Female	126	127	129
Male	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Not Hispanic or Latino	106	91	96
Hispanic or Latino	18	34	32
Not reported	2	2	1
Geographic Region Units: Subjects			
North America	94	94	96
Rest of World	32	33	33
Race Units: Subjects			
American Indian or Alaska Native	0	2	1

Asian	0	3	1
Black or African American	63	66	74
Native Hawaiian or Other Pacific Islander	0	0	0
White	58	50	49
Other	1	2	3
Multiple	1	1	0
Not reported	3	3	1
Mean MBL Volume			
Units: mL			
arithmetic mean	247.62	227.41	211.75
standard deviation	± 185.553	± 134.350	± 129.903

Reporting group values	Total		
Number of subjects	382		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	382		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	382		
Male	0		
Ethnicity (NIH/OMB)			
Units: Subjects			
Not Hispanic or Latino	293		
Hispanic or Latino	84		
Not reported	5		
Geographic Region			
Units: Subjects			
North America	284		
Rest of World	98		
Race			
Units: Subjects			
American Indian or Alaska Native	3		
Asian	4		
Black or African American	203		
Native Hawaiian or Other Pacific Islander	0		
White	157		

Other	6		
Multiple	2		
Not reported	7		
Mean MBL Volume			
Units: mL			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Baseline Analysis Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All participants who were randomized to treatment and who received at least 1 dose of study drug.

Reporting group values	Baseline Analysis Population		
Number of subjects	381		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	381		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	42.1		
standard deviation	± 5.29		
Gender categorical			
Units: Subjects			
Female	381		
Male	0		
Ethnicity (NIH/OMB)			
Units: Subjects			
Not Hispanic or Latino	292		
Hispanic or Latino	84		
Not reported	5		
Geographic Region			
Units: Subjects			
North America	283		
Rest of World	98		
Race			
Units: Subjects			
American Indian or Alaska Native	3		
Asian	4		

Black or African American	202		
Native Hawaiian or Other Pacific Islander	0		
White	157		
Other	6		
Multiple	2		
Not reported	7		
Mean MBL Volume			
Units: mL			
arithmetic mean	228.45		
standard deviation	± 152.205		

End points

End points reporting groups

Reporting group title	Relugolix plus E2/NETA (Group A)
Reporting group description:	
Relugolix co-administered with E2/NETA for 24 weeks.	
Reporting group title	Relugolix plus Delayed E2/NETA (Group B)
Reporting group description:	
Relugolix co-administered with E2/NETA placebo for 12 weeks, followed by relugolix co-administered with E2/NETA for 12 weeks.	
Reporting group title	Placebo (Group C)
Reporting group description:	
Relugolix placebo co-administered with E2/NETA placebo for 24 weeks.	
Subject analysis set title	Baseline Analysis Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All participants who were randomized to treatment and who received at least 1 dose of study drug.	

Primary: Percentage Of Participants Who Achieved A Menstrual Blood Loss (MBL) Volume Of < 80 mL And A ≥ 50% Reduction From Baseline MBL Volume With Relugolix Plus E2/NETA

End point title	Percentage Of Participants Who Achieved A Menstrual Blood Loss (MBL) Volume Of < 80 mL And A ≥ 50% Reduction From Baseline MBL Volume With Relugolix Plus E2/NETA[1]
End point description:	
A responder was a participant who had MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment (up to Week 24). All returned feminine products collected at each clinical visit were analyzed by the alkaline hematin method to obtain the MBL volume. MBL volume was measured over the Week 24/early termination feminine product collection interval (up to 35 days prior to the last dose of treatment). The percentage of participants who were responders are presented.	
End point type	Primary
End point timeframe:	
From Baseline up to last 35 days of treatment (up to Week 24)	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, the pre-specified primary efficacy analyses compared Relugolix plus E2/NETA with Placebo. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[2]	129[3]		
Units: percentage of participants				
number (confidence interval 95%)	71.2 (62.42 to 78.95)	14.73 (9.11 to 22.04)		

Notes:

[2] - Modified Intention-to-Treat Population

[3] - Modified Intention-to-Treat Population

Statistical analyses

Statistical analysis title	Number of responders at Week 24

Statistical analysis description:

The primary efficacy analysis was the comparison of the Relugolix plus E2/NETA group with the Placebo group with respect to responder rate.

Comparison groups	Relugolix plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	56.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	46.45
upper limit	66.49

Notes:

[4] - Treatment difference is Relugolix plus E2/NETA minus Placebo and unadjusted 95% confidence interval (CI).
[5] - P-value was based on Cochran-Mantel-Haenszel test stratified by baseline MBL volume (< 225 mL or ≥ 225 mL) and geographic region (North America or Rest of World). Assessed at a two-sided α = 0.05 significance level.

Secondary: Percentage Of Participants With Amenorrhea Over The Last 35 Days Of Treatment

End point title	Percentage Of Participants With Amenorrhea Over The Last 35 Days Of Treatment[6]

End point description:

Amenorrhea was defined as meeting one of the following criteria for 2 consecutive visits:
1. No feminine product returned due to reported amenorrhea;
2. No feminine product returned due to reports of spotting/negligible bleeding coupled with eDiary data indicating infrequent non-cyclic bleeding/spotting;
3. Feminine product collection with a negligible observed MBL volume coupled with eDiary data indicating infrequent non-cyclic bleeding/spotting.

End point type	Secondary

End point timeframe:

From Baseline up to last 35 days of treatment (up to Week 24)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, the pre-specified secondary efficacy analyses compared Relugolix plus E2/NETA with Placebo. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[7]	129[8]		
Units: percentage of participants				
number (confidence interval 95%)	50.40 (41.32 to 59.46)	3.10 (0.85 to 7.75)		

Notes:

[7] - Modified Intention-to-Treat Population

[8] - Modified Intention-to-Treat Population

Statistical analyses

Statistical analysis title	Achieved Amenorrhea with Relugolix plus E2/NETA
Comparison groups	Relugolix plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	47.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	38.04
upper limit	56.56

Notes:

[9] - Treatment difference is Relugolix plus E2/NETA minus Placebo. 95% CI for difference based on the normal approximation.
[10] - P-value was based on Cochran-Mantel-Haenszel test stratified by Baseline MBL volume (< 225 mL, ≥ 225 mL) and geographic region (North America or Rest of World). Assessed at a two-sided α = 0.05 significance level.

Secondary: Percent Change From Baseline At Week 24 In MBL Volume

End point title	Percent Change From Baseline At Week 24 In MBL Volume[11]

End point description:

MBL volume was measured using the alkaline hematin method. Least square (LS) means for test of difference is Relugolix plus E2/NETA minus Placebo based on mixed-effect model with treatment, visit, region, Baseline MBL, and treatment by visit interaction included as fixed effects.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, the pre-specified secondary efficacy analyses compared Relugolix plus E2/NETA with Placebo. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[12]	129[13]		
Units: percent change				
least squares mean (confidence interval 95%)	-84.3 (-95.0 to -73.6)	-15.1 (-25.8 to -4.3)		

Notes:

[12] - Modified Intention-to-Treat Population

[13] - Modified Intention-to-Treat Population

Statistical analyses

Statistical analysis title	MBL Volume Percent Change with Relugolix + E2/NETA
Comparison groups	Placebo (Group C) v Relugolix plus E2/NETA (Group A)

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-69.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-84.1
upper limit	-54.3
Variability estimate	Standard error of the mean
Dispersion value	7.58

Notes:

[14] - P-value for difference was Relugolix plus E2/NETA minus Placebo based on mixed-effect model with treatment, visit, region, Baseline MBL, and treatment by visit interaction included as fixed effects. Assessed at a two-sided α = 0.05 significance.

Secondary: Percentage Of Participants With A Hemoglobin Level ≤ 10.5 g/dL At Baseline Who Achieved An Increase Of > 2 g/dL From Baseline At Week 24

End point title	Percentage Of Participants With A Hemoglobin Level ≤ 10.5 g/dL At Baseline Who Achieved An Increase Of > 2 g/dL From Baseline At Week 24[15]

End point description:

Blood samples were collected from participants for hemoglobin measurements. Percentages are based on number of participants with hemoglobin ≤ 10.5 gram (g)/decilitre (dL) at Baseline and reported at Week 24.

End point type	Secondary

End point timeframe:

From Baseline up to Week 24

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, the pre-specified secondary efficacy analyses compared Relugolix plus E2/NETA with Placebo. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	37		
Units: percentage of participants				
number (confidence interval 95%)	61.29 (42.19 to 78.15)	5.41 (0.66 to 18.19)		

Statistical analyses

Statistical analysis title	Change in Hemoglobin with Relugolix plus E2/NETA
Comparison groups	Relugolix plus E2/NETA (Group A) v Placebo (Group C)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.0001 [17]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	55.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	37.25
upper limit	74.52

Notes:

[16] - Treatment difference is Relugolix plus E2/NETA minus Placebo. 95% CI for difference is based on the normal approximation.
[17] - P-value based on Cochran-Mantel-Haenszel test stratified by Baseline MBL volume (< 225 mL, ≥ 225 mL). Assessed at a two-sided α = 0.05 significance level.

Secondary: Percentage Of Participants With A Maximum NRS Score ≤ 1 For Uterine Fibroid-Associated Pain Over The Last 35 Days Of Treatment

End point title	Percentage Of Participants With A Maximum NRS Score ≤ 1 For Uterine Fibroid-Associated Pain Over The Last 35 Days Of Treatment[18]

End point description:

Uterine fibroid-associated pain was assessed by a pain numerical rating scale (NRS). The pain NRS is a validated, single-item, self-reported measure, which asks respondents to rank their pain on an 11-point scale as follows: 0 (no pain), 1 to 3 (mild pain), 4 to 6 (moderate pain), and 7 to 10 (severe pain). Participants were asked to document, in an electronic diary, the worst pain associated with their uterine fibroids that they experienced during the last 24 hours, every day until the end of study drug administration. Pain evaluable participants, defined as those who had maximum NRS score ≥ 4 at baseline and had at least 28 days (80% of the last 35 days of treatment) of pain scores recorded in the e-Diary, were analyzed.

End point type	Secondary

End point timeframe:

From Baseline up to Week 24

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, the pre-specified secondary efficacy analyses compared Relugolix plus E2/NETA with Placebo. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	82		
Units: percentage of participants				
number (confidence interval 95%)	47.06 (34.83 to 59.55)	17.07 (9.66 to 26.98)		

Statistical analyses

Statistical analysis title	Pain Assessment with Relugolix plus E2/NETA
Comparison groups	Relugolix plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	29.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.6
upper limit	44.38

Notes:

[19] - Treatment difference is Relugolix plus E2/NETA minus Placebo. 95% CI for difference is based on the normal approximation.
[20] - P-value is based on Cochran-Mantel-Haenszel test stratified by Baseline MBL volume (< 225 mL, ≥ 225 mL). Assessed at a two-sided α = 0.05 significance level.

Secondary: Percent Change From Baseline At Week 24 In Primary Uterine Fibroid Volume

End point title	Percent Change From Baseline At Week 24 In Primary Uterine Fibroid Volume[21]

End point description:

The volume of the primary uterine fibroid was measured by transvaginal or transabdominal ultrasound. LS Means based on analysis of covariance model including treatment, randomization stratification factors, Baseline MBL volume (< 225 mL, ≥ 225 mL) and geographic region (North America, Rest of World), and Baseline values as covariate.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, the pre-specified secondary efficacy analyses compared Relugolix plus E2/NETA with Placebo. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent change				
least squares mean (confidence interval 95%)	-17.4 (-29.1 to -5.7)	-7.4 (-19.1 to 4.2)		

Statistical analyses

Statistical analysis title	Uterine Fibroid Volume with Relugolix plus E2/NETA
Comparison groups	Relugolix plus E2/NETA (Group A) v Placebo (Group C)

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.2153 [23]
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	-10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.8
upper limit	5.8
Variability estimate	Standard error of the mean
Dispersion value	8.03

Notes:

[22] - Based on analysis of covariance model with treatment, randomization stratification factors, Baseline MBL volume (< 225 mL, ≥ 225 mL), geographic region (North America, Rest of World), and Baseline values as covariate.

[23] - Assessed at a two-sided α = 0.05 significance level.

Secondary: Percent Change From Baseline At Week 24 In Uterine Volume

End point title	Percent Change From Baseline At Week 24 In Uterine

End point description:

The volume of the uterus was measured by transvaginal or transabdominal ultrasound. LS means for test of difference is Relugolix plus E2/NETA minus Placebo at Week 24 is based on analysis of covariance model including treatment, randomization stratification factors, Baseline MBL volume (< 225 mL, ≥ 225 mL) and geographic region (North America, Rest of World), and Baseline values as covariate.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As per the objective of the study, the pre-specified secondary efficacy analyses compared Relugolix plus E2/NETA with Placebo. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	100		
Units: percent change				
least squares mean (confidence interval 95%)	-13.8 (-20.4 to -7.1)	-1.5 (-8.2 to 5.1)		

Statistical analyses

Statistical analysis title	Uterine Volume with Relugolix plus E2/NETA
Comparison groups	Relugolix plus E2/NETA (Group A) v Placebo (Group C)

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.0078 [26]
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	-12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.3
upper limit	-3.2
Variability estimate	Standard error of the mean
Dispersion value	4.57

Notes:

[25] - Based on analysis of covariance model including treatment, randomization stratification factors, Baseline MBL volume (< 225 mL, ≥ 225 mL), geographic region (North America, Rest of World), and Baseline values as covariate.
[26] - Assessed at a two- sided α = 0.05 significance level.

Secondary: Change From Baseline At Week 24 In UFS-QoL Bleeding And Pelvic Discomfort Scale Score As Measured By The UFS-QoL (Q1, Q2, Q5)

End point title	Change From Baseline At Week 24 In UFS-QoL Bleeding And Pelvic Discomfort Scale Score As Measured By The UFS-QoL (Q1, Q2, Q5)[27]

End point description:

The Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) Bleeding and Pelvic Discomfort (BPD) Scale has been derived from the UFS-QoL Symptoms Scale. The scale consists of the following 3 symptoms proximal to uterine fibroids: Heavy bleeding during your menstrual period (Question [Q] 1), passing blood clots during your menstrual period (Q2), and feeling tightness or pressure in your pelvic area (Q5). The lowest possible raw score is 3 and the highest possible raw score is 15. The possible raw score range is 12. The following formula was used to transform the raw score to a normalized score:
Transformed Score = [(Actual raw score – lowest possible raw score)/(Possible raw score range)] * 100
Transformed score ranges from 0 to 100 based on Likert scale (None of time, a little of time, some of the time, most of the time and all of the time). Lower score indicates minimal symptom severity and higher score indicates maximum symptom severity.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, the pre-specified secondary efficacy analyses compared Relugolix plus E2/NETA with Placebo. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: units on a scale				
least squares mean (confidence interval 95%)	-51.7 (-57.4 to -46.0)	-18.3 (-24.1 to -12.6)		

Statistical analyses

Statistical analysis title	UFS-QoL BPD Score with Relugolix plus E2/NETA
Comparison groups	Placebo (Group C) v Relugolix plus E2/NETA (Group A)
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	< 0.0001 [29]
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-33.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.2
upper limit	-25.5
Variability estimate	Standard error of the mean
Dispersion value	3.98

Notes:

[28] - Treatment difference is Relugolix plus E2/NETA minus Placebo based on mixed-effect model with treatment, visit, region, Baseline MBL, and treatment by visit interaction included as fixed effects. The multiple visits for each participant were the repeated measures as random effect within each participant and an unstructured covariance.
[29] - Assessed at a two-sided α = 0.05 significance level.

Other pre-specified: Percent Change From Baseline At Week 12 In Bone Mineral Density At The Lumbar Spine (L1-L4) As Assessed By DXA

End point title	Percent Change From Baseline At Week 12 In Bone Mineral Density At The Lumbar Spine (L1-L4) As Assessed By DXA[30]

End point description:

Bone mineral density (BMD) was assessed by dual-energy x-ray absorptiometry (DXA) at the lumbar spine (L1, L2, L3, and L4) at Baseline and at Week 12. The scans were read by the central radiology laboratory in accordance with the imaging charter. The same DXA machine was used at the local imaging center at each site and operated in the same scan mode for all images procured for an individual participant. All images were submitted for central reading. The central radiology laboratory collected and evaluated all DXA scans for acceptability and measured BMD. The LS means were based on a mixed-effect model with visit, region, Baseline menstrual blood loss volume, age at Baseline, body mass index at Baseline, bone mineral density at Baseline, race, and treatment by visit interaction included as fixed effects.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, the pre-specified secondary analyses compared Relugolix plus E2/NETA with Relugolix plus Delayed E2/NETA at Week 12. Therefore, only the Relugolix plus E2/NETA and Relugolix plus Delayed E2/NETA arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Relugolix plus Delayed E2/NETA (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	95		
Units: percent change				
least squares mean (standard error)	-0.819 (± 0.2686)	-1.919 (± 0.2767)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline At Week 24 In Bone Mineral Density At The Lumbar Spine (L1-L4), Total Hip, And Femoral Neck As Assessed By DXA

End point title	Percent Change From Baseline At Week 24 In Bone Mineral Density At The Lumbar Spine (L1-L4), Total Hip, And Femoral Neck As Assessed By DXA[31]

End point description:

BMD was assessed by DXA at the lumbar spine (L1, L2, L3, and L4), total hip, and femoral neck (same leg across participants) at Baseline and at Week 24. The scans were read by the central radiology laboratory in accordance with the imaging charter. The same DXA machine was used at the local imaging center at each site and operated in the same scan mode for all images procured for an individual participant. All images were submitted for central reading. The central radiology laboratory collected and evaluated all DXA scans for acceptability and measured BMD. The LS means were based on a mixed-effect model with visit, region, Baseline menstrual blood loss volume, age at Baseline, body mass index at Baseline, bone mineral density at Baseline, race, and treatment by visit interaction included as fixed effects. For Relugolix plus E2/NETA Lumbar Spine (L1-L4), n=95.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 24

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, the pre-specified secondary analyses compared Relugolix plus E2/NETA with Placebo at Week 24. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[32]	95		
Units: percent change				
least squares mean (standard error)				
Lumbar Spine (L1-L4)	-0.126 (± 0.2971)	0.315 (± 0.2909)		
Total Hip	-0.173 (± 0.2221)	-0.044 (± 0.2200)		
Femoral Neck	-0.684 (± 0.3730)	0.019 (± 0.3697)		

Notes:

[32] - For Lumbar Spine (L1-L4), N=95

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage Of Participants Experiencing Vasomotor Symptoms Through Week 12

End point title	Percentage Of Participants Experiencing Vasomotor Symptoms Through Week 12[33]

End point description:

An adverse event was defined as an unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The preferred terms of hyperhidrosis, feeling hot, hot flush, night sweats, and flushing were combined to describe vasomotor symptoms. Participants with multiple events for a given preferred term were counted only once for each preferred term. Reported CI based on exact binomial 95% CI (Clopper-Pearson).

End point type	Other pre-specified

End point timeframe:

Baseline through Week 12

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, the secondary analysis compared Relugolix plus E2/NETA with Relugolix plus Delayed E2/NETA at Week 12. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Relugolix plus Delayed E2/NETA (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: percentage of participants				
number (confidence interval 95%)	5.56 (2.26 to 11.11)	35.71 (27.38 to 44.74)		

Statistical analyses

Statistical analysis title	Vasomotor Symptoms Through Week 12
Comparison groups	Relugolix plus E2/NETA (Group A) v Relugolix plus Delayed E2/NETA (Group B)
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.33

Notes:

[34] - Relative risk ratio is Relugolix plus E2/NETA over Relugolix plus Delayed E2/NETA.

Other pre-specified: Percentage Of Participants Experiencing Vasomotor Symptoms Through Week 24

End point title	Percentage Of Participants Experiencing Vasomotor Symptoms Through Week 24[35]

End point description:

An adverse event was defined as an unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The preferred terms of hyperhidrosis, feeling hot, hot flush, night sweats, and flushing were combined to describe vasomotor symptoms. Participants with multiple events for a given preferred term were counted only once for each preferred term. Reported percentages based on the total number of participants in each treatment group.

End point type	Other pre-specified

End point timeframe:

Baseline through Week 24

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As per the objective of the study, the pre-specified secondary analyses compared Relugolix plus E2/NETA with Placebo. Therefore, only the Relugolix plus E2/NETA and Placebo arms are presented.

End point values	Relugolix plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	129		
Units: percentage of participants				
number (not applicable)	6.3	3.9		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Predose Trough Concentrations Of Relugolix And Norethindrone (NET) In The Relugolix Plus E2/NETA Group At Week 24

End point title	Predose Trough Concentrations Of Relugolix And Norethindrone (NET) In The Relugolix Plus E2/NETA Group At Week 24[36]

End point description:

Blood samples for determination of relugolix and NET plasma concentrations were collected predose at Week 24. On clinic visit days, participants were instructed to hold their dose of study drug until blood samples for determination of plasma drug concentrations were collected at the clinic and to record the time of their previous dose (that is, the time they took their dose on the day before the clinic visit). Relugolix and NET plasma concentrations were determined using validated bioanalytical methodology. The lower limit of quantification for relugolix and NET plasma concentrations were both 0.05 nanograms (ng)/mL. Concentrations below the quantification limit (BQL) were set to 0 for analysis of summary statistics.

End point type	Other pre-specified

End point timeframe:

Week 24

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, only Relugolix plus E2/NETA concentrations are presented.

End point values	Relugolix plus E2/NETA (Group A)			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: ng/mL				
arithmetic mean (standard deviation)				
Relugolix (N=93) NET (N=93)	1.96 (± 2.025) 0.28 (± 0.285)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Predose Trough Concentrations Of Estradiol In The Relugolix Plus E2/NETA Group At Week 24

End point title	Predose Trough Concentrations Of Estradiol In The Relugolix Plus E2/NETA Group At Week 24[37]

End point description:

Blood samples for determination of estradiol serum concentrations were collected predose at Baseline and Week 24. On clinic visit days, participants were instructed to hold their dose of study drug until blood samples for determination of serum concentrations were collected at the clinic and to record the time of their previous dose (that is, the time they took their dose on the day before the clinic visit). Summary data for estradiol trough serum concentrations are descriptive only and values were not baseline-adjusted, which is an approach that has been employed for assessment of endogenously-produced substances upon exogenous administration. Estradiol serum concentrations were determined using validated bioanalytical methodology. The lower limit of quantification for estradiol serum concentration was 2.5 picograms (pg)/mL. Concentrations BQL were set to 0 for analysis of summary statistics.

End point type	Other pre-specified

End point timeframe:

Week 24

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, only Relugolix plus E2/NETA concentrations are presented.

End point values	Relugolix plus E2/NETA (Group A)			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: pg/mL				
arithmetic mean (standard deviation)	45.34 (± 46.330)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline At Week 24 In Predose Concentrations Of Estradiol In The Relugolix Plus E2/NETA Group

End point title	Change From Baseline At Week 24 In Predose Concentrations Of Estradiol In The Relugolix Plus E2/NETA Group[38]

End point description:

Blood samples for determination of estradiol concentrations were collected predose at Baseline and at Weeks 4, 12, and 24 and were analyzed at a central laboratory using a standard, validated clinical methodology. For pharmacokinetic analysis of estradiol, a separate pharmacokinetic sample was obtained to be analyzed at the bioanalytical laboratory. The lower limit of quantification for estradiol was 19 pg/mL. Concentrations BQL were set to 0 for analysis of summary statistics. Data reported as pg/mL.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 24

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per the objective of the study, only Relugolix plus E2/NETA concentrations are presented.

End point values	Relugolix plus E2/NETA (Group A)			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: pg/mL				
arithmetic mean (standard deviation)	-22.30 (± 66.552)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 to End of Study (24 Weeks)

Adverse event reporting additional description:

One participant was randomized to Group A, but was dispensed and received Group B therapy. Per the statistical analysis plan, data from this participant was included in Group A for efficacy analyses and in Group B for safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Relugolix plus E2/NETA (Group A)

Reporting group description:

Relugolix co-administered with E2/NETA for 24 weeks.

Reporting group title	Relugolix plus Delayed E2/NETA (Group B)

Reporting group description:

Relugolix co-administered with E2/NETA placebo for 12 weeks, followed by relugolix co-administered with E2/NETA for 12 weeks.

Reporting group title	Placebo (Group C)

Reporting group description:

Relugolix placebo co-administered with E2/NETA placebo for 24 weeks.

Serious adverse events	Relugolix plus E2/NETA (Group A)	Relugolix plus Delayed E2/NETA (Group B)	Placebo (Group C)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 126 (0.79%)	2 / 126 (1.59%)	4 / 129 (3.10%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 126 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 126 (0.00%)	0 / 126 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Syncope			
subjects affected / exposed	0 / 126 (0.00%)	0 / 126 (0.00%)	1 / 129 (0.78%)
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 / 126 (0.00%)	0 / 126 (0.00%)	1 / 129 (0.78%)
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			
Cholecystitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 126 (0.00%)	0 / 129 (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
Cholecystitis acute			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	0 / 129 (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 degeneration			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	0 / 129 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	0 / 129 (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
Infections and infestations			
Necrotising fasciitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 126 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Relugolix plus E2/NETA (Group A)	Relugolix plus Delayed E2/NETA (Group B)	Placebo (Group C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 126 (60.32%)	90 / 126 (71.43%)	75 / 129 (58.14%)
Vascular disorders			
Hot flush			
subjects affected / exposed	7 / 126 (5.56%)	44 / 126 (34.92%)	5 / 129 (3.88%)
occurrences (all)	7	46	5
Hypertension			
subjects affected / exposed	5 / 126 (3.97%)	7 / 126 (5.56%)	4 / 129 (3.10%)
occurrences (all)	5	7	4
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 126 (8.73%)	28 / 126 (22.22%)	15 / 129 (11.63%)
occurrences (all)	15	34	21
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 126 (1.59%)	2 / 126 (1.59%)	7 / 129 (5.43%)
occurrences (all)	2	2	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 126 (0.79%)	7 / 126 (5.56%)	2 / 129 (1.55%)
occurrences (all)	1	7	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 126 (4.76%)	4 / 126 (3.17%)	10 / 129 (7.75%)
occurrences (all)	6	4	11
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 126 (0.79%)	8 / 126 (6.35%)	4 / 129 (3.10%)
occurrences (all)	1	11	6
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 126 (4.76%)	3 / 126 (2.38%)	7 / 129 (5.43%)
occurrences (all)	6	3	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported