Clinical trial results:
HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer

Summary

EudraCT number	2017-000160-15
Trial protocol	NL SE GB BE AT SK DK FI ES DE PL FR IT
Global end of trial date	26 November 2021

Results information

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

Trial information

Trial identification

Sponsor protocol code	MVT-601-3201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03085095
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Myovant Sciences GmbH
Sponsor organisation address	Aeschengraben 27, Basel, Switzerland, 4051
Public contact	Clinical Trials at Myovant, Myovant Sciences GmbH, 001 6502788749, clinicaltrials@myovant.com
Scientific contact	Clinical Trials at Myovant, Myovant Sciences GmbH, 001 6502788743, clinicaltrials@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	14 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2019
Global end of trial reached?	Yes
Global end of trial date	26 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (< 50 ng/dL [1.7 nmol/L]) in men with androgen-sensitive advanced prostate cancer.

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	29 September 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	Netherlands: 16
Country: Number of subjects enrolled	Poland: 73
Country: Number of subjects enrolled	Slovakia: 112
Country: Number of subjects enrolled	Spain: 59
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Denmark: 21
Country: Number of subjects enrolled	Finland: 23
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	China: 12
Country: Number of subjects enrolled	Japan: 121
Country: Number of subjects enrolled	Korea, Republic of: 84
Country: Number of subjects enrolled	New Zealand: 21
Country: Number of subjects enrolled	Taiwan: 25
Country: Number of subjects enrolled	Brazil: 69

Country: Number of subjects enrolled	Canada: 50
Country: Number of subjects enrolled	United States: 261
Worldwide total number of subjects	1078
EEA total number of subjects	396

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)	203
From 65 to 84 years	829
85 years and over	46

Subject disposition

Recruitment

Recruitment details:

To support registration in China, the study continued to enroll additional nonmetastatic or metastatic participants from China after the final analysis to reach the target enrollment of approximately 90 participants.

Pre-assignment

Screening details:

The primary analysis of efficacy and safety included 934 participants.

Period 1

Period 1 title	Randomized Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Primary Analysis Population - Relugolix

Arm description:

Relugolix 120-milligram (mg) tablet administered orally once daily for 48 weeks following an oral loading dose of 360 mg (3 x 120-mg tablets) on Day 1.

Arm type	Experimental
Investigational medicinal product name	Relugolix
Investigational medicinal product code	
Other name	TAK-385, MVT-601, RVT-601, T-1331285
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Loading dose of 360 mg on Day 1 followed by 120 mg once daily

Arm title	Primary Analysis Population - Leuprolide Acetate

Arm description:

Leuprolide acetate depot suspension, 22.5 mg (or 11.25 mg in Japan and Taiwan), every 3 months by subcutaneous injection.

Arm type	Active comparator
Investigational medicinal product name	Leuprolide acetate
Investigational medicinal product code	
Other name	Leuprolide
Pharmaceutical forms	Suspension for injection
Routes of administration	Injection

Dosage and administration details:

22.5 mg (or 11.25 mg in Japan, Taiwan, and China), every 3 months by subcutaneous injection

Number of subjects in period 1[1]	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate
Started	624	310
Completed	563	276
Not completed	61	34
Consent withdrawn by subject	17	6
Physician decision	9	3
Dosing interruption (logistical reason)	1	-
Adverse event	23	8
Did not receive study drug	2	2
Lost to follow-up	2	1
Testosterone suppression level not met	7	13
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of four patients were randomized and not treated (two each in the relugolix and leuprolide groups).

Baseline characteristics

Reporting groups	
Reporting group title	Primary Analysis Population - Relugolix
Reporting group description:	
Relugolix 120-milligram (mg) tablet administered orally once daily for 48 weeks following an oral loading dose of 360 mg (3 x 120-mg tablets) on Day 1.	
Reporting group title	Primary Analysis Population - Leuprolide Acetate
Reporting group description:	
Leuprolide acetate depot suspension, 22.5 mg (or 11.25 mg in Japan and Taiwan), every 3 months by subcutaneous injection.	

Reporting group values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate	Total
Number of subjects	624	310	934
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults (18 years and over)	622	308	930
Not recorded	2	2	4
Age continuous Units: years			
arithmetic mean	71.2	71.0	
standard deviation	± 7.75	± 8.03	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	622	308	930
Not recorded	2	2	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	52	31	83
Not Hispanic or Latino	558	269	827
Unknown or Not Reported	12	8	20
Not recorded	2	2	4
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	127	71	198

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	30	16	46
White	434	202	636
More than one race	11	4	15
Unknown or Not Reported	20	15	35
Not recorded	2	2	4

End points

End points reporting groups

Reporting group title	Primary Analysis Population - Relugolix
Reporting group description:	
Relugolix 120-milligram (mg) tablet administered orally once daily for 48 weeks following an oral loading dose of 360 mg (3 x 120-mg tablets) on Day 1.	
Reporting group title	Primary Analysis Population - Leuprolide Acetate
Reporting group description:	
Leuprolide acetate depot suspension, 22.5 mg (or 11.25 mg in Japan and Taiwan), every 3 months by subcutaneous injection.	
Subject analysis set title	Final Analysis Population - Relugolix
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients with or without metastatic disease	
Subject analysis set title	Final Analysis Population - Leuprolide Acetate
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients with or without metastatic disease	
Subject analysis set title	mITT Metastatic Population - Relugolix
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Patients with metastatic prostate cancer	
Subject analysis set title	mITT Metastatic Population - Leuprolide Acetate
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Patients with metastatic prostate cancer	
Subject analysis set title	Greater China Patient Population - Relugolix
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
To support registration in China, data were analyzed separately for patients enrolled in China and Taiwan.	
Subject analysis set title	Greater China Patient Population - Leuprolide Acetate
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
To support registration in China, data were analyzed separately for patients enrolled in China and Taiwan.	

Primary: Sustained Castration Rate

End point title	Sustained Castration Rate
End point description:	
Sustained castration rate defined as the cumulative probability of testosterone suppression to < 50 nanogram (ng)/deciliter (dL). The rate was estimated for each treatment group using the Kaplan–Meier method and reported as percentage of participants. The lower bound of the 95% confidence interval (CI) for the cumulative probability of sustained testosterone suppression in the relugolix treatment group must have been ≥ 90% to meet evaluation criteria for efficacy.	
End point type	Primary
End point timeframe:	
From Week 5 Day 1 (Day 29) to Week 49 Day 1 (Day 337)	

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate	Greater China Patient Population - Relugolix	Greater China Patient Population - Leuprolide Acetate
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	622	308	63	29
Units: Percentage of Participants				
number (confidence interval 95%)	96.7 (94.9 to 97.9)	88.8 (84.6 to 91.8)	98.0 (86.9 to 99.7)	93.0 (74.7 to 98.2)

Statistical analyses

Statistical analysis title	Analysis 1 for Sustained Castration Rate

Statistical analysis description:

Following statistical analysis of the lower bound of the 95% CI ≥ 90% for the relugolix group, secondary statistical analysis of non-inferiority was conducted.

Comparison groups	Primary Analysis Population - Leuprolide Acetate v Primary Analysis Population - Relugolix
Number of subjects included in analysis	930
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Treatment Difference
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.1
upper limit	11.8

Notes:

[1] - The lower bound of the 95% CI for the difference in the cumulative probability of sustained profound castration rate between the 2 treatment groups was calculated with a noninferiority margin of -10%.

Statistical analysis title	Analysis 2 for Sustained Castration Rate

Statistical analysis description:

Following statistical analysis of the lower bound of the 95% CI ≥ 90% for the relugolix group, secondary statistical analysis of superiority was conducted.

Comparison groups	Primary Analysis Population - Relugolix v Primary Analysis Population - Leuprolide Acetate
Number of subjects included in analysis	930
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	t-test, 2-sided

Notes:

[2] - If non-inferiority was demonstrated, superiority could be claimed if the lower bound of the 95% CI for the difference in the cumulative probability of sustained profound castration rate between the 2 treatment groups also excluded 0%. The p value was calculated post hoc.
[3] - Two-sided type I error of 0.05.

Secondary: Castration Rate At Week 1 Day 4

End point title	Castration Rate At Week 1 Day 4

End point description:

Castration rate was defined as the cumulative probability of testosterone suppression to < 50 ng/dL. The rate was estimated for each treatment group using the Kaplan–Meier method and reported as percentage of participants.

End point type	Secondary

End point timeframe:

Week 1 Day 4 (Day 4)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate	Greater China Patient Population - Relugolix	Greater China Patient Population - Leuprolide Acetate
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	622	308	63	29
Units: Percentage of Participants				
number (confidence interval 95%)	56.04 (52.18 to 59.97)	0.00 (0 to 0)	56.45 (44.63 to 68.93)	0.00 (0.00 to 0.00)

Statistical analyses

Statistical analysis title	Analysis 1 for Castration Rate At Week 1 Day 4

Statistical analysis description:

Alpha-protected statistical analysis.

Comparison groups	Primary Analysis Population - Relugolix v Primary Analysis Population - Leuprolide Acetate
Number of subjects included in analysis	930
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	t-test, 2-sided

Notes:

[4] - Statistically significance was met if p-value < 0.05.
Two-sided type I error rate of 0.05.

Secondary: Castration Rate At Week 3 Day 1

End point title	Castration Rate At Week 3 Day 1

End point description:

Castration rate was defined as the cumulative probability of testosterone suppression to < 50 ng/dL. The rate was estimated for each treatment group using the Kaplan–Meier method and reported as percentage of participants.

End point type	Secondary

End point timeframe:

Week 3 Day 1 (Day 15)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate	Greater China Patient Population - Relugolix	Greater China Patient Population - Leuprolide Acetate
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	622	308	63	29
Units: Percentage of Participants				
number (confidence interval 95%)	98.71 (97.56 to 99.39)	12.05 (8.88 to 16.25)	96.77 (90.06 to 99.39)	17.24 (7.57 to 36.57)

Statistical analyses

Statistical analysis title	Analysis 1 for Castration Rate At Week 3 Day 1
Statistical analysis description: Alpha-protected statistical analysis.	
Comparison groups	Primary Analysis Population - Relugolix v Primary Analysis Population - Leuprolide Acetate
Number of subjects included in analysis	930
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	t-test, 2-sided

Notes:

[5] - Statistically significance was met if p-value < 0.05.
Two-sided type I error rate of 0.05.

Secondary: Confirmed Prostate-specific Antigen (PSA) Response Rate

End point title	Confirmed Prostate-specific Antigen (PSA) Response Rate
End point description: Confirmed PSA response defined as > 50% reduction in PSA from baseline at Week 3 Day 1 followed with confirmation at Week 5 Day 1.	
End point type	Secondary
End point timeframe: Week 3 Day 1 (Day 15) and Week 5 Day 1 (Day 29)	

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate	Greater China Patient Population - Relugolix	Greater China Patient Population - Leuprolide Acetate
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	622	308	63	29
Units: Percentage of Participants				
number (confidence interval 95%)	79.4 (76.03 to 82.53)	19.8 (15.50 to 24.70)	88.9 (78.44 to 95.41)	55.2 (35.69 to 73.55)

Statistical analyses

Statistical analysis title	Analysis 1 for Confirmed PSA Response Rate
Statistical analysis description:	
Alpha-protected statistical analysis.	
Comparison groups	Primary Analysis Population - Relugolix v Primary Analysis Population - Leuprolide Acetate
Number of subjects included in analysis	930
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel

Notes:

[6] - Statistically significance was met if p-value < 0.05.

Secondary: Profound Castration Rate At Week 3 Day 1 (Day 15)

End point title	Profound Castration Rate At Week 3 Day 1 (Day 15)
End point description:	
Castration rate defined as the cumulative probability of testosterone suppression to < 20 ng/dL. The rate was estimated for each treatment group using the Kaplan–Meier method and reported as percentage of participants.	
End point type	Secondary
End point timeframe:	
Week 3 Day 1 (Day 15)	

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate	Greater China Patient Population - Relugolix	Greater China Patient Population - Leuprolide Acetate
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	622	308	63	29
Units: Percentage of Participants				
number (confidence interval 95%)	78.38 (75.06 to 81.53)	0.98 (0.32 to 3.00)	72.58 (61.18 to 82.96)	0.00 (0.00 to 0.00)

Statistical analyses

Statistical analysis title	Analysis 1 for Profound Castration Rate
Statistical analysis description:	
Alpha-protected statistical analysis.	
Comparison groups	Primary Analysis Population - Relugolix v Primary Analysis Population - Leuprolide Acetate

Number of subjects included in analysis	930
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	t-test, 2-sided
Parameter estimate	Treatment Difference
Point estimate	77.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	73.98
upper limit	80.83

Notes:

[7] - Statistically significance was met if p-value < 0.05.
Two-sided type I error rate of 0.05.

Secondary: Follicle-stimulating Hormone (FSH) Level

End point title	Follicle-stimulating Hormone (FSH) Level

End point description:

To evaluate the effect of relugolix and leuprolide acetate on FSH suppression.

End point type	Secondary

End point timeframe:

Week 25 Day 1 (Day 169)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate	Greater China Patient Population - Relugolix	Greater China Patient Population - Leuprolide Acetate
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	622	308	63	29
Units: IU/L				
least squares mean (standard deviation)	1.72 (± 1.376)	5.95 (± 3.071)	1.72 (± 1.455)	6.95 (± 2.768)

Statistical analyses

Statistical analysis title	Analysis 1 for FSH Level

Statistical analysis description:

Alpha-protected statistical analysis.

Comparison groups	Primary Analysis Population - Relugolix v Primary Analysis Population - Leuprolide Acetate
Number of subjects included in analysis	930
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	t-test, 2-sided

Notes:

[8] - Statistically significance was met if p-value < 0.05.
Two-sided type I error rate of 0.05.

Secondary: PSA Response Rate At Week 3 Day 1

End point title	PSA Response Rate At Week 3 Day 1

End point description:

PSA response defined as > 50% reduction in PSA from baseline. The rate was estimated for each treatment group using the Kaplan–Meier method and reported as percentage of participants.

End point type	Secondary

End point timeframe:

Week 5 Day 1 (Day 29)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percentage of Participants				
number (confidence interval 95%)	94.5 (92.44 to 96.19)	79.2 (74.26 to 83.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Testosterone Recovery Rate

End point title	Testosterone Recovery Rate

End point description:

The cumulative probability of testosterone recovery back to > 280 ng/dL (lower limit of the normal range), back to ≥ 50 ng/dL (definition of castration), and back to > 280 ng/dL or baseline at 90 days after drug discontinuation was assessed. The rate was estimated for each treatment group using the Kaplan–Meier method and reported as percentage of participants.

End point type	Secondary

End point timeframe:

Day 90 follow-up

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percentage of Participants				
number (confidence interval 95%)				

≥ 50 ng/dL	93.01 (87.82 to 96.54)	10.12 (3.84 to 25.24)		
>280 ng/dL	53.93 (45.20 to 63.16)	3.23 (0.46 to 20.77)		
> Baseline level or 280 ng/dL	54.73 (45.97 to 63.94)	3.23 (0.46 to 20.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sustained Profound Castration Rate From Week 5 Day 1 Through Week 49 Day 1

End point title	Sustained Profound Castration Rate From Week 5 Day 1 Through Week 49 Day 1

End point description:

Sustained profound castration rate was defined as the cumulative probability of testosterone suppression to < 20 ng/dL.
The rate was estimated by the Kaplan-Meier method and reported as percentage of participants.

End point type	Secondary

End point timeframe:

Week 5 Day 1 (Day 29) through Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percentage of Participants				
number (confidence interval 95%)	81.6 (78.1 to 84.5)	68.6 (63.0 to 73.5)		

Statistical analyses

Statistical analysis title	Analysis 1 for Sustained Profound Castration Rate
Comparison groups	Primary Analysis Population - Relugolix v Primary Analysis Population - Leuprolide Acetate
Number of subjects included in analysis	930
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment Difference
Point estimate	13

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.9
upper limit	19.1

Secondary: Profound Castration Rate At Week 1 Day 4 (Day 4)

End point title	Profound Castration Rate At Week 1 Day 4 (Day 4)

End point description:

Castration rate defined as the cumulative probability of testosterone suppression to < 20 ng/dL. The rate was estimated for each treatment group using the Kaplan–Meier method and reported as percentage of participants.

End point type	Secondary

End point timeframe:

At Week 1 Day 4 (Day 4)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percentage of Participants				
number (confidence interval 95%)	6.92 (5.18 to 9.22)	0.0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sustained Profound Castration Rate From Week 25 Day 1 Through Week 49 Day 1

End point title	Sustained Profound Castration Rate From Week 25 Day 1 Through Week 49 Day 1

End point description:

Sustained profound castration rate was defined as the cumulative probability of testosterone suppression to < 20 ng/dL.
The rate was estimated by the Kaplan-Meier method and reported as percentage of participants.

End point type	Secondary

End point timeframe:

Week 25 Day 1 (Day 169) through Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percentage of Participants				
number (confidence interval 95%)	84.6 (81.3 to 87.3)	87.5 (83.0 to 90.8)		

Statistical analyses

Statistical analysis title	Analysis 1 for Sustained Profound Castration Rate
Comparison groups	Primary Analysis Population - Relugolix v Primary Analysis Population - Leuprolide Acetate
Number of subjects included in analysis	930
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment Difference
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	2

Secondary: Undetectable PSA Rate

End point title	Undetectable PSA Rate
End point description:	
Defined as the proportion of participants with PSA concentration < 0.02 ng/milliliter (mL).The rate was estimated by the Kaplan-Meier method and reported as percentage of participants.	
End point type	Secondary
End point timeframe:	
Week 25 Day 1 (Day 169)	

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percentage of Participants				
number (confidence interval 95%)	20.7 (17.62 to 24.14)	20.8 (16.39 to 25.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of PSA Progression-free Survival

End point title	Rate of PSA Progression-free Survival

End point description:

PSA progression was defined as the first increase in PSA of 25% or greater and 2 ng/mL or greater above the nadir with confirmation by a second consecutive PSA measurement at least 3 weeks later. For participants without declining PSA from baseline, a PSA increase of ≥ 25% and ≥ 2 ng/mL from baseline beyond 12 weeks was considered PSA progression. The rate of progression-free survival was estimated using the Kaplan-Meier method and reported as percentage of participants.

End point type	Secondary

End point timeframe:

Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percentage of Participants				
number (confidence interval 95%)	89.31 (86.52 to 91.55)	89.50 (85.39 to 92.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Quality Of Life (QoL) Total Score As Assessed By The Global Health Domain Of The European Organisation Of Research And Treatment Of Cancer (EORTC)-Quality Of Life Questionnaire (QLQ)-C30

End point title	Change From Baseline In Quality Of Life (QoL) Total Score As Assessed By The Global Health Domain Of The European Organisation Of Research And Treatment Of Cancer (EORTC)-Quality Of Life Questionnaire (QLQ)-C30

End point description:

The EORTC QLQ-C30 core measurement was used to capture distal outcomes, including physical, social functioning, and overall health-related quality of life. The questionnaire incorporates 30 questions comprising nine multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality of life scale. All raw domain scores are linearly transformed to a 0-100 scale. The global health and quality of life domain is presented. An increase in activity or functioning scores indicates improvement

(higher/healthier level of functioning) and a decrease in symptom scores indicates improvement (lower level of symptoms/problems).

End point type	Secondary

End point timeframe:

Baseline, Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	543	257		
Units: Score on a Scale				
least squares mean (standard deviation)				
Physical functioning	-4.6 (± 13.09)	-4.4 (± 12.29)		
Role functioning	-6.2 (± 19.92)	-5.6 (± 17.84)		
Emotional functioning	0.5 (± 16.12)	-0.5 (± 13.23)		
Cognitive functioning	-3.7 (± 16.77)	-3.8 (± 16.37)		
Social functioning	-2.7 (± 18.31)	-4.0 (± 18.18)		
Fatigue	6.1 (± 19.46)	7.0 (± 18.40)		
Nausea and vomiting	0.2 (± 7.12)	0.8 (± 6.02)		
Pain	1.7 (± 20.19)	4.0 (± 21.96)		
Dyspnoea	5.3 (± 19.16)	7.9 (± 20.25)		
Insomnia	4.8 (± 25.88)	4.8 (± 21.82)		
Appetite loss	-0.6 (± 17.82)	-0.6 (± 14.86)		
Constipation	1.4 (± 23.26)	3.5 (± 18.88)		
Diarrhoea	2.0 (± 16.70)	1.4 (± 19.60)		
Financial difficulties	0.2 (± 18.28)	0.1 (± 19.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In QoL Total Score As Assessed By The EORTC-QLQ-PR25 Sexual Activity And Functioning And Hormonal-Treatment-Related Symptom Subdomains

End point title	Change From Baseline In QoL Total Score As Assessed By The EORTC-QLQ-PR25 Sexual Activity And Functioning And Hormonal-Treatment-Related Symptom Subdomains

End point description:

Subscales for assessment of hormonal treatment-related symptoms (6 items) and sexual activity and function (6 items) from the EORTC-QLQ-PR25 25-item prostate cancer module of the EORTC are presented. Questions used 4 point scale (1 'Not at all' to 4 'Very much'). All raw domain scores are linearly transformed to a 0-100 scale. An increase in activity or functioning scores indicates improvement (higher/healthier level of functioning) and a decrease in symptom scores indicates improvement (lower level of symptoms/problems).

End point type	Secondary

End point timeframe:

Baseline, Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	537	256		
Units: Score on a Scale				
least squares mean (standard deviation)				
Sexual activity	13.9 (± 26.51)	10.8 (± 27.90)		
Sexual functioning	-9.0 (± 23.37)	-10.4 (± 21.10)		
Hormonal treatment-related symptoms	10.6 (± 12.25)	11.4 (± 13.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In QoL Total Score For Urinary And Bowel Symptoms Domains As Assessed By The EORTCQLQ- PR25

End point title	Change From Baseline In QoL Total Score For Urinary And Bowel Symptoms Domains As Assessed By The EORTCQLQ-PR25

End point description:

Subscale assessments of urinary symptoms (9 items) and bowel symptoms (4 items) from the EORTC-QLQ-PR25 25-item prostate cancer module of the EORTC are presented. Questions used 4 point scale (1 'Not at all' to 4 'Very much'). All raw domain scores are linearly transformed to a 0-100 scale. A decrease in symptom scores indicates improvement
(lower level of symptoms/problems).

End point type	Secondary

End point timeframe:

Baseline, Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	537	256		
Units: Score on a Scale				
least squares mean (standard deviation)				
Urinary symptoms	1.1 (± 15.29)	-0.4 (± 13.78)		
Incontinence aid use	1.0 (± 15.41)	0.0 (± 19.80)		
Bowel symptoms	1.2 (± 8.92)	2.0 (± 9.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In QoL Total Score As Assessed By The European Quality Of Life 5-Dimension 5-Level Questionnaire (EuroQoL EQ-5D-5L)

End point title	Change From Baseline In QoL Total Score As Assessed By The European Quality Of Life 5-Dimension 5-Level Questionnaire (EuroQoL EQ-5D-5L)

End point description:

The EuroQoL EQ-5D-5L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 levels: no problems (1 as numerical score), slight problems (2 as numerical score), moderate problems (3 as numerical score), severe problems (4 as numerical score), and extreme problems (5 as numerical score). The total score ranges from 0 to 100. A decrease in score indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	259		
Units: Score on a Scale				
least squares mean (standard deviation)	-1.5 (± 14.36)	-2.7 (± 14.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline In Serum Concentrations Of Luteinizing Hormone

End point title	Percent Change From Baseline In Serum Concentrations Of Luteinizing Hormone

End point description:

Blood samples were collected from participants for hormonal measurements.

End point type	Secondary

End point timeframe:

Week 1 Day 4 (Day 4), Week 5 Day 1 (Day 29), Week 25 Day 1 (Day 169), and Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percent Change				
least squares mean (standard deviation)				
Week 1 Day 4 (Day 4)	-88.25 (± 20.696)	147.71 (± 122.735)		
Week 5 Day 1 (Day 29)	-94.54 (± 8.500)	-82.67 (± 27.146)		
Week 25 Day 1 (Day 169)	-93.93 (± 7.242)	-93.45 (± 13.202)		
Week 49 Day 1 (Day 337)	-91.54 (± 16.779)	-95.14 (± 4.507)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline In Serum Concentrations Of FSH

End point title	Percent Change From Baseline In Serum Concentrations Of FSH

End point description:

Blood samples were collected from participants for hormonal measurements.

End point type	Secondary

End point timeframe:

Week 1 Day 4 (Day 4), Week 5 Day 1 (Day 29), Week 25 Day 1 (Day 169), and Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percent Change				
least squares mean (standard deviation)				
Week 1 Day 4 (Day 4)	-62.59 (± 9.051)	-4.74 (± 36.121)		
Week 5 Day 1 (Day 29)	-90.80 (± 8.151)	-67.73 (± 27.311)		
Week 25 Day 1 (Day 169)	-86.32 (± 10.699)	-47.53 (± 32.560)		
Week 49 Day 1 (Day 337)	-79.39 (± 21.987)	-47.23 (± 30.112)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline In Serum Concentrations Of Dihydrotestosterone

End point title	Percent Change From Baseline In Serum Concentrations Of Dihydrotestosterone

End point description:

Blood samples were collected from participants for hormonal measurements.

End point type	Secondary

End point timeframe:

Week 5 Day 1 (Day 29), Week 25 Day 1 (Day 169), and Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percent Change				
least squares mean (standard deviation)				
Week 5 Day 1 (Day 29)	-87.61 (± 12.225)	-81.95 (± 23.733)		
Week 25 Day 1 (Day 169)	-88.06 (± 11.810)	-85.45 (± 32.261)		
Week 49 Day 1 (Day 337	-88.23 (± 11.235)	-87.56 (± 12.088)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline In Serum Concentrations Of Sex Hormone-Binding Globulin

End point title	Percent Change From Baseline In Serum Concentrations Of Sex Hormone-Binding Globulin

End point description:

Blood samples were collected from participants for hormonal measurements.

End point type	Secondary

End point timeframe:

Week 5 Day 1 (Day 29), Week 25 Day 1 (Day 169), and Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percent Change				
least squares mean (standard deviation)				
Week 5 Day 1 (Day 29)	1.08 (± 22.068)	-1.21 (± 20.430)		
Week 25 Day 1 (Day 169)	7.24 (± 28.265)	3.59 (± 24.947)		
Week 49 Day 1 (Day 337)	6.54 (± 28.787)	2.59 (± 27.051)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) Of Relugolix

End point title	Maximum Observed Plasma Concentration (Cmax) Of Relugolix

End point description:

The Cmax of relugolix was determined for single and repeat doses in subsets of participants from Japan. Single dose pharmacokinetics (PK) was assessed on Day 1 following an initial 360 mg dose of relugolix. Repeat dose PK was assessed following repeat dosing of relugolix 120 mg once daily for 2 weeks.

End point type	Secondary

End point timeframe:

Predose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose on Day 1 and Week 2

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	125 (± 220)	46.4 (± 141)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Concentration-Time Curve (AUC0-τ) Of Relugolix

End point title	Area Under The Concentration-Time Curve (AUC0-τ) Of Relugolix

End point description:

The AUC0-τ of relugolix was determined for single and repeat doses in subsets of participants from Japan. Single dose PK was assessed on Day 1 following an initial 360 mg dose of relugolix. Repeat dose PK was assessed following repeat dosing of relugolix 120 mg once daily for 2 weeks.

End point type	Secondary

End point timeframe:

Predose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose on Day 1 and Week 2

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: ng#hr/mL				
geometric mean (geometric coefficient of variation)	663 (± 151)	373 (± 51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Maximum Observed Plasma Concentration (Tmax) Of Relugolix

End point title	Time To Maximum Observed Plasma Concentration (Tmax) Of Relugolix

End point description:

The Tmax of relugolix was determined for single and repeat doses in subsets of participants from Japan. Single dose PK was assessed on Day 1 following an initial 360 mg dose of relugolix. Repeat dose PK was assessed following repeat dosing of relugolix 120 mg once daily for 2 weeks.

End point type	Secondary

End point timeframe:

Predose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose on Day 1 and Week 2

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: Hours				

median (full range (min-max))	1.03 (0.400 to 4.05)	0.983 (0.433 to 4.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Castration Resistance-Free Survival

End point title	Castration Resistance-Free Survival

End point description:

Castration resistance-free survival during the 48-week treatment in patients with or without metastatic prostate cancer

End point type	Secondary

End point timeframe:

Day 337

End point values	Final Analysis Population - Relugolix	Final Analysis Population - Leuprolide Acetate	mITT Metastatic Population - Relugolix	mITT Metastatic Population - Leuprolide Acetate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	717	357	290	144
Units: Percentage of Participants				
number (confidence interval 95%)	86.82 (84.00 to 89.18)	87.33 (83.21 to 90.50)	74.31 (68.56 to 79.17)	75.27 (66.71 to 81.93)

End point values	Greater China Patient Population - Relugolix	Greater China Patient Population - Leuprolide Acetate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	29		
Units: Percentage of Participants				
number (confidence interval 95%)	68.71 (55.01 to 79.01)	70.28 (49.09 to 83.96)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants Who Experienced Major Adverse

Cardiovascular Events (MACE)

End point title	Percentage of Participants Who Experienced Major Adverse Cardiovascular Events (MACE)

End point description:

MACE were defined as nonfatal myocardial infarction, nonfatal stroke, and death from any cause.

End point type	Other pre-specified

End point timeframe:

Week 49 Day 1 (Day 337)

End point values	Primary Analysis Population - Relugolix	Primary Analysis Population - Leuprolide Acetate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	308		
Units: Percentage of Participants				
number (not applicable)	2.9	6.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 (after dosing) through up to 52 weeks	
Adverse event reporting additional description:	
All randomized participants who received at least 1 dose of study drug in the primary analysis part of the study.	
Assessment type	Systematic

Dictionary used	
Dictionary name	Vocabulary
Dictionary version	22.0

Reporting groups	
Reporting group title	Relugolix
Reporting group description:	
Relugolix 120-mg tablet administered orally once daily for 48 weeks following an oral loading dose of 360 mg (3 x 120-mg tablets) on Day 1.	
Reporting group title	Leuprolide Acetate
Reporting group description:	
Leuprolide acetate depot suspension, 22.5 mg (or 11.25 mg in Japan, and Taiwan), every 3 months by subcutaneous injection.	

Serious adverse events	Relugolix	Leuprolide Acetate	
Total subjects affected by serious adverse events			
subjects affected / exposed	76 / 622 (12.22%)	47 / 308 (15.26%)	
number of deaths (all causes)	12	10	
number of deaths resulting from adverse events	7	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma stage II			

subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma stage I			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	2 / 622 (0.32%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer metastatic			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			

subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	2 / 622 (0.32%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Schwannoma			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transitional cell cancer of the renal pelvis and ureter			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	1 / 622 (0.16%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			

subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Social circumstances			
Homicide			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 622 (0.32%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 622 (0.32%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood sodium decreased			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachial plexus injury			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis radiation			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary contusion			
subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt aneurysm			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			

subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 622 (0.16%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	5 / 622 (0.80%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 622 (0.32%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			

subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 622 (0.16%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 622 (0.16%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 622 (0.00%)	3 / 308 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Cardiopulmonary failure			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus arrest			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			

subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 622 (0.00%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 622 (0.00%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 622 (0.00%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 622 (0.00%)	3 / 308 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 622 (0.00%)	3 / 308 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 622 (0.16%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal incarcerated hernia			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	0 / 622 (0.00%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 622 (0.64%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bladder neck obstruction			

subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder obstruction			
subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder outlet obstruction			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 622 (0.16%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower urinary tract symptoms			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Micturition urgency			

subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthropathy			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Appendicitis perforated			
subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 622 (0.32%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 622 (0.32%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 622 (0.32%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			

subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 622 (0.48%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 622 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 622 (0.16%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Relugolix	Leuprolide Acetate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	578 / 622 (92.93%)	288 / 308 (93.51%)	
Investigations			
Weight increased			
subjects affected / exposed	49 / 622 (7.88%)	20 / 308 (6.49%)	
occurrences (all)	49	20	
Vascular disorders			
Hot flush			
subjects affected / exposed	338 / 622 (54.34%)	159 / 308 (51.62%)	
occurrences (all)	338	159	
Hypertension			
subjects affected / exposed	49 / 622 (7.88%)	36 / 308 (11.69%)	
occurrences (all)	49	36	
Nervous system disorders			
Dizziness			
subjects affected / exposed	35 / 622 (5.63%)	17 / 308 (5.52%)	
occurrences (all)	35	17	
Headache			
subjects affected / exposed	35 / 622 (5.63%)	13 / 308 (4.22%)	
occurrences (all)	35	13	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	32 / 622 (5.14%)	21 / 308 (6.82%)	
occurrences (all)	32	21	
Fatigue			
subjects affected / exposed	134 / 622 (21.54%)	57 / 308 (18.51%)	
occurrences (all)	134	57	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	76 / 622 (12.22%)	30 / 308 (9.74%)	
occurrences (all)	76	30	
Diarrhoea			
subjects affected / exposed	76 / 622 (12.22%)	21 / 308 (6.82%)	
occurrences (all)	76	21	
Nausea			
subjects affected / exposed	36 / 622 (5.79%)	13 / 308 (4.22%)	
occurrences (all)	36	13	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	15 / 622 (2.41%)	16 / 308 (5.19%)	
occurrences (all)	15	16	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	43 / 622 (6.91%)	14 / 308 (4.55%)	
occurrences (all)	43	14	
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	36 / 622 (5.79%)	19 / 308 (6.17%)	
occurrences (all)	36	19	
Pollakiuria			
subjects affected / exposed	37 / 622 (5.95%)	20 / 308 (6.49%)	
occurrences (all)	37	20	
Urinary incontinence			
subjects affected / exposed	30 / 622 (4.82%)	16 / 308 (5.19%)	
occurrences (all)	30	16	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	75 / 622 (12.06%)	28 / 308 (9.09%)	
occurrences (all)	75	28	
Back pain			
subjects affected / exposed	50 / 622 (8.04%)	28 / 308 (9.09%)	
occurrences (all)	50	28	
Pain in extremity			

subjects affected / exposed occurrences (all)	32 / 622 (5.14%) 32	19 / 308 (6.17%) 19	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	59 / 622 (9.49%) 59	29 / 308 (9.42%) 29	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 January 2018	The primary purpose of Amendment 1 was to provide clarification regarding entry criteria, prohibited medications, schedule of activities, and update on safety reporting. However, because of a typographical error in an exclusion criterion, the meaning of that criterion was inadvertently changed. This amendment was initially submitted to a regulatory authority, then withdrawn.
18 January 2018	The typographical error in the exclusion criterion was corrected and all other clarifications previously stated above were included in a new version, Amendment 2. To alleviate the burden of study visits on participants, this amendment also eliminated the Day 22 visit, resulting in fewer patients having data at this visit compared with the rest of the study visits. All patients enrolled under the original protocol and Amendment 2 were part of the primary analysis to assess the safety and efficacy of relugolix in achieving castration within 4 weeks and maintaining it over an additional 44 weeks.
23 October 2018	The primary purpose of Amendment 3 was to include an additional alpha-protected key secondary endpoint of castration resistance-free survival, an important indicator of disease progression, in the final analysis. To support this analysis, the protocol allowed for an additional cohort of approximately 100 patients with metastatic disease to be enrolled to ensure an appropriate level of statistical power for the analysis (targeting ~390 metastatic patients in total including those enrolled with the initial cohort of 925 patients). The choice to enrich the study with metastatic patients was due to the higher incidence of castration resistance in patients with metastatic disease. In addition, to support registration in China, a target number of 138 metastatic and nonmetastatic patients from China (enrolled in China and Taiwan) was specified, including those enrolled in Taiwan as part of the initial cohort of 915 patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported