Clinical trial results:
A randomized, double-blind, double-dummy, parallel- group, multi-center phase IIb study to assess the efficacy and safety of different dose combinations of an aromatase inhibitor and a progestin in an intravaginal ring versus placebo and leuprorelin / leuprolide acetate in women with symptomatic endometriosis over a 12-week treatment period

Summary

EudraCT number	2013-005090-53
Trial protocol	FI CZ DK AT BE NL PL ES
Global end of trial date	24 October 2016

Results information

Result version number	v1 (current)
This version publication date	28 October 2017
First version publication date	28 October 2017

Trial information

Trial identification

Sponsor protocol code	BAY98-7196/15832

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02203331
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	24 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the dose-response relationship and demonstrate efficacy of BAY98-7196 versus placebo in women with symptomatic endometriosis.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Japan: 62
Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czech Republic: 56
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	Germany: 37
Worldwide total number of subjects	319
EEA total number of subjects	196

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)	319
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted in fourteen countries in Austria, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Japan, Netherlands, Norway, Poland, Spain, Switzerland, United States, between 16 October 2014 (first subject first visit) and 24 October 2016 (last subject last visit).

Pre-assignment

Screening details:

Overall, 605 subjects were screened, of them 286 failed screening, remaining 319 subjects were randomized and allocated to treatment, of them 14 subjects did not receive study treatment for various reasons, remaining 305 subjects were treated and 272 subjects completed study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LNG 40 mcg IVR + Placebo Injection

Arm description:

Subjects wore an intra-vaginal ring (IVR) of Levonorgestrel (LNG) 40 microgram (mcg) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin intramuscular (i.m.) injection (3 month depot) on the first day of study treatment.

Arm type	Experimental
Investigational medicinal product name	Levonorgestrel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Subjects wore IVR of LNG 40 mcg continuously for 84 days, with exchange of the IVR every 28 days.

Investigational medicinal product name	Placebo Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Arm title	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection

Arm description:

Subjects wore IVR of Anastrozole (ATZ) 300 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Arm type	Experimental

Investigational medicinal product name	Anastrozole + Levonorgestrel
Investigational medicinal product code	BAY98-7196
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Subjects wore IVR of ATZ 300 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days.

Investigational medicinal product name	Placebo Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Arm title	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection

Arm description:

Subjects wore IVR of ATZ 600 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Arm type	Experimental
Investigational medicinal product name	Anastrozole + Levonorgestrel
Investigational medicinal product code	BAY98-7196
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Subjects wore IVR of ATZ 600 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days.

Investigational medicinal product name	Placebo Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Arm title	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection

Arm description:

Subjects wore IVR of ATZ 1050 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Arm type	Experimental
Investigational medicinal product name	Anastrozole + Levonorgestrel
Investigational medicinal product code	BAY98-7196
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Subjects wore IVR of ATZ 1050 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days.

Investigational medicinal product name	Placebo Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Arm title	Placebo IVR + Leuprorelin Injection

Arm description:

Subjects wore IVR of placebo matched to BAY98-7196 continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of 11.25 milligram (mg) leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Arm type	Experimental
Investigational medicinal product name	Placebo IVR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Subjects wore IVR of placebo matched to BAY98-7196 continuously for 84 days, with exchange of the IVR every 28 days.

Investigational medicinal product name	Leuprorelin Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were administered a single dose of 11.25 mg leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Arm title	Placebo IVR + Placebo Injection

Arm description:

Subjects wore IVR of placebo matched to BAY98-7196 continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Arm type	Experimental
Investigational medicinal product name	Placebo IVR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Subjects wore IVR of placebo matched to BAY98-7196 continuously for 84 days, with exchange of the IVR every 28 days.

Investigational medicinal product name	Placebo Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Number of subjects in period 1	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection
Started	52	53	55
Treated	49	50	54
Completed	45	39	50
Not completed	7	14	5
Consent withdrawn by subject	1	-	1
Protocol violation	-	2	-
Other	1	2	-
Pregnancy	1	-	-
Adverse event	4	8	3
Lost to follow-up	-	-	-
Lack of efficacy	-	2	1

Number of subjects in period 1	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection	Placebo IVR + Leuprorelin Injection	Placebo IVR + Placebo Injection
Started	53	53	53
Treated	49	50	53
Completed	46	46	46
Not completed	7	7	7
Consent withdrawn by subject	-	-	3
Protocol violation	1	1	-
Other	2	-	-
Pregnancy	-	2	-
Adverse event	4	3	3
Lost to follow-up	-	1	-
Lack of efficacy	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	LNG 40 mcg IVR + Placebo Injection
Reporting group description:	
Subjects wore an intra-vaginal ring (IVR) of Levonorgestrel (LNG) 40 microgram (mcg) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin intramuscular (i.m.) injection (3 month depot) on the first day of study treatment.	
Reporting group title	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection
Reporting group description:	
Subjects wore IVR of Anastrozole (ATZ) 300 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.	
Reporting group title	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection
Reporting group description:	
Subjects wore IVR of ATZ 600 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.	
Reporting group title	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection
Reporting group description:	
Subjects wore IVR of ATZ 1050 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.	
Reporting group title	Placebo IVR + Leuprorelin Injection
Reporting group description:	
Subjects wore IVR of placebo matched to BAY98-7196 continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of 11.25 milligram (mg) leuprorelin i.m. injection (3 month depot) on the first day of study treatment.	
Reporting group title	Placebo IVR + Placebo Injection
Reporting group description:	
Subjects wore IVR of placebo matched to BAY98-7196 continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.	

Reporting group values	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection
Number of subjects	52	53	55
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.27	32.96	33.96
standard deviation	± 7.4	± 8.79	± 5.73
Gender categorical Units: Subjects			
Female	52	53	55
Body Mass Index (BMI)			
Body mass index was an estimate of body fat based on body weight divided by height.			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	24.19	26.07	23.84

standard deviation	± 4.52	± 6.71	± 6.15
Mean Pain of the 7 Days With Worst Endometriosis Associated Pelvic Pain (EAPP)			
Pain intensity was assessed on 11-point (0-10) numerical rating scale (NRS) by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in an endometriosis symptom diary (ESD). The mean pain of the 7 days with worst EAPP within a 28-day window was calculated as the sum of ESD item 1 on 7 days with worst EAPP within that 28-day window divided by 7. Here, (n=39, 34, 42, 35, 40, 39) for mean pain of the 7 days with worst EAPP.			
Units: units on a scale			
arithmetic mean	7.8205	7.4664	8.1905
standard deviation	± 1.171	± 0.9893	± 1.068
Percentage of Days With Pain Greater Than or Equal to (>=) 7			
Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The percentage of days with pain >=7 within a 28-day window was calculated as 100 divided by the number of non-missing days within that 28-day window multiplied by the number of days within that 28-day window where item 1 of the ESD was >=7. Here, (n=39, 34, 42, 35, 40, 39) for percentage of days with pain >=7.			
Units: percentage of days			
arithmetic mean	50.094	40.1521	55.1155
standard deviation	± 35.5201	± 29.8714	± 33.7625
Percentage of Days With Pain >=4			
Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The percentage of days with pain >=4 within a 28-day window was calculated as 100 divided by the number of non-missing days within that 28-day window multiplied by the number of days within that window where Item 1 of the ESD was >=4. Here, (n=39, 34, 42, 35, 40, 39) for percentage of days with pain >=4.			
Units: percentage of days			
arithmetic mean	86.0058	84.7239	89.029
standard deviation	± 19.3136	± 18.1713	± 16.3667

Reporting group values	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection	Placebo IVR + Leuprorelin Injection	Placebo IVR + Placebo Injection
Number of subjects	53	53	53
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	33.72	33.7	34.89
standard deviation	± 7.85	± 6.29	± 7.13
Gender categorical			
Units: Subjects			
Female	53	53	53
Body Mass Index (BMI)			
Body mass index was an estimate of body fat based on body weight divided by height.			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	25.47	25.47	24.43
standard deviation	± 5.68	± 5.51	± 5.08
Mean Pain of the 7 Days With Worst Endometriosis Associated Pelvic Pain (EAPP)			

Pain intensity was assessed on 11-point (0-10) numerical rating scale (NRS) by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in an endometriosis symptom diary (ESD). The mean pain of the 7 days with worst EAPP within a 28-day window was calculated as the sum of ESD item 1 on 7 days with worst EAPP within that 28-day window divided by 7. Here, (n=39, 34, 42, 35, 40, 39) for mean pain of the 7 days with worst EAPP.			
Units: units on a scale			
arithmetic mean	7.5429	7.8964	7.6886
standard deviation	± 1.2568	± 1.1952	± 1.2389
Percentage of Days With Pain Greater Than or Equal to (>=) 7			
Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The percentage of days with pain >=7 within a 28-day window was calculated as 100 divided by the number of non-missing days within that 28-day window multiplied by the number of days within that 28-day window where item 1 of the ESD was >=7. Here, (n=39, 34, 42, 35, 40, 39) for percentage of days with pain >=7.			
Units: percentage of days			
arithmetic mean	37.3044	48.7001	41.1847
standard deviation	± 30.2894	± 33.6685	± 33.0479
Percentage of Days With Pain >=4			
Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The percentage of days with pain >=4 within a 28-day window was calculated as 100 divided by the number of non-missing days within that 28-day window multiplied by the number of days within that window where Item 1 of the ESD was >=4. Here, (n=39, 34, 42, 35, 40, 39) for percentage of days with pain >=4.			
Units: percentage of days			
arithmetic mean	85.8451	92.9141	80.4397
standard deviation	± 17.9466	± 11.6008	± 20.1004

Reporting group values	Total		
Number of subjects	319		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	319		
Body Mass Index (BMI)			
Body mass index was an estimate of body fat based on body weight divided by height.			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean			
standard deviation	-		
Mean Pain of the 7 Days With Worst Endometriosis Associated Pelvic Pain (EAPP)			
Pain intensity was assessed on 11-point (0-10) numerical rating scale (NRS) by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in an endometriosis symptom diary (ESD). The mean pain of the 7 days with worst EAPP within a 28-day window was calculated as the sum of ESD item 1 on 7 days with worst EAPP within that 28-day window divided by 7. Here, (n=39, 34, 42, 35, 40, 39) for mean pain of the 7 days with worst EAPP.			

Units: units on a scale arithmetic mean standard deviation	- 		
Percentage of Days With Pain Greater Than or Equal to (>=) 7			
Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The percentage of days with pain >=7 within a 28-day window was calculated as 100 divided by the number of non-missing days within that 28-day window multiplied by the number of days within that 28-day window where item 1 of the ESD was >=7. Here, (n=39, 34, 42, 35, 40, 39) for percentage of days with pain >=7.			
Units: percentage of days arithmetic mean standard deviation	- 		
Percentage of Days With Pain >=4			
Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The percentage of days with pain >=4 within a 28-day window was calculated as 100 divided by the number of non-missing days within that 28-day window multiplied by the number of days within that window where Item 1 of the ESD was >=4. Here, (n=39, 34, 42, 35, 40, 39) for percentage of days with pain >=4.			
Units: percentage of days arithmetic mean standard deviation	- 		

End points reporting groups

Reporting group title	LNG 40 mcg IVR + Placebo Injection

Reporting group description:

Subjects wore an intra-vaginal ring (IVR) of Levonorgestrel (LNG) 40 microgram (mcg) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin intramuscular (i.m.) injection (3 month depot) on the first day of study treatment.

Reporting group title	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection

Reporting group description:

Subjects wore IVR of Anastrozole (ATZ) 300 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Reporting group title	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection

Reporting group description:

Subjects wore IVR of ATZ 600 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Reporting group title	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection

Reporting group description:

Subjects wore IVR of ATZ 1050 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Reporting group title	Placebo IVR + Leuprorelin Injection

Reporting group description:

Subjects wore IVR of placebo matched to BAY98-7196 continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of 11.25 milligram (mg) leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Reporting group title	Placebo IVR + Placebo Injection

Reporting group description:

Subjects wore IVR of placebo matched to BAY98-7196 continuously for 84 days, with exchange of the IVR every 28 days and subjects were administered a single dose of placebo matched to leuprorelin i.m. injection (3 month depot) on the first day of study treatment.

Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

PPS (N=232) included all full analysis set subjects diagnosed by surgery who had no major protocol violations.

Primary: Absolute Change in Mean Pain of the 7Days With Worst EAPP From Baseline (Last 28Days Before Randomization) to End of Treatment (Last 28Days of Treatment Period,Days 57-84) as Measured on NRS by Question 1 of ESD

End point title	Absolute Change in Mean Pain of the 7Days With Worst EAPP From Baseline (Last 28Days Before Randomization) to End of Treatment (Last 28Days of Treatment Period,Days 57-84) as Measured on NRS by Question 1 of ESD

End point description:

Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The mean pain of the 7 days with worst EAPP within a 28-day window was calculated as the sum of ESD item 1 on 7 days with worst EAPP within that 28-day window divided by 7.

End point type	Primary

End point timeframe:

Baseline (last 28 days before randomization), end of treatment (Treatment 3) (last 28 days of the treatment period, Day 57-84)

End point values	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[1]	33[2]	42[3]	35[4]
Units: units on a scale				
arithmetic mean (standard deviation)	-1.8974 (± 1.6416)	-1.6061 (± 1.6652)	-2.4014 (± 2.1833)	-2.2653 (± 1.5972)

Notes:

[1] - PPS with evaluable subjects for this endpoint.

[2] - PPS with evaluable subjects for this endpoint.

[3] - PPS with evaluable subjects for this endpoint.

[4] - PPS with evaluable subjects for this endpoint.

End point values	Placebo IVR + Leuprorelin Injection	Placebo IVR + Placebo Injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[5]	39[6]		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.7679 (± 2.3507)	-2.293 (± 1.8247)		

Notes:

[5] - PPS with evaluable subjects for this endpoint.

[6] - PPS with evaluable subjects for this endpoint.

Statistical analyses

Statistical analysis title	Statistical analysis for Emax

Statistical analysis description:

The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.

Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3875
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2925

Statistical analysis title	Statistical analysis for Linear

Statistical analysis description:

The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.

Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2676
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2975

Statistical analysis title	Statistical analysis for Sigmoidal Emax 1

Statistical analysis description:

The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.

Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3211
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2922

Statistical analysis title	Statistical analysis for Sigmoidal Emax 2

Statistical analysis description:

The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.

Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1721
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2994

Secondary: Absolute Change in Mean Pain of the 7 Days With Worst EAPP From Baseline (Last 28 Days Before Randomization) to First Cycle Under Study Treatment (Day 1-28) and to Second Cycle Under Study Treatment (Day 29-56) as Measured on

NRS by Question 1 of ESD

End point title	Absolute Change in Mean Pain of the 7 Days With Worst EAPP From Baseline (Last 28 Days Before Randomization) to First Cycle Under Study Treatment (Day 1-28) and to Second Cycle Under Study Treatment (Day 29-56) as Measured on NRS by Question 1 of ESD

End point description:

Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The mean pain of the 7 days with worst EAPP within a 28-day window was calculated as the sum of ESD item 1 on 7 days with worst EAPP within that 28-day window divided by 7.

End point type	Secondary

End point timeframe:

Baseline (last 28 days before randomization), first cycle (Treatment 1) (Day 1-28), second cycle (Treatment 2) (Day 29-56)

End point values	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[7]	34[8]	42[9]	35[10]
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Treatment 1	-0.7582 (± 1.1518)	-0.6849 (± 1.3832)	-1.1463 (± 1.3992)	-1 (± 1.2579)
Change at Treatment 2	-1.6447 (± 1.4831)	-1.5126 (± 2.0161)	-2.1224 (± 2.2791)	-1.9959 (± 1.3978)

Notes:

[7] - PPS with evaluable subjects for this endpoint.

[8] - PPS with evaluable subjects for this endpoint.

[9] - PPS with evaluable subjects for this endpoint.

[10] - PPS with evaluable subjects for this endpoint.

End point values	Placebo IVR + Leuprorelin Injection	Placebo IVR + Placebo Injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[11]	39[12]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Treatment 1	-1.2071 (± 1.1978)	-0.9048 (± 1.1686)		
Change at Treatment 2	-2.8607 (± 2.0665)	-1.8022 (± 1.5131)		

Notes:

[11] - PPS with evaluable subjects for this endpoint.

[12] - PPS with evaluable subjects for this endpoint.

Statistical analyses

Statistical analysis title	Statistical analysis for Emax

Statistical analysis description:

The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.

Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.231
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2878

Statistical analysis title	Statistical analysis for Linear

Statistical analysis description:

The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.

Comparison groups	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1865
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2927

Statistical analysis title	Statistical analysis for Sigmoidal Emax 1

Statistical analysis description:

The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.

Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1955
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2875

Statistical analysis title	Statistical analysis for Sigmoidal Emax 2

Statistical analysis description:

The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.

Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1416
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2944

Secondary: Absolute Change in Mean Pain From Baseline(Last 28Days Before Randomization) to First Cycle Under Study Treatment(Day1-28),Second Cycle Under Study Treatment(Day29-56),Third Cycle Under Study Treatment(Day57-84) as Measured on NRS by Question1 of ESD

End point title	Absolute Change in Mean Pain From Baseline(Last 28Days Before Randomization) to First Cycle Under Study Treatment(Day1-28),Second Cycle Under Study Treatment(Day29-56),Third Cycle Under Study Treatment(Day57-84) as Measured on NRS by Question1 of

End point description:

Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The mean pain within a 28-day window was calculated as the sum of ESD item 1 within that 28-day window divided by the number with non-missing days within that 28-day window. Here, number of subjects 'n' signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

Baseline (last 28 days before randomization), first cycle (Treatment 1) (Day 1-28), second cycle (Treatment 2) (Day 29-56), and third cycle (Treatment 3) (last 28 days of the treatment period, Day 57-84)

End point values	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[13]	34[14]	42[15]	35[16]
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=39,34,42,35,40,39)	6.0938 (± 1.5314)	5.7409 (± 1.3044)	6.3694 (± 1.53)	5.7128 (± 1.4415)
Change at Treatment 1 (n=39,34,42,35,40,39)	-0.8472 (± 1.1905)	-0.9009 (± 1.3434)	-1.0931 (± 1.4002)	-1.1257 (± 1.3317)
Change at Treatment 2 (n=39,34,42,35,40,39)	-1.5774 (± 1.6278)	-1.5068 (± 1.8707)	-1.7349 (± 1.9403)	-1.9615 (± 1.3966)

Change at Treatment 3 (n=39,33,42,35,40,39)	-1.8001 (± 1.7687)	-1.6411 (± 1.8071)	-2.0112 (± 1.9575)	-2.1268 (± 1.6877)

Notes:

[13] - PPS with evaluable subjects for this endpoint.

[14] - PPS with evaluable subjects for this endpoint.

[15] - PPS with evaluable subjects for this endpoint.

[16] - PPS with evaluable subjects for this endpoint.

End point values	Placebo IVR + Leuprorelin Injection	Placebo IVR + Placebo Injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[17]	39[18]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=39,34,42,35,40,39)	6.3962 (± 1.4575)	5.6399 (± 1.5312)		
Change at Treatment 1 (n=39,34,42,35,40,39)	-1.5315 (± 1.4809)	-0.9777 (± 1.068)		
Change at Treatment 2 (n=39,34,42,35,40,39)	-2.6855 (± 2.0601)	-1.8994 (± 1.3069)		
Change at Treatment 3 (n=39,33,42,35,40,39)	-3.502 (± 2.3096)	-2.2228 (± 1.4957)		

Notes:

[17] - PPS with evaluable subjects for this endpoint.

[18] - PPS with evaluable subjects for this endpoint.

Statistical analyses

Statistical analysis title	Statistical analysis for Emax

Statistical analysis description:

The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.

Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5794
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2832

Statistical analysis title	Statistical analysis for Linear

Statistical analysis description:

The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.

Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4301
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.288

Statistical analysis title	Statistical analysis for Sigmoidal Emax 1
Statistical analysis description: The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.	
Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5337
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2829

Statistical analysis title	Statistical analysis for Sigmoidal Emax 2
Statistical analysis description: The analysis was performed by using MCP-Mod method using pre-defined candidate dose-response model.	
Comparison groups	LNG 40 mcg IVR + Placebo Injection v ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection v ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection v Placebo IVR + Placebo Injection
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3396
Method	Contrast tests for dose-response model
Variability estimate	Standard error of the mean
Dispersion value	0.2899

Secondary: Percentage of Days During Baseline (Last 28 Days Before Randomization) and Cycles 1, 2, and 3 With Pain Greater Than or Equal to (>=) 7 as Measured on NRS by Question 1 of ESD as Measured on NRS by Question 1 of ESD

End point title	Percentage of Days During Baseline (Last 28 Days Before Randomization) and Cycles 1, 2, and 3 With Pain Greater Than or Equal to (>=) 7 as Measured on NRS by Question 1 of ESD as Measured on NRS by Question 1 of ESD

End point description:

Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The percentage of days with pain >=7 within a 28-day window was calculated as 100 divided by the number of non-missing days within that 28-day window multiplied by the number of days within that 28-day window where item 1 of the ESD was >=7.

End point type	Secondary

End point timeframe:

Baseline (last 28 days before randomization), Cycle 1 (Treatment 1), Cycle 2 (Treatment 2), and Cycle 3 (Treatment 3)

End point values	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41[19]	34[20]	42[21]	35[22]
Units: percentage of days				
arithmetic mean (standard deviation)				
Treatment 1 (n=41,34,42,35,41,39)	35.6034 (± 34.3126)	27.5659 (± 27.6426)	40.0813 (± 37.2694)	23.9322 (± 28.6234)
Treatment 2 (n=41,34,42,35,41,39)	25.6257 (± 33.9315)	22.8695 (± 28.3443)	34.4364 (± 40.5623)	14.9331 (± 23.8028)
Treatment 3 (n=41,33,42,35,41,39)	23.1293 (± 33.9451)	19.9332 (± 26.054)	29.8103 (± 39.0434)	14.3362 (± 25.677)

Notes:

[19] - PPS with evaluable subjects for this endpoint.

[20] - PPS with evaluable subjects for this endpoint.

[21] - PPS with evaluable subjects for this endpoint.

[22] - PPS with evaluable subjects for this endpoint.

End point values	Placebo IVR + Leuprorelin Injection	Placebo IVR + Placebo Injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[23]	39[24]		
Units: percentage of days				
arithmetic mean (standard deviation)				
Treatment 1 (n=41,34,42,35,41,39)	28.2015 (± 28.843)	25.1742 (± 24.2811)		
Treatment 2 (n=41,34,42,35,41,39)	12.132 (± 25.1638)	14.1869 (± 17.7364)		
Treatment 3 (n=41,33,42,35,41,39)	8.5351 (± 20.7819)	12.7574 (± 18.5154)		

Notes:

[23] - PPS with evaluable subjects for this endpoint.

[24] - PPS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (Last 28 Days Before Randomization) to Cycle 1, 2, and 3 in Percentage of Days With Pain >=7 as Measured on NRS by Question 1 of

ESD

End point title	Change From Baseline (Last 28 Days Before Randomization) to Cycle 1, 2, and 3 in Percentage of Days With Pain >=7 as Measured on NRS by Question 1 of ESD

End point description:

Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The percentage of days with pain >=7 within a 28-day window was calculated as 100 divided by the number of non-missing days within that 28-day window multiplied by the number of days within that 28-day window where item 1 of the ESD was >=7. Here, number of subjects 'n' signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

Baseline (last 28 days before randomization), Cycle 1 (Treatment 1), Cycle 2 (Treatment 2), and Cycle 3 (Treatment 3)

End point values	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[25]	34[26]	42[27]	35[28]
Units: percentage of days				
arithmetic mean (standard deviation)				
Change at Treatment 1 (n=39,34,42,35,40,39)	-13.6756 (± 22.6822)	-12.5862 (± 21.4336)	-15.0341 (± 21.0071)	-13.3722 (± 19.6416)
Change at Treatment 2 (n=39,34,42,35,40,39)	-24.1404 (± 28.5082)	-17.2826 (± 29.0007)	-20.6791 (± 30.2152)	-22.3713 (± 24.4098)
Change at Treatment 3 (n=39,33,42,35,40,39)	-26.4197 (± 31.4648)	-20.8529 (± 28.3939)	-25.3052 (± 33.5497)	-22.9682 (± 28.8677)

Notes:

[25] - PPS with evaluable subjects for this endpoint.

[26] - PPS with evaluable subjects for this endpoint.

[27] - PPS with evaluable subjects for this endpoint.

[28] - PPS with evaluable subjects for this endpoint.

End point values	Placebo IVR + Leuprorelin Injection	Placebo IVR + Placebo Injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[29]	39[30]		
Units: percentage of days				
arithmetic mean (standard deviation)				
Change at Treatment 1 (n=39,34,42,35,40,39)	-19.8898 (± 25.9273)	-16.0105 (± 19.019)		
Change at Treatment 2 (n=39,34,42,35,40,39)	-36.354 (± 34.9706)	-26.9979 (± 24.9493)		
Change at Treatment 3 (n=39,33,42,35,40,39)	-39.9516 (± 33.8277)	-28.4273 (± 29.6186)		

Notes:

[29] - PPS with evaluable subjects for this endpoint.

[30] - PPS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Days During Baseline (Last 28 Days Before Randomization) and Cycles 1, 2, and 3 With Pain >=4 as Measured on NRS by Question 1 of ESD

End point title	Percentage of Days During Baseline (Last 28 Days Before Randomization) and Cycles 1, 2, and 3 With Pain >=4 as Measured on NRS by Question 1 of ESD

End point description:

Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The percentage of days with pain >=4 within a 28-day window was calculated as 100 divided by the number of non-missing days within that 28-day window multiplied by the number of days within that window where Item 1 of the ESD was >=4. Here, number of subjects 'n' signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

Baseline (last 28 days before randomization), Cycle 1 (Treatment 1), Cycle 2 (Treatment 2), and Cycle 3 (Treatment 3)

End point values	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41[31]	34[32]	42[33]	35[34]
Units: percentage of days				
arithmetic mean (standard deviation)				
Treatment 1 (n=41, 34, 42, 35, 41, 39)	71.8037 (± 32.3658)	69.3092 (± 27.8642)	73.8956 (± 31.6868)	70.6504 (± 27.8528)
Treatment 2 (n=41, 34, 42, 35, 41, 39)	61.8199 (± 37.1217)	57.8777 (± 34.7429)	62.5822 (± 37.6989)	52.6028 (± 35.6106)
Treatment 3 (n=41, 33, 42, 35, 41, 39)	60.2902 (± 37.8585)	57.0171 (± 34.3642)	56.7691 (± 40.3803)	50.7332 (± 36.2903)

Notes:

[31] - PPS with evaluable subjects for this endpoint.

[32] - PPS with evaluable subjects for this endpoint.

[33] - PPS with evaluable subjects for this endpoint.

[34] - PPS with evaluable subjects for this endpoint.

End point values	Placebo IVR + Leuprorelin Injection	Placebo IVR + Placebo Injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[35]	39[36]		
Units: percentage of days				
arithmetic mean (standard deviation)				
Treatment 1 (n=41, 34, 42, 35, 41, 39)	70.2066 (± 28.9333)	65.9074 (± 30.0166)		
Treatment 2 (n=41, 34, 42, 35, 41, 39)	54.0965 (± 38.9629)	49.487 (± 31.3566)		

Treatment 3 (n=41, 33, 42, 35, 41, 39)	38.6986 (± 39.6045)	47.0976 (± 35.3227)		

Notes:

[35] - PPS with evaluable subjects for this endpoint.

[36] - PPS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (Last 28 Days Before Randomization) to Cycle 1, 2, and 3 in Percentage of Days With Pain >=4 as Measured on NRS by Question 1 of ESD

End point title	Change From Baseline (Last 28 Days Before Randomization) to Cycle 1, 2, and 3 in Percentage of Days With Pain >=4 as Measured on NRS by Question 1 of ESD

End point description:

Pain intensity was assessed on 11-point (0-10) NRS by question 1. In question 1, subjects were asked to rate the pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. The percentage of days with pain >=4 within a 28-day window was calculated as 100 divided by the number of non-missing days within that 28-day window multiplied by the number of days within that window where Item 1 of the ESD was >=4. Here, number of subjects 'n' signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

Baseline (last 28 days before randomization), Cycle 1 (Treatment 1), Cycle 2 (Treatment 2), and Cycle 3 (Treatment 3)

End point values	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[37]	34[38]	42[39]	35[40]
Units: percentage of days				
arithmetic mean (standard deviation)				
Change at Treatment 1 (n=39,34,42,35,40,39)	-12.8228 (± 20.433)	-15.4147 (± 24.0608)	-15.1334 (± 22.5347)	-15.1947 (± 21.174)
Change at Treatment 2 (n=39,34,42,35,40,39)	-22.495 (± 28.1535)	-26.8462 (± 32.6194)	-26.4468 (± 34.4661)	-33.2423 (± 27.3686)
Change at Treatment 3 (n=39,33,42,35,40,39)	-23.5498 (± 30.2853)	-27.477 (± 34.2051)	-32.26 (± 37.4997)	-35.1119 (± 30.9316)

Notes:

[37] - PPS with evaluable subjects for this endpoint.

[38] - PPS with evaluable subjects for this endpoint.

[39] - PPS with evaluable subjects for this endpoint.

[40] - PPS with evaluable subjects for this endpoint.

End point values	Placebo IVR + Leuprorelin Injection	Placebo IVR + Placebo Injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[41]	39[42]		

Units: percentage of days				
arithmetic mean (standard deviation)				
Change at Treatment 1 (n=39,34,42,35,40,39)	-21.4331 (± 23.4546)	-14.5323 (± 20.967)		
Change at Treatment 2 (n=39,34,42,35,40,39)	-37.733 (± 36.9484)	-30.9527 (± 25.4665)		
Change at Treatment 3 (n=39,33,42,35,40,39)	-53.4266 (± 38.8452)	-33.3421 (± 25.7105)		

Notes:

[41] - PPS with evaluable subjects for this endpoint.

[42] - PPS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to 30 days after end of treatment (Day 114)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	LNG 40 mcg IVR + Placebo Injection

Reporting group description:

Subjects wore IVR of LNG 40 mcg continuously for 84 days, with exchange of the IVR every 28 days and subjs were admin. single dose of placebo matched to leuprorelin i.m. injn. (3 month depot) on the first day of trtmt.

Reporting group title	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection

Reporting group description:

Subjects wore IVR of ATZ 300 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjs were admin. single dose of placebo matched to leuprorelin i.m. injn. (3 month depot) on the first day of trtmt.

Reporting group title	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection

Reporting group description:

Subjects wore IVR of ATZ 600 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjs were admin. single dose of placebo matched to leuprorelin i.m. injn. (3 month depot) on the first day of trtmt.

Reporting group title	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection

Reporting group description:

Subjects wore IVR of ATZ 1050 mcg and LNG 40 mcg (BAY98-7196) continuously for 84 days, with exchange of the IVR every 28 days and subjs were admin. single dose of placebo matched to leuprorelin i.m. injn. (3 month depot) on the first day of trtmt.

Reporting group title	Placebo IVR + Leuprorelin 11.25 mg Injection

Reporting group description:

Subjects wore IVR of placebo matched to BAY98-7196 continuously for 84 days, with exchange of the IVR every 28 days and subjs were admin. a single dose of 11.25 mg leuprorelin i.m. injn. (3 month depot) on the first day of trtmt.

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Serious adverse events	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 49 (4.08%)	0 / 50 (0.00%)	0 / 54 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			

Pregnancy of unknown location			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (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
Menorrhagia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dyshidrotic eczema			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			

subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal atrophy			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection	Placebo IVR + Leuprorelin 11.25 mg Injection	Placebo IVR + Placebo Injection
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 49 (4.08%)	3 / 50 (6.00%)	4 / 53 (7.55%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Pregnancy of unknown location			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (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
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			

subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dyshidrotic eczema			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (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
Renal atrophy			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (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			
Pyelonephritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
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: 0 %

Non-serious adverse events	LNG 40 mcg IVR + Placebo Injection	ATZ 300 mcg / LNG 40 mcg IVR + Placebo Injection	ATZ 600 mcg / LNG 40 mcg IVR + Placebo Injection
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 49 (77.55%)	40 / 50 (80.00%)	40 / 54 (74.07%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Schwannoma			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Uterine leiomyoma			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	2 / 54 (3.70%)
occurrences (all)	1	0	2
Ovarian adenoma			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Thrombophlebitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	3 / 54 (5.56%)
occurrences (all)	1	0	3
Surgical and medical procedures			
Wisdom teeth removal			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Chest pain			

subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Face oedema			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 49 (0.00%)	3 / 50 (6.00%)	1 / 54 (1.85%)
occurrences (all)	0	3	1
Feeling hot			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Hunger			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Pelvic mass			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	1	1	0
Swelling			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			

subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	0	1	1
Medical device discomfort			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Haemorrhagic cyst			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Medical device site discomfort			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Breast cyst			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Breast enlargement			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Breast pain			
subjects affected / exposed	2 / 49 (4.08%)	2 / 50 (4.00%)	1 / 54 (1.85%)
occurrences (all)	2	2	1
Breast tenderness			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	0	1	1
Dysmenorrhoea			

subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Dyspareunia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	1	1	0
Endometriosis			
subjects affected / exposed	3 / 49 (6.12%)	2 / 50 (4.00%)	3 / 54 (5.56%)
occurrences (all)	3	2	4
Fibrocystic breast disease			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Galactorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Hydrosalpinx			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Hypomenorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Menorrhagia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Menstruation irregular			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Metrorrhagia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	2 / 54 (3.70%)
occurrences (all)	1	1	2
Ovarian cyst			
subjects affected / exposed	20 / 49 (40.82%)	20 / 50 (40.00%)	24 / 54 (44.44%)
occurrences (all)	25	21	28
Ovarian rupture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			

subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	2 / 54 (3.70%)
occurrences (all)	1	1	2
Polymenorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Uterine haemorrhage			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	3	0	3
Uterine polyp			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Uterine prolapse			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Vaginal discharge			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Vaginal haemorrhage			
subjects affected / exposed	1 / 49 (2.04%)	3 / 50 (6.00%)	2 / 54 (3.70%)
occurrences (all)	1	5	2
Vaginal odour			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Varicose veins pelvic			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal discomfort			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal dryness			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	0	1	1
Breast discomfort			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	0	1	1
Adenomyosis			

subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Vulvovaginal pruritus			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Adnexa uteri pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 49 (0.00%)	2 / 50 (4.00%)	0 / 54 (0.00%)
occurrences (all)	0	2	0
Genital haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	0	1	1
Uterine haematoma			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Vaginal flatulence			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Abnormal withdrawal bleeding			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Sinus congestion			

subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 49 (0.00%)	2 / 50 (4.00%)	1 / 54 (1.85%)
occurrences (all)	0	2	1
Depressed mood			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Libido decreased			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	0	1	1
Loss of libido			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Mood altered			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Mood swings			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	2 / 54 (3.70%)
occurrences (all)	1	1	2
Depressive symptom			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0

Affect lability			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Product issues			
Device breakage			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Device expulsion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 49 (2.04%)	2 / 50 (4.00%)	0 / 54 (0.00%)
occurrences (all)	2	2	0
Aspartate aminotransferase abnormal			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Blood triglycerides increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Colonoscopy			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Blood urine present			

subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	1	1	0
Prothrombin time shortened			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Red blood cells urine positive			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	2 / 49 (4.08%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	2	1	1
White blood cells urine positive			
subjects affected / exposed	3 / 49 (6.12%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	3	1	0
Urine bilirubin increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Nitrite urine present			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Protein urine present			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Urine ketone body present			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Smear vaginal abnormal			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Gardnerella test positive			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural			

complications			
Animal bite			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Arthropod sting			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Epicondylitis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Road traffic accident			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Thermal burn			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Post-traumatic pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Bone contusion			

subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Closed globe injury			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Mitral valve incompetence			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	5 / 49 (10.20%)	8 / 50 (16.00%)	3 / 54 (5.56%)
occurrences (all)	9	8	3
Migraine			
subjects affected / exposed	2 / 49 (4.08%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	2	0	0
Neuralgia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Presyncope			

subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	1	1	0
Haemorrhagic disorder			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Lymph node pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Haemorrhagic anaemia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness transitory			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Eyelid oedema			

subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Eyelid rash			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	0	1	1
Abdominal pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	0	2	1
Abdominal pain upper			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 49 (0.00%)	3 / 50 (6.00%)	0 / 54 (0.00%)
occurrences (all)	0	3	0
Dyspepsia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Enteritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1

Haemorrhoids			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 49 (4.08%)	2 / 50 (4.00%)	2 / 54 (3.70%)
occurrences (all)	3	2	2
Periodontal disease			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Dyschezia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Noninfectious peritonitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Faeces soft			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 49 (4.08%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	2	1	1
Alopecia			

subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Dermatitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Dermatitis bullous			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Purpura			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Pruritus generalised			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Hand dermatitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	2	0	0
Pigmentation disorder			

subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Back pain			
subjects affected / exposed	2 / 49 (4.08%)	2 / 50 (4.00%)	0 / 54 (0.00%)
occurrences (all)	3	2	0
Groin pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 49 (0.00%)	2 / 50 (4.00%)	1 / 54 (1.85%)
occurrences (all)	0	2	1
Tendonitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal disorder			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			

subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	2 / 54 (3.70%)
occurrences (all)	1	0	2
Bronchitis			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	1	1	1
Cellulitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	2 / 49 (4.08%)	1 / 50 (2.00%)	2 / 54 (3.70%)
occurrences (all)	3	1	2
Ear infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	2 / 54 (3.70%)
occurrences (all)	1	0	2
Hordeolum			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 49 (0.00%)	2 / 50 (4.00%)	0 / 54 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	2 / 49 (4.08%)	2 / 50 (4.00%)	7 / 54 (12.96%)
occurrences (all)	2	2	8

Oral candidiasis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Periodontitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Pulpitis dental			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Pyelonephritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	3 / 54 (5.56%)
occurrences (all)	1	1	3
Upper respiratory tract infection			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	1	1	0
Urethritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	1 / 49 (2.04%)	2 / 50 (4.00%)	2 / 54 (3.70%)
occurrences (all)	1	2	3
Vulvovaginal candidiasis			
subjects affected / exposed	2 / 49 (4.08%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	2	0	0

Nail infection			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Borrelia infection			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 49 (4.08%)	1 / 50 (2.00%)	2 / 54 (3.70%)
occurrences (all)	3	1	2
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Increased appetite			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1

Non-serious adverse events	ATZ 1050 mcg / LNG 40 mcg IVR + Placebo Injection	Placebo IVR + Leuprorelin 11.25 mg Injection	Placebo IVR + Placebo Injection
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 49 (71.43%)	35 / 50 (70.00%)	38 / 53 (71.70%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Schwannoma			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Uterine leiomyoma			
subjects affected / exposed	0 / 49 (0.00%)	2 / 50 (4.00%)	0 / 53 (0.00%)
occurrences (all)	0	2	0

Ovarian adenoma			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Haematoma			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Thrombophlebitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	3 / 49 (6.12%)	17 / 50 (34.00%)	2 / 53 (3.77%)
occurrences (all)	3	26	2
Surgical and medical procedures			
Wisdom teeth removal			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	2 / 53 (3.77%)
occurrences (all)	1	0	2
Feeling hot			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0

Hunger			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Injection site reaction			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Pelvic mass			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Swelling			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Medical device discomfort			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Haemorrhagic cyst			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Medical device site discomfort			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Breast cyst			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Breast enlargement			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Breast pain			
subjects affected / exposed	0 / 49 (0.00%)	2 / 50 (4.00%)	0 / 53 (0.00%)
occurrences (all)	0	2	0
Breast tenderness			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Dysmenorrhoea			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	2 / 53 (3.77%)
occurrences (all)	1	1	3
Dyspareunia			
subjects affected / exposed	0 / 49 (0.00%)	3 / 50 (6.00%)	0 / 53 (0.00%)
occurrences (all)	0	4	0
Endometriosis			
subjects affected / exposed	2 / 49 (4.08%)	2 / 50 (4.00%)	5 / 53 (9.43%)
occurrences (all)	2	3	5
Fibrocystic breast disease			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Galactorrhoea			

subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Hydrosalpinx			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Hypomenorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Menorrhagia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	2	1	0
Menstruation irregular			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	2 / 53 (3.77%)
occurrences (all)	0	1	2
Metrorrhagia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	3	1	0
Ovarian cyst			
subjects affected / exposed	16 / 49 (32.65%)	5 / 50 (10.00%)	7 / 53 (13.21%)
occurrences (all)	22	5	9
Ovarian rupture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Pelvic pain			
subjects affected / exposed	2 / 49 (4.08%)	0 / 50 (0.00%)	2 / 53 (3.77%)
occurrences (all)	2	0	2
Polymenorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Uterine haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Uterine polyp			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Uterine prolapse			

subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Vaginal discharge			
subjects affected / exposed	2 / 49 (4.08%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	2	0	1
Vaginal haemorrhage			
subjects affected / exposed	4 / 49 (8.16%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	7	0	0
Vaginal odour			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Varicose veins pelvic			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Vulvovaginal discomfort			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal dryness			
subjects affected / exposed	0 / 49 (0.00%)	4 / 50 (8.00%)	1 / 53 (1.89%)
occurrences (all)	0	4	1
Breast discomfort			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Adenomyosis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Vulvovaginal pruritus			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Adnexa uteri pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Haemorrhagic ovarian cyst			
subjects affected / exposed	2 / 49 (4.08%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Genital haemorrhage			

subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	1	1	0
Uterine haematoma			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Vaginal flatulence			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Abnormal withdrawal bleeding			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	2 / 49 (4.08%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Depression			

subjects affected / exposed	2 / 49 (4.08%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	3	1	0
Insomnia			
subjects affected / exposed	0 / 49 (0.00%)	2 / 50 (4.00%)	0 / 53 (0.00%)
occurrences (all)	0	3	0
Irritability			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Libido decreased			
subjects affected / exposed	0 / 49 (0.00%)	4 / 50 (8.00%)	0 / 53 (0.00%)
occurrences (all)	0	4	0
Loss of libido			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Mood altered			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	1	1	0
Mood swings			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Depressive symptom			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Affect lability			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Product issues			
Device breakage			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Device expulsion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Investigations			

Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Aspartate aminotransferase abnormal			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Colonoscopy			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Blood urine present			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Prothrombin time shortened			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Red blood cells urine positive			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Weight increased			

subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
White blood cells urine positive			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Urine bilirubin increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Nitrite urine present			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Protein urine present			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Urine ketone body present			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Smear vaginal abnormal			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Gardnerella test positive			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Arthropod sting			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Epicondylitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Road traffic accident			

subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	1	1	0
Muscle strain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Wound			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Thermal burn			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 49 (0.00%)	2 / 50 (4.00%)	0 / 53 (0.00%)
occurrences (all)	0	2	0
Post-traumatic pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Bone contusion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Closed globe injury			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Mitral valve incompetence			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1

Tachycardia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Disturbance in attention			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 49 (0.00%)	2 / 50 (4.00%)	3 / 53 (5.66%)
occurrences (all)	0	2	3
Headache			
subjects affected / exposed	8 / 49 (16.33%)	8 / 50 (16.00%)	6 / 53 (11.32%)
occurrences (all)	9	13	6
Migraine			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Haemorrhagic disorder			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Lymph node pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			

subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Deafness transitory			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	3	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Eyelid rash			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	4 / 49 (8.16%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	4	0	0
Abdominal pain upper			

subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Constipation			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	2 / 53 (3.77%)
occurrences (all)	0	1	3
Diarrhoea			
subjects affected / exposed	3 / 49 (6.12%)	1 / 50 (2.00%)	4 / 53 (7.55%)
occurrences (all)	3	1	4
Dyspepsia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Enteritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	2
Gastritis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	4 / 49 (8.16%)	3 / 50 (6.00%)	3 / 53 (5.66%)
occurrences (all)	4	3	4
Periodontal disease			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Toothache			

subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	2 / 49 (4.08%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Dyschezia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Noninfectious peritonitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Faeces soft			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 49 (10.20%)	1 / 50 (2.00%)	2 / 53 (3.77%)
occurrences (all)	5	2	2
Alopecia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Dermatitis bullous			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	2	0
Dry skin			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Eczema			

subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Purpura			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Urticaria			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Pruritus generalised			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Hand dermatitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Pigmentation disorder			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	1 / 53 (1.89%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	1	1	0
Groin pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal disorder			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Muscle tightness			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bacterial vaginosis			

subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Cellulitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Ear infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 49 (2.04%)	2 / 50 (4.00%)	0 / 53 (0.00%)
occurrences (all)	1	2	0
Hordeolum			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 49 (2.04%)	3 / 50 (6.00%)	0 / 53 (0.00%)
occurrences (all)	1	3	0
Nasopharyngitis			
subjects affected / exposed	5 / 49 (10.20%)	1 / 50 (2.00%)	3 / 53 (5.66%)
occurrences (all)	5	1	4
Oral candidiasis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Periodontitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Pharyngitis streptococcal			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Pneumonia			

subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Pulpitis dental			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Pyelonephritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	2
Sinusitis			
subjects affected / exposed	1 / 49 (2.04%)	2 / 50 (4.00%)	0 / 53 (0.00%)
occurrences (all)	1	2	0
Tonsillitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Urethritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	1 / 49 (2.04%)	1 / 50 (2.00%)	2 / 53 (3.77%)
occurrences (all)	1	1	3
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Nail infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Borrelia infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 49 (2.04%)	2 / 50 (4.00%)	2 / 53 (3.77%)
occurrences (all)	1	2	2
Metabolism and nutrition disorders			

Fluid retention			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2014	This amendment was issued for - A more detailed specification of the Japanese subjects diagnosed by imaging was provided in inclusion criterion, based on local amendment for Japan. - The number of Japanese subjects diagnosed by imaging was changed based on local Japanese amendment, this number was reduced to 30 subjects and became identical to the number of Japanese subjects diagnosed by surgery. Consequently, the total number of subjects was updated. - The additions and rearrangement in the plan for statistical analysis described in the local amendment for Japan were incorporated into the global amendment. - Collection of data on the condom use was introduced, following a request from the Device Division of food and drug administration (FDA) to collect functional outcome data on condom use while intravaginal rings were worn by the subjects. - Hormone tests were removed from the safety laboratory analysis and added to "other variables and evaluations". - Text related to subject information and informed consent was updated based on the new Informed Consent standard operating procedure (SOP).
05 June 2015	This amendment was issued for - The wording of exclusion criterion ("History of, and current anxiety and/or depression disorder") was changed to "Current unstable anxiety and/or depression disorder (stable, well-managed symptoms of anxiety or mood disorders including depression are not exclusionary)".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Occurrence of "±" in relation with geometric CV is auto-generated and cannot be deleted. Decimal places were automatically truncated if last decimal equals zero.

Notes: