Clinical trial results:
A randomized, parallel-group, multicenter study to assess the efficacy and safety of vilaprisan in subjects with uterine fibroids

Summary

EudraCT number	2016-002855-48
Trial protocol	IE SE CZ HU FI AT NO DE ES GB DK BE SK LT NL PT BG IT
Global end of trial date	25 October 2021

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022

Trial information

Trial identification

Sponsor protocol code	BAY1002670/15789

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03240523
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, 49 30 300139003, 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	02 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to describe the efficacy of vilaprisan in subjects with uterine fibroids compared to ulipristal.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the 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	31 July 2017
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	Australia: 1
Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Belgium: 40
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Finland: 15
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Norway: 30
Country: Number of subjects enrolled	Portugal: 8
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	Korea, Republic of: 80
Country: Number of subjects enrolled	Taiwan: 57
Country: Number of subjects enrolled	Bulgaria: 89
Country: Number of subjects enrolled	Czechia: 2

Country: Number of subjects enrolled	Hungary: 97
Country: Number of subjects enrolled	Lithuania: 54
Country: Number of subjects enrolled	Poland: 167
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	Canada: 31
Worldwide total number of subjects	766
EEA total number of subjects	591

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)	766
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in 22 countries worldwide between 31-Jul-2017 (first subject first visit) and 25-Oct-2021 (last subject last visit).

Pre-assignment

Screening details:

Overall, 1333 subjects were screened. Of the 1333 screened subjects, 567 subjects were screen failures and 766 subjects were randomized. Full analysis set (FAS) included 756 subjects excluding 10 subjects who were randomized but did not receive any study drug due to temporary pause.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	A1 (VPR-3/1)

Arm description:

Subjects received vilaprisan (VPR) 2 mg for up to 4 treatment periods of 12 weeks, each separated by 1 bleeding episode (3/1 regimen).

Arm type	Experimental
Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vilaprisan 2 mg, once daily

Arm title	A2 (VPR-6/2)

Arm description:

Subjects received vilaprisan 2 mg for up to 2 treatment periods of 24 weeks, separated by 2 bleeding episodes (6/2 regimen).

Arm type	Experimental
Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vilaprisan 2 mg, once daily

Arm title	A3 (VPR-3/2)

Arm description:

Subjects received vilaprisan 2 mg and matching placebo to ulipristal (UPA) for up to 2 treatment periods of 12 weeks, separated by 2 bleeding episodes (3/2 regimen), followed by the open-label VPR treatment up to one year.

Arm type	Experimental

Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vilaprisan 2 mg, once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to ulipristal tablet once daily.

Arm title	B (UPA-3/2)

Arm description:

Subjects received ulipristal 5 mg and matching placebo to vilaprisan for up to 2 treatment periods of 12 weeks, separated by 2 bleeding episodes (3/2 regimen), followed by the open-label VPR treatment up to one year.

Arm type	Active comparator
Investigational medicinal product name	Ulipristal (Esmya)
Investigational medicinal product code	
Other name	Ulipristal acetate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ulipristal 5 mg, once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to vilaprisan tablet once daily.

Number of subjects in period 1[1]	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)
Started	280	279	99
Treated	271	266	90
Completed	43	55	0
Not completed	237	224	99
Physician decision	3	9	1
Consent withdrawn by subject	88	96	43
Adverse event, non-fatal	24	19	4
Pregnancy	-	1	-
Study terminated by sponsor	80	55	34

Non-compliance with study drug	-	-	2
Unspecified	32	29	11
Lost to follow-up	1	-	-
Missing	1	8	-
Lack of efficacy	1	1	-
Protocol deviation	7	6	4

Number of subjects in period 1[1]	B (UPA-3/2)
Started	98
Treated	89
Completed	0
Not completed	98
Physician decision	5
Consent withdrawn by subject	38
Adverse event, non-fatal	6
Pregnancy	1
Study terminated by sponsor	26
Non-compliance with study drug	-
Unspecified	17
Lost to follow-up	-
Missing	-
Lack of efficacy	-
Protocol deviation	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In total 766 subjects were randomized. 756 subjects excluding 10 subjects who were randomized but did not receive any study drug due to temporary pause were included in Full analysis set (FAS) and FAS population was used in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	A1 (VPR-3/1)
Reporting group description:	
Subjects received vilaprisan (VPR) 2 mg for up to 4 treatment periods of 12 weeks, each separated by 1 bleeding episode (3/1 regimen).	
Reporting group title	A2 (VPR-6/2)
Reporting group description:	
Subjects received vilaprisan 2 mg for up to 2 treatment periods of 24 weeks, separated by 2 bleeding episodes (6/2 regimen).	
Reporting group title	A3 (VPR-3/2)
Reporting group description:	
Subjects received vilaprisan 2 mg and matching placebo to ulipristal (UPA) for up to 2 treatment periods of 12 weeks, separated by 2 bleeding episodes (3/2 regimen), followed by the open-label VPR treatment up to one year.	
Reporting group title	B (UPA-3/2)
Reporting group description:	
Subjects received ulipristal 5 mg and matching placebo to vilaprisan for up to 2 treatment periods of 12 weeks, separated by 2 bleeding episodes (3/2 regimen), followed by the open-label VPR treatment up to one year.	

Reporting group values	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)
Number of subjects	280	279	99
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	43.2	43.0	43.7
standard deviation	± 5.3	± 5.7	± 5.4
Gender Categorical			
Units: Subjects			
Female	280	279	99
Male	0	0	0
Volume of the largest fibroid at baseline (measured by ultrasound)			
Largest fibroid diameter by ultrasound at baseline			
Units: millimeter			
arithmetic mean	40.9	44.7	39.3
standard deviation	± 20.4	± 21.7	± 20.0

Reporting group values	B (UPA-3/2)	Total	
Number of subjects	98	756	
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	43.6		
standard deviation	± 5.0	-	

Gender Categorical Units: Subjects			
Female	98	756	
Male	0	0	
Volume of the largest fibroid at baseline (measured by ultrasound)			
Largest fibroid diameter by ultrasound at baseline			
Units: millimeter			
arithmetic mean	39.2		
standard deviation	± 22.7	-	

End points

End points reporting groups

Reporting group title	A1 (VPR-3/1)

Reporting group description:

Subjects received vilaprisan (VPR) 2 mg for up to 4 treatment periods of 12 weeks, each separated by 1 bleeding episode (3/1 regimen).

Reporting group title	A2 (VPR-6/2)

Reporting group description:

Subjects received vilaprisan 2 mg for up to 2 treatment periods of 24 weeks, separated by 2 bleeding episodes (6/2 regimen).

Reporting group title	A3 (VPR-3/2)

Reporting group description:

Subjects received vilaprisan 2 mg and matching placebo to ulipristal (UPA) for up to 2 treatment periods of 12 weeks, separated by 2 bleeding episodes (3/2 regimen), followed by the open-label VPR treatment up to one year.

Reporting group title	B (UPA-3/2)

Reporting group description:

Subjects received ulipristal 5 mg and matching placebo to vilaprisan for up to 2 treatment periods of 12 weeks, separated by 2 bleeding episodes (3/2 regimen), followed by the open-label VPR treatment up to one year.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

FAS consisted of all randomized subjects, excluding randomized subjects who did not receive study drug because of the temporary pause: 756 (98.7%) subjects with 10 (1.3%) randomized subjects excluded from FAS.

Subject analysis set title	Total VPR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Total VPR combined vilaprisan groups VPR-3/1, VPR-6/2, and VPR-3/2. All subjects treated with VPR providing information only during the time of VPR treatment. Thus, for subjects who switched from UPA to VPR the period of UPA treatment is excluded.

Primary: Number of subjects with amenorrhea

End point title	Number of subjects with amenorrhea[1]

End point description:

Amenorrhea was defined as menstrual blood loss (MBL) <2 mL during the last 28 days of the first 12 weeks of treatment (in the first treatment period (TP) following randomization) based on the menstrual pictogram (MP).

End point type	Primary

End point timeframe:

At 12 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The amenorrhea rate of VPR-treated subjects (total VPR group) was compared with the amenorrhea rate of UPA treated subjects.

End point values	B (UPA-3/2)	Total VPR		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	89	627		
Units: Subjects	66	520		

Statistical analyses

Statistical analysis title	Difference of amenorrhea rate_Non-inferiority

Statistical analysis description:

The 95% CI of the difference between amenorrhea rates was estimated by the Farrington and Manning's method, and its lower limit was -0.78% which was above the non- inferiority threshold (-10%) defined for the study.

Comparison groups	B (UPA-3/2) v Total VPR
Number of subjects included in analysis	716
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference of percentage of subjects
Point estimate	8.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7824
upper limit	18.3371

Statistical analysis title	Difference of amenorrhea rate_Superiority

Statistical analysis description:

The hypothesis of superiority of the Total VPR group vs. UPA-3/2 group on the primary variable amenorrhea rate after 12 weeks of treatment was tested by two-sided Fisher's exact test at a significance level of 5%.

Comparison groups	B (UPA-3/2) v Total VPR
Number of subjects included in analysis	716
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0553
Method	Fisher exact
Parameter estimate	Difference of percentage of subjects

Secondary: Number of bleeding days by Uterine Fibroid Daily Bleeding Diary (UF-DBD)

End point title	Number of bleeding days by Uterine Fibroid Daily Bleeding Diary (UF-DBD)

End point description:

Treatment and drug-free break periods which are part of the treatment regimen were included in the computation. The analysis of number of bleeding days was shown after normalization by 28 days or 365 days, i.e. the number of bleeding days was multiplied by 28 days or 365 days and then divided by total number of bleeding days.

End point type	Secondary

End point timeframe:

From day 1 of TP1 until the day before a new TP would start again assuming treatment would continue.

End point values	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)	B (UPA-3/2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	271	266	90	89
Units: Days				
arithmetic mean (standard deviation)				
Normalized to 28 days	1.60 (± 1.48)	1.77 (± 1.75)	2.31 (± 2.99)	2.37 (± 2.09)
Normalized to 365 days	20.82 (± 19.27)	23.05 (± 22.77)	30.11 (± 38.99)	30.95 (± 27.30)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with absence of bleeding (spotting allowed) during the last 28 days of treatment based on UF-DBD in each treatment period

End point title	Number of subjects with absence of bleeding (spotting allowed) during the last 28 days of treatment based on UF-DBD in each treatment period

End point description:

Absence of bleeding was defined as no scheduled or unscheduled bleeding (spotting allowed) during the last 28 days of a treatment period based on subjects' daily responses to the UF-DBD. 99999 in group A3 (VPR-3/2) and B (UPA-3/2) denotes subjects were switched from the double-blind treatment to open-label VPR-3/2 treatment for TP1-OL and had no TP3 or TP4.

End point type	Secondary

End point timeframe:

Up to 4 TPs (1 TP= 84 days for VPR- 3/1, VPR-3/2, and UPA-3/2 group. 1 TP = 168 days for VPR-6/2 group)

End point values	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)	B (UPA-3/2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277[2]	261[3]	90[4]	89[5]
Units: Subjects				
Subjects analyzed in TP1	271	266	90	89
Subjects with absence of bleeding in TP1	232	223	81	68
Subjects analyzed in TP2	217	266	3	4
Subjects with absence of bleeding in TP2	184	182	2	3
Subjects analyzed in TP3	121	126	99999	99999
Subjects with absence of bleeding in TP3	114	113	99999	99999
Subjects analyzed in TP4	48	126	99999	99999

Subjects with absence of bleeding in TP4	39	62	99999	99999
Subjects analyzed in TP1-OL	99999	99999	16	22
Subjects with absence of bleeding in TP1-OL	99999	99999	15	20

Notes:

[2] - Codes 99999 indicate missing. No subjects entered TP1-OL.

[3] - Codes 99999 indicate missing. No subjects entered TP1-OL.

[4] - Codes 99999 indicate missing. Subjects had no TP3 or TP4.

[5] - Codes 99999 indicate missing. Subjects had no TP3 or TP4.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of controlled bleeding

End point title	Time to onset of controlled bleeding

End point description:

Onset of controlled bleeding was defined by the first day, for which the MBL (assessed by MP) and for all subsequent 28-day periods up to the end of a TP is less than 80 mL. 99999 in group A1 (VPR-3/1) and A2 (VPR-6/2) denotes no subjects entered TP1-OL and 99999 in group A3 (VPR-3/2) and B (UPA-3/2) denotes subjects were switched from the double-blind treatment to open-label VPR-3/2 treatment for TP1-OL and had no TP3 or TP4.

End point type	Secondary

End point timeframe:

Up to 4 TPs (1 TP= 84 days for VPR- 3/1, VPR-3/2, and UPA-3/2 group. 1 TP = 168 days for VPR-6/2 group)

End point values	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)	B (UPA-3/2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	280[6]	279[7]	99[8]	98[9]
Units: Days				
median (inter-quartile range (Q1-Q3))				
TP1	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)
TP2	1 (1 to 2)	1 (1 to 1)	1 (1 to 26)	1.5 (1 to 99999)
TP3	1 (1 to 1)	1 (1 to 1)	99999 (99999 to 99999)	99999 (99999 to 99999)
TP4	1 (1 to 1)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)
TP1-OL	99999 (99999 to 99999)	99999 (99999 to 99999)	1 (1 to 1)	1 (1 to 3)

Notes:

[6] - Events in TP1: 244; in TP2: 188; in TP3: 110; in TP4: 39. Codes 99999 in table indicate missing.

[7] - Events in TP1: 204; in TP2: 57; in TP3: 1; in TP4: 0. Codes 99999 in table indicate missing.

[8] - Events in TP1: 77; in TP2: 3; in TP3: 0; in TP4: 0. Codes 99999 in table indicate missing.

[9] - Events in TP1: 70; in TP2: 3; in TP3: 0; in TP4: 0. Codes 99999 in table indicate missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in volume of largest fibroid compared to baseline (measured by MRI)

End point title	Percent change in volume of largest fibroid compared to baseline (measured by MRI)

End point description:

The fibroid volume was monitored by ultrasound and Magnetic Resonance Imaging (MRI) at baseline, end of treatment (EoT) and follow-up period (FUP) visits. But for this endpoint, MRI values were used. Due to the temporary pause and the closure of the study, the EoT and the FUP visit timepoints may have been different to the originally scheduled ones. Also, subjects may have not completed all TPs that were originally planned before coming to the EoT visit. Frequently, there might have been a long period between the end of receiving study drug and the EoT visit and FUP visit.

End point type	Secondary

End point timeframe:

From baseline to FUP visit

End point values	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)	B (UPA-3/2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	280[10]	279[11]	99[12]	98[13]
Units: millimeter				
arithmetic mean (standard deviation)				
EOT visit	-29.0 (± 56.2)	-37.2 (± 55.4)	-3.2 (± 49.8)	-20.4 (± 42.0)
FUP visit	-34.1 (± 57.6)	-32.7 (± 64.1)	39.4 (± 99999)	99999 (± 99999)

Notes:

[10] - EOT visit: 101; FUP visit: 39.

[11] - EOT visit: 115; FUP visit: 54

[12] - EOT visit: 13; FUP visit: 1. Codes 99999 indicate missing.

[13] - EOT visit: 17. Codes 99999 indicate missing. Subjects had no FUP visits.

Statistical analyses

No statistical analyses for this end point

Secondary: Change of endometrial thickness from baseline

End point title	Change of endometrial thickness from baseline

End point description:

Ultrasound examinations were performed. Endometrial thickness was measured in the medio-sagittal section as double-layer in millimeters. Summary statistics for change from baseline in endometrial thickness was provided in below table. 99999 in Group A1 (VPR-3/1) and A2 (VPR-6/2) denotes no subjects entered TP1-OL and 99999 in group A3 (VPR-3/2) and B (UPA-3/2) denotes subjects were switched from the double-blind treatment to open-label VPR-3/2 treatment for TP1-OL and had no TP3 or TP4 and not results for TP2. New baseline data was collected from groups A3 (VPR-3/2) and B (UPA-3/2) before subjects entered the OL VPR-3/2 treatment (TP1-OL).
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End point type	Secondary

End point timeframe:

Up to 4 TPs (1 TP= 84 days for VPR- 3/1, VPR-3/2, and UPA-3/2 group. 1 TP = 168 days for VPR-6/2 group)

End point values	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)	B (UPA-3/2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	271[14]	266[15]	90[16]	89[17]
Units: mm				
arithmetic mean (standard deviation)				
Baseline	10.6 (± 3.4)	10.8 (± 3.2)	11.0 (± 2.9)	10.4 (± 3.5)
TP1	-2.5 (± 4.1)	-2.8 (± 6.5)	-0.8 (± 3.3)	-0.4 (± 4.1)
TP2	0.3 (± 7.2)	-1.8 (± 5.3)	99999 (± 99999)	99999 (± 99999)
TP3	-1.1 (± 7.4)	-1.8 (± 3.6)	99999 (± 99999)	99999 (± 99999)
TP4	-2.5 (± 4.3)	-1.1 (± 5.3)	99999 (± 99999)	99999 (± 99999)
New baseline	99999 (± 99999)	99999 (± 99999)	7.5 (± 1.7)	7.6 (± 2.9)
TP1-OL	99999 (± 99999)	99999 (± 99999)	-1.7 (± 0.6)	-1.3 (± 2.0)

Notes:

[14] - Baseline: 269; TP1: 27; TP2: 19; TP3: 20; TP4: 42. Codes 99999 indicate missing.

[15] - Baseline: 264; TP1: 15; TP2: 232; TP3: 21; TP4: 85. Codes 99999 indicate missing.

[16] - Baseline: 90; TP1: 6; TP2, TP3, TP4: 0; New Baseline: 16; TP1-OL: 3. Codes 99999 indicate missing.

[17] - Baseline: 90; TP1: 10; TP2, TP3, TP4: 0; New Baseline: 22; TP1-OL: 6. Codes 99999 indicate missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects by endometrial biopsy main results (majority read, main diagnosis)

End point title	Number of subjects by endometrial biopsy main results (majority read, main diagnosis)

End point description:

Number of subjects with endometrial histology findings, e.g. benign endometrium, Malignant Neoplasm, Hyperplasia WHO 2014, no atypia or Hyperplasia 2014, atypia and Endometrial Polyps.

End point type	Secondary

End point timeframe:

Up to 4 TPs (1 TP= 84 days for VPR- 3/1, VPR-3/2, and UPA-3/2 group. 1 TP = 168 days for VPR-6/2 group)

End point values	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)	B (UPA-3/2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	268	260	90	88
Units: Subjects				
Adequate endometrial tissue	268	260	90	88
Benign Endometrium	268	260	90	88
Hyperplasia WHO 2014, no atypia	0	0	0	0
Hyperplasia WHO 2014, atypia	0	0	0	0
Malignant Neoplasm	0	0	0	0
Endometrial Polyps	7	11	8	3

Statistical analyses

No statistical analyses for this end point

Secondary: Total volume (mL) of MBL

End point title	Total volume (mL) of MBL

End point description:

Volume of MBL were normalized by 28 days. Bleeding on the day of endometrial biopsy and the 3 days thereafter did not contribute to the MBL in this evaluation

End point type	Secondary

End point timeframe:

From Day 1 of TP1 until the day before a new TP would start.

End point values	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)	B (UPA-3/2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	271	266	90	89
Units: mL				
arithmetic mean (standard deviation)	41.24 (± 62.42)	46.26 (± 54.11)	65.89 (± 89.04)	80.53 (± 157.68)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with amenorrhea during the last 28 days of each treatment period based on MP

End point title	Number of subjects with amenorrhea during the last 28 days of each treatment period based on MP

End point description:

Defined as MBL <2 mL during the last 28 days of each treatment period based on MP. 99999 in group A3 (VPR-3/2) and B (UPA-3/2) denotes subjects were switched from the double-blind treatment to open-label VPR-3/2 treatment for TP1-OL and had no TP3 or TP4.

End point type	Secondary

End point timeframe:

Up to 4 TPs (1 TP= 84 days for VPR- 3/1, VPR-3/2, and UPA-3/2 group. 1 TP = 168 days for VPR-6/2 group)

End point values	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)	B (UPA-3/2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	271[18]	266[19]	90[20]	89[21]
Units: Subjects				
Subjects analyzed in TP1	271	266	90	89
Subjects with amenorrhea in TP1	222	218	80	66
Subjects analyzed in TP2	217	247	3	4
Subjects with amenorrhea in TP2	182	176	2	3
Subjects analyzed in TP3	121	126	99999	99999
Subjects with amenorrhea in TP3	111	110	99999	99999
Subjects analyzed in TP4	48	95	99999	99999
Subjects with amenorrhea in TP4	39	60	99999	99999
Subjects analyzed in TP1-OL	99999	99999	16	22
Subjects with amenorrhea in TP1-OL	99999	99999	15	20

Notes:

[18] - Codes 99999 indicate missing. No subjects entered TP1-open label (OL).

[19] - Codes 99999 indicate missing. No subjects entered TP1-OL.

[20] - Codes 99999 indicate missing. Subjects had no TP3 or TP4.

[21] - Codes 99999 indicate missing. Subjects had no TP3 or TP4.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with HMB response during the last 28 days of each treatment period (based on the MP)

End point title	Number of subjects with HMB response during the last 28 days of each treatment period (based on the MP)

End point description:

HMB response was defined as MBL <80.00 ml and >50% reduction from baseline during the last 28 days of TP considered (assessed by the MP method). 99999 in group A3 (VPR-3/2) and B (UPA-3/2) denotes subjects were switched from the double-blind treatment to open-label VPR-3/2 treatment for TP1-OL and had no TP3 or TP4.

End point type	Secondary

End point timeframe:

Up to 4 TPs (1 TP= 84 days for VPR- 3/1, VPR-3/2, and UPA-3/2 group. 1 TP = 168 days for VPR-6/2 group)

End point values	A1 (VPR-3/1)	A2 (VPR-6/2)	A3 (VPR-3/2)	B (UPA-3/2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	271[22]	266[23]	90[24]	89[25]
Units: Subjects				
Subjects analyzed in TP1	271	266	90	89
Subjects with HMB response in TP1	257	244	84	74
Subjects analyzed in TP2	217	247	3	4
Subjects with HMB response in TP2	203	210	3	3
Subjects analyzed in TP3	121	126	99999	99999
Subjects with HMB response in TP3	118	115	99999	99999
Subjects analyzed in TP4	48	95	99999	99999
Subjects with HMB response in TP4	43	68	99999	99999

Subjects analyzed in TP1-OL	99999	99999	16	22
Subjects with HMB response in TP1-OL	99999	99999	15	21

Notes:

[22] - Codes 99999 indicate missing. No subjects entered TP1-OL.

[23] - Codes 99999 indicate missing. No subjects entered TP1-OL.

[24] - Codes 99999 indicate missing. Subjects had no TP3 or TP4.

[25] - Codes 99999 indicate missing. Subjects had no TP3 or TP4.

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

The observation period for AEs will start with signing the informed consent and will end with the last visit. For reporting of the deaths (all causes), it considers all deaths that occurred at any time during the study before the last contact.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	VPR-6/2 - Treatment emergent AEs

Reporting group description:

Subjects received vilaprisan 2 mg for up to 2 treatment periods of 24 weeks, separated by 2 bleeding episodes (6/2 regimen). TEAEs were defined as any AEs that occurred after the first study drug intake until 60 days after the last study drug intake.

Reporting group title	VPR-3/1 - Treatment emergent AEs

Reporting group description:

Subjects received vilaprisan 2 mg for up to 4 treatment periods of 12 weeks, each separated by 1 bleeding episode (3/1 regimen). TEAEs were defined as any AEs that occurred after the first study drug intake until 60 days after the last study drug intake.

Reporting group title	VPR-3/2 (A3-DB) - Treatment emergent AEs

Reporting group description:

Subjects received vilaprisan 2 mg and matching placebo to ulipristal for up to 2 treatment periods of 12 weeks, separated by 2 bleeding episodes (3/2 regimen - in double-blind phase). TEAEs were defined as any AEs that occurred after the first study drug intake until 60 days after the last study drug intake.

Reporting group title	VPR-3/2 (A3-OL) - Treatment emergent AEs

Reporting group description:

Subjects received vilaprisan 2 mg, open-label, for 1 treatment period of 12 weeks (3/2 regimen - in open label phase). TEAEs were defined as any AEs that occurred after the first study drug intake until 60 days after the last study drug intake.

Reporting group title	UPA-3/2 (B-DB) - Treatment emergent AEs

Reporting group description:

Subjects received ulipristal 5 mg and matching placebo to vilaprisan for up to 2 treatment periods of 12 weeks, separated by 2 bleeding episodes (3/2 regimen - in double-blind phase). TEAEs were defined as any AEs that occurred after the first study drug intake until 60 days after the last study drug intake.

Reporting group title	VPR-3/2 (B-OL) - Treatment emergent AEs

Reporting group description:

Subjects received vilaprisan 2 mg, open-label, for 1 treatment period of 12 weeks (3/2 regimen - in open-label phase). TEAEs were defined as any AEs that occurred after the first study drug intake until 60 days after the last study drug intake.

Reporting group title	VPR-3/1 - Post-treatment AEs

Reporting group description:

Subjects received vilaprisan 2 mg for up to 4 treatment periods of 12 weeks, each separated by 1 bleeding episode (3/1 regimen). Post-treatment AEs were defined as all AEs that started from Day 61 after the end of treatment with study medication. (All AEs identified during the safety follow-up are included in this portion).

Reporting group title	VPR-6/2 - Post-treatment AEs

Reporting group description:

Subjects received vilaprisan 2 mg for up to 2 treatment periods of 24 weeks, separated by 2 bleeding episodes (6/2 regimen). Post-treatment AEs were defined as all AEs that started from Day 61 after the end of treatment with study medication. (All AEs identified during the safety follow-up are included in this portion).

Reporting group title	VPR-3/2 (A3-DB) - Post-treatment AEs

Reporting group description:

Subjects received vilaprisan 2 mg and matching placebo to ulipristal for up to 2 treatment periods of 12 weeks, separated by 2 bleeding episodes (3/2 regimen - in double-blind phase). Post-treatment AEs were defined as all AEs that started from Day 61 after the end of treatment with study medication. (All AEs identified during the safety follow-up are included in this portion).

Reporting group title	UPA-3/2 (B-DB) - Post-treatment AEs

Reporting group description:

Subjects received ulipristal 5 mg and matching placebo to vilaprisan for up to 2 treatment periods of 12 weeks, separated by 2 bleeding episodes (3/2 regimen - in double-blind phase). Post-treatment AEs were defined as all AEs that started from Day 61 after the end of treatment with study medication. (All AEs identified during the safety follow-up are included in this portion).

Reporting group title	VPR-3/2 (A3-OL) - Post-treatment AEs

Reporting group description:

Subjects received vilaprisan 2 mg, open-label, for 1 treatment period of 12 weeks (3/2 regimen - in open label phase). Post-treatment AEs were defined as all AEs that started from Day 61 after the end of treatment with study medication. (All AEs identified during the safety follow-up are included in this portion).

Reporting group title	VPR-3/2 (B-OL) - Post-treatment AEs

Reporting group description:

Subjects received vilaprisan 2 mg, open-label, for 1 treatment period of 12 weeks (3/2 regimen - in open-label phase). Post-treatment AEs were defined as all AEs that started from Day 61 after the end of treatment with study medication. (All AEs identified during the safety follow-up are included in this portion).

Serious adverse events	VPR-6/2 - Treatment emergent AEs	VPR-3/1 - Treatment emergent AEs	VPR-3/2 (A3-DB) - Treatment emergent AEs
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 266 (3.76%)	15 / 271 (5.54%)	0 / 86 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Basal cell carcinoma			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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
Breast cancer			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Fallopian tube cancer			

subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Fibroadenoma of breast			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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 germ cell teratoma benign			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 86 (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
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Breast cancer female			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Surgical and medical procedures			
Hysterectomy			
subjects affected / exposed	1 / 266 (0.38%)	2 / 271 (0.74%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Mastectomy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Modified radical mastectomy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Myomectomy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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 cystectomy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Salpingectomy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Salpingo-oophorectomy unilateral			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Tonsillectomy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polypectomy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Hysterosalpingo-oophorectomy			

subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial ablation			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Hysterosalpingectomy			
subjects affected / exposed	0 / 266 (0.00%)	2 / 271 (0.74%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraovarian cystectomy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Meniscus operation			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Adhesiolysis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine dilation and curettage			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Intervertebral disc operation			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Therapeutic embolisation			

subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Endometriosis ablation			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Varicose vein operation			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Mammoplasty			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma embolisation			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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			
Endometrial hyperplasia			

subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermenstrual bleeding			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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
Uterine polyp			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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
Vaginal haemorrhage			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Adnexa uteri cyst			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Adenomyosis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine adhesions			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Heavy menstrual bleeding			

subjects affected / exposed	0 / 266 (0.00%)	2 / 271 (0.74%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal uterine bleeding			
subjects affected / exposed	0 / 266 (0.00%)	2 / 271 (0.74%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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
Biopsy breast			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Endocrine test			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 86 (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
Limb injury			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Upper limb fracture			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 86 (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
Meniscus injury			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Cardiac disorders			
Stress cardiomyopathy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Nervous system disorders			
Vertigo CNS origin			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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
Hepatic steatosis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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			
Stress urinary incontinence			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 86 (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
Ureterolithiasis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 86 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Hyperplasia adrenal			

subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Primary hyperaldosteronism			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Autoimmune thyroiditis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenomegaly			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Adrenal mass			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Knee deformity			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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			
Appendicitis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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

Cellulitis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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
Gastroenteritis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 86 (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
Escherichia bacteraemia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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
Post procedural infection			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (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	VPR-3/2 (A3-OL) - Treatment emergent AEs	UPA-3/2 (B-DB) - Treatment emergent AEs	VPR-3/2 (B-OL) - Treatment emergent AEs
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	1 / 23 (4.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Breast cancer			

subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Fallopian tube cancer			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Fibroadenoma of breast			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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 germ cell teratoma benign			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Breast cancer female			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Surgical and medical procedures			

Hysterectomy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Mastectomy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Modified radical mastectomy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Myomectomy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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 cystectomy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Salpingectomy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Salpingo-oophorectomy unilateral			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Tonsillectomy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polypectomy			

subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Hysterosalpingo-oophorectomy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial ablation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Hysterosalpingectomy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraovarian cystectomy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Meniscus operation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Adhesiolysis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine dilation and curettage			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Intervertebral disc operation			

subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Therapeutic embolisation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Endometriosis ablation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Varicose vein operation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Mammoplasty			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma embolisation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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			
Endometrial hyperplasia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Intermenstrual bleeding			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Adnexa uteri cyst			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Adenomyosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine adhesions			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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

Heavy menstrual bleeding			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Abnormal uterine bleeding			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Biopsy breast			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Endocrine test			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Limb injury			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Upper limb fracture			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Meniscus injury			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Cardiac disorders			
Stress cardiomyopathy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Nervous system disorders			
Vertigo CNS origin			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Hepatic steatosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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			
Stress urinary incontinence			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Ureterolithiasis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Hyperplasia adrenal			

subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Primary hyperaldosteronism			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Autoimmune thyroiditis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Adrenomegaly			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Adrenal mass			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Knee deformity			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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			
Appendicitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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

Cellulitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Gastroenteritis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Escherichia bacteraemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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
Post procedural infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (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	VPR-3/1 - Post-treatment AEs	VPR-6/2 - Post-treatment AEs	VPR-3/2 (A3-DB) - Post-treatment AEs
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 271 (19.56%)	46 / 266 (17.29%)	10 / 86 (11.63%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	7 / 271 (2.58%)	9 / 266 (3.38%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	4 / 7	3 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Breast cancer			

subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Fallopian tube cancer			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Fibroadenoma of breast			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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 germ cell teratoma benign			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Uterine leiomyoma			
subjects affected / exposed	2 / 271 (0.74%)	3 / 266 (1.13%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer female			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Surgical and medical procedures			

Hysterectomy			
subjects affected / exposed	18 / 271 (6.64%)	12 / 266 (4.51%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 18	1 / 12	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastectomy			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Modified radical mastectomy			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Myomectomy			
subjects affected / exposed	13 / 271 (4.80%)	10 / 266 (3.76%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 13	0 / 10	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cystectomy			
subjects affected / exposed	1 / 271 (0.37%)	1 / 266 (0.38%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingectomy			
subjects affected / exposed	2 / 271 (0.74%)	1 / 266 (0.38%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingo-oophorectomy unilateral			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Tonsillectomy			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polypectomy			

subjects affected / exposed	2 / 271 (0.74%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hysterosalpingo-oophorectomy			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial ablation			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Hysterosalpingectomy			
subjects affected / exposed	2 / 271 (0.74%)	1 / 266 (0.38%)	3 / 86 (3.49%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraovarian cystectomy			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Meniscus operation			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Adhesiolysis			
subjects affected / exposed	2 / 271 (0.74%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine dilation and curettage			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc operation			

subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Therapeutic embolisation			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis ablation			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Varicose vein operation			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Mammoplasty			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Uterine leiomyoma embolisation			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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

Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Intermenstrual bleeding			
subjects affected / exposed	1 / 271 (0.37%)	1 / 266 (0.38%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Adnexa uteri cyst			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Adenomyosis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Uterine adhesions			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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

Heavy menstrual bleeding			
subjects affected / exposed	5 / 271 (1.85%)	3 / 266 (1.13%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal uterine bleeding			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Biopsy breast			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Endocrine test			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Limb injury			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Upper limb fracture			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Meniscus injury			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Cardiac disorders			
Stress cardiomyopathy			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Nervous system disorders			
Vertigo CNS origin			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Hepatic steatosis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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			
Stress urinary incontinence			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Ureterolithiasis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Hyperplasia adrenal			

subjects affected / exposed	2 / 271 (0.74%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Primary hyperaldosteronism			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Autoimmune thyroiditis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Adrenomegaly			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Adrenal mass			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Knee deformity			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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			
Appendicitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (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

Cellulitis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Gastroenteritis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (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
Escherichia bacteraemia			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (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
Post procedural infection			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	UPA-3/2 (B-DB) - Post-treatment AEs	VPR-3/2 (A3-OL) - Post-treatment AEs	VPR-3/2 (B-OL) - Post-treatment AEs
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 89 (19.10%)	2 / 19 (10.53%)	4 / 23 (17.39%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	1 / 89 (1.12%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Breast cancer			

subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Fallopian tube cancer			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Fibroadenoma of breast			
subjects affected / exposed	1 / 89 (1.12%)	0 / 19 (0.00%)	0 / 23 (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
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Breast cancer female			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Surgical and medical procedures			

Hysterectomy			
subjects affected / exposed	8 / 89 (8.99%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 8	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastectomy			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Modified radical mastectomy			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Myomectomy			
subjects affected / exposed	4 / 89 (4.49%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cystectomy			
subjects affected / exposed	1 / 89 (1.12%)	0 / 19 (0.00%)	0 / 23 (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
Salpingectomy			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Salpingo-oophorectomy unilateral			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Tonsillectomy			
subjects affected / exposed	1 / 89 (1.12%)	0 / 19 (0.00%)	0 / 23 (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
Uterine polypectomy			

subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Hysterosalpingo-oophorectomy			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial ablation			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Hysterosalpingectomy			
subjects affected / exposed	1 / 89 (1.12%)	0 / 19 (0.00%)	0 / 23 (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
Paraovarian cystectomy			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Meniscus operation			
subjects affected / exposed	1 / 89 (1.12%)	0 / 19 (0.00%)	0 / 23 (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
Adhesiolysis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine dilation and curettage			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc operation			

subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Therapeutic embolisation			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Endometriosis ablation			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Varicose vein operation			
subjects affected / exposed	1 / 89 (1.12%)	0 / 19 (0.00%)	0 / 23 (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
Mammoplasty			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma embolisation			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	2 / 89 (2.25%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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			
Endometrial hyperplasia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Intermenstrual bleeding			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	1 / 89 (1.12%)	0 / 19 (0.00%)	0 / 23 (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
Adnexa uteri cyst			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Adenomyosis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine adhesions			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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

Heavy menstrual bleeding			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Abnormal uterine bleeding			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Biopsy breast			
subjects affected / exposed	1 / 89 (1.12%)	0 / 19 (0.00%)	0 / 23 (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
Endocrine test			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Limb injury			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Upper limb fracture			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Meniscus injury			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Cardiac disorders			
Stress cardiomyopathy			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Nervous system disorders			
Vertigo CNS origin			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Hepatic steatosis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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			
Stress urinary incontinence			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Ureterolithiasis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Hyperplasia adrenal			

subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Primary hyperaldosteronism			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Autoimmune thyroiditis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Adrenomegaly			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Adrenal mass			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Knee deformity			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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			
Appendicitis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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

Cellulitis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Gastroenteritis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Escherichia bacteraemia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (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
Post procedural infection			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	VPR-6/2 - Treatment emergent AEs	VPR-3/1 - Treatment emergent AEs	VPR-3/2 (A3-DB) - Treatment emergent AEs
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 266 (45.49%)	110 / 271 (40.59%)	21 / 86 (24.42%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 266 (3.38%)	5 / 271 (1.85%)	2 / 86 (2.33%)
occurrences (all)	10	5	2
Blood cholesterol increased			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Dehydroepiandrosterone increased			

subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Blood 25-hydroxycholecalciferol decreased			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Haemangioma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Melanocytic naevus			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 86 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hot flush			
subjects affected / exposed	46 / 266 (17.29%)	32 / 271 (11.81%)	5 / 86 (5.81%)
occurrences (all)	52	38	5
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	43 / 266 (16.17%)	34 / 271 (12.55%)	11 / 86 (12.79%)
occurrences (all)	62	61	12
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	17 / 266 (6.39%)	14 / 271 (5.17%)	0 / 86 (0.00%)
occurrences (all)	18	14	0
Pyrexia			
subjects affected / exposed	5 / 266 (1.88%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	5	0	0
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	1 / 266 (0.38%)	2 / 271 (0.74%)	0 / 86 (0.00%)
occurrences (all)	1	2	0
Abdominal pain lower			
subjects affected / exposed	5 / 266 (1.88%)	8 / 271 (2.95%)	1 / 86 (1.16%)
occurrences (all)	5	8	1
Diarrhoea			
subjects affected / exposed	2 / 266 (0.75%)	4 / 271 (1.48%)	0 / 86 (0.00%)
occurrences (all)	2	4	0
Vomiting			
subjects affected / exposed	1 / 266 (0.38%)	2 / 271 (0.74%)	0 / 86 (0.00%)
occurrences (all)	2	2	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 266 (0.38%)	1 / 271 (0.37%)	0 / 86 (0.00%)
occurrences (all)	2	1	0
Endometrial thickening			
subjects affected / exposed	33 / 266 (12.41%)	18 / 271 (6.64%)	3 / 86 (3.49%)
occurrences (all)	39	25	3
Heavy menstrual bleeding			
subjects affected / exposed	9 / 266 (3.38%)	6 / 271 (2.21%)	2 / 86 (2.33%)
occurrences (all)	9	6	2
Skin and subcutaneous tissue disorders			
Rosacea			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 266 (0.00%)	3 / 271 (1.11%)	0 / 86 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Endometritis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Gingivitis			

subjects affected / exposed	0 / 266 (0.00%)	3 / 271 (1.11%)	1 / 86 (1.16%)
occurrences (all)	0	3	1
Nasopharyngitis			
subjects affected / exposed	15 / 266 (5.64%)	16 / 271 (5.90%)	2 / 86 (2.33%)
occurrences (all)	23	23	2
COVID-19			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	2 / 266 (0.75%)	1 / 271 (0.37%)	1 / 86 (1.16%)
occurrences (all)	2	1	1

Non-serious adverse events	VPR-3/2 (A3-OL) - Treatment emergent AEs	UPA-3/2 (B-DB) - Treatment emergent AEs	VPR-3/2 (B-OL) - Treatment emergent AEs
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 19 (47.37%)	23 / 89 (25.84%)	4 / 23 (17.39%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Blood cholesterol increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Blood glucose increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Dehydroepiandrosterone increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood 25-hydroxycholecalciferol decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Neoplasms benign, malignant and			

unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Haemangioma			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Melanocytic naevus			
subjects affected / exposed	0 / 19 (0.00%)	1 / 89 (1.12%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 19 (5.26%)	3 / 89 (3.37%)	2 / 23 (8.70%)
occurrences (all)	1	3	2
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 19 (5.26%)	11 / 89 (12.36%)	2 / 23 (8.70%)
occurrences (all)	1	17	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 19 (5.26%)	1 / 89 (1.12%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Abdominal pain lower			
subjects affected / exposed	1 / 19 (5.26%)	1 / 89 (1.12%)	0 / 23 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			

subjects affected / exposed	1 / 19 (5.26%)	1 / 89 (1.12%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)	0 / 89 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Endometrial thickening			
subjects affected / exposed	0 / 19 (0.00%)	6 / 89 (6.74%)	0 / 23 (0.00%)
occurrences (all)	0	6	0
Heavy menstrual bleeding			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rosacea			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Endometritis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 19 (10.53%)	4 / 89 (4.49%)	0 / 23 (0.00%)
occurrences (all)	2	4	0
COVID-19			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 89 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	VPR-3/1 - Post-treatment AEs	VPR-6/2 - Post-treatment AEs	VPR-3/2 (A3-DB) - Post-treatment AEs
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 271 (19.56%)	56 / 266 (21.05%)	19 / 86 (22.09%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 271 (1.48%)	0 / 266 (0.00%)	1 / 86 (1.16%)
occurrences (all)	5	0	1
Blood cholesterol increased			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences (all)	1	0	0
Blood glucose increased			
subjects affected / exposed	1 / 271 (0.37%)	2 / 266 (0.75%)	1 / 86 (1.16%)
occurrences (all)	1	2	1
Dehydroepiandrosterone increased			
subjects affected / exposed	3 / 271 (1.11%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences (all)	3	0	0
Blood 25-hydroxycholecalciferol decreased			
subjects affected / exposed	5 / 271 (1.85%)	5 / 266 (1.88%)	4 / 86 (4.65%)
occurrences (all)	5	5	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	8 / 271 (2.95%)	9 / 266 (3.38%)	1 / 86 (1.16%)
occurrences (all)	9	10	1
Haemangioma			
subjects affected / exposed	3 / 271 (1.11%)	2 / 266 (0.75%)	0 / 86 (0.00%)
occurrences (all)	3	2	0
Melanocytic naevus			

subjects affected / exposed	11 / 271 (4.06%)	13 / 266 (4.89%)	1 / 86 (1.16%)
occurrences (all)	11	13	1
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 271 (0.37%)	2 / 266 (0.75%)	0 / 86 (0.00%)
occurrences (all)	1	2	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 271 (2.58%)	6 / 266 (2.26%)	2 / 86 (2.33%)
occurrences (all)	15	8	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 271 (0.74%)	3 / 266 (1.13%)	2 / 86 (2.33%)
occurrences (all)	2	3	2
Pyrexia			
subjects affected / exposed	2 / 271 (0.74%)	2 / 266 (0.75%)	0 / 86 (0.00%)
occurrences (all)	2	2	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 271 (0.00%)	2 / 266 (0.75%)	1 / 86 (1.16%)
occurrences (all)	0	2	1
Abdominal pain lower			
subjects affected / exposed	3 / 271 (1.11%)	0 / 266 (0.00%)	1 / 86 (1.16%)
occurrences (all)	3	0	2
Diarrhoea			
subjects affected / exposed	2 / 271 (0.74%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	2 / 271 (0.74%)	2 / 266 (0.75%)	0 / 86 (0.00%)
occurrences (all)	2	2	0
Reproductive system and breast disorders			

Amenorrhoea			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Endometrial thickening			
subjects affected / exposed	4 / 271 (1.48%)	4 / 266 (1.50%)	0 / 86 (0.00%)
occurrences (all)	4	4	0
Heavy menstrual bleeding			
subjects affected / exposed	12 / 271 (4.43%)	10 / 266 (3.76%)	4 / 86 (4.65%)
occurrences (all)	12	10	7
Skin and subcutaneous tissue disorders			
Rosacea			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Endometritis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 86 (1.16%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 86 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	3 / 271 (1.11%)	5 / 266 (1.88%)	0 / 86 (0.00%)
occurrences (all)	4	6	0
COVID-19			
subjects affected / exposed	3 / 271 (1.11%)	2 / 266 (0.75%)	0 / 86 (0.00%)
occurrences (all)	3	2	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	2 / 86 (2.33%)
occurrences (all)	0	0	2

Non-serious adverse events	UPA-3/2 (B-DB) - Post-treatment AEs	VPR-3/2 (A3-OL) - Post-treatment AEs	VPR-3/2 (B-OL) - Post-treatment AEs
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 89 (17.98%)	10 / 19 (52.63%)	7 / 23 (30.43%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 89 (1.12%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	0 / 89 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Dehydroepiandrosterone increased			
subjects affected / exposed	0 / 89 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Blood 25-hydroxycholecalciferol decreased			
subjects affected / exposed	3 / 89 (3.37%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	3	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	1 / 89 (1.12%)	2 / 19 (10.53%)	2 / 23 (8.70%)
occurrences (all)	1	2	2
Haemangioma			
subjects affected / exposed	0 / 89 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Melanocytic naevus			
subjects affected / exposed	2 / 89 (2.25%)	4 / 19 (21.05%)	2 / 23 (8.70%)
occurrences (all)	2	4	4
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

Arrhythmia			
subjects affected / exposed	1 / 89 (1.12%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 89 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Endometrial thickening			
subjects affected / exposed	2 / 89 (2.25%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Heavy menstrual bleeding			

subjects affected / exposed	5 / 89 (5.62%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	5	1	0
Skin and subcutaneous tissue disorders			
Rosacea			
subjects affected / exposed	0 / 89 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Endometritis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Gingivitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
COVID-19			
subjects affected / exposed	0 / 89 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 89 (0.00%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Hypertriglyceridaemia			
subjects affected / exposed	1 / 89 (1.12%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2017	Amendment 1 (Version 2.0) was valid globally; it specified the following modifications: - To exclude the use of moderate CYP3A4 inhibitors and strong CYP3A4 inducers - To prevent simultaneous intake of UPA and P-gp substrates
30 June 2017	Amendment 2 (Version 3.0) was valid globally; it specified the following modifications: - To update 2 sections regarding moderate CYP3A4 inhibitors.
13 September 2017	Amendment 5 (Version 4.0) was valid globally; it specified the following modifications: - Changes requested by Norwegian HA and updated wording based on discussions with other Health Authorities and Ethic Committees deemed to provide further helpful clarification. - Rifabutin was removed from the list of strong CYP3A4 inducers in exclusion criteria 4. - Modifications on the tabular schedule of evaluations - footnotes were modified. - Gynecological examination was added to the visit description of the premature discontinuation visit. - Ultrasound could be performed by an experienced examiner. - Section on hemoglobin was moved from efficacy to safety. - Description of sampling of endometrial biopsies was revised to make sure that the biopsy sampling via a disposable device Pipelle de Cornier did not require a hysteroscopy.
04 July 2018	Amendment 7 (Version 5.0) was valid globally; it specified the following modifications: - This amendment was based on recommendations provided for UPA on 18 May 2018 from the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) and guidance from Health Authorities regarding hepatic monitoring to provide a robust data base for evaluation of hepatic safety of VPR. In addition to health authority triggered changes additional updates were performed. - Study design update - randomized, parallel-group, double-blind, double-dummy, active-controlled study design was exchanged by open-label, uncontrolled 2-arm design leading to deletion of respective treatment arms and update of statistical considerations. The comparator drug (UPA) was removed from the study due to the recommendations provided for UPA by the PRAC. - AEs of special interest - Added more detailed instructions for the monitoring of liver parameters and liver disorders and for close observation in cases with increased liver enzymes and liver disorders; added a flow chart aiding the understanding of the intended processes for liver function monitoring.
11 December 2018	Amendment 8 (Version 6.0) was valid globally; it specified the following modifications: - Preliminary findings from 2-year animal carcinogenicity studies (rat/mouse) with VPR that were received very recently showed evidence of an increased incidence in endometrial and adrenal neoplasms. While these unexpected findings and their relevance for humans were being further evaluated, Bayer decided to temporarily pause enrollment and randomization, and to temporarily withdraw study treatment in already randomized patients after completion of the ongoing treatment period. This global amendment provided background, justification, as well as a detailed description of the temporary measures that were taken.
22 November 2019	Amendment 9, dated (Version 7.0) was valid globally to close the study. It specified the following modifications: - Bayer decided to close all clinical studies with VPR, which were put on temporary pause in December 2018, while pre-clinical toxicology findings and their relevance to humans were being further investigated. Although the outcome of this investigation revealed that the observed pre-clinical findings were regarded to be of limited relevance to the human situation, a comprehensive safety follow up was conducted to provide additional confirmatory evidence. This amendment introduced measures and processes to prepare the study for an orderly closure, including safety follow up measures in all study subjects who received at least one dose of study drug.

17 February 2020	Amendment 10 (Version 8.0) was valid globally; it specified the following modifications: - Protocol amendment 9, Version 7.0, introduced measures and processes to prepare the study for an orderly closure, including safety follow up measures in all study subjects who received at least one dose of study drug. Bayer received comments from FDA regarding details of the safety follow-up measures that were introduced in protocol amendment 9 (Version 7.0). The protocol amendment 10, version 8.0 implemented these FDA recommendations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 December 2018	Bayer decided to temporarily pause enrollment and randomization, and to temporarily stop study treatment in already randomized patients after completion of the ongoing treatment period.	-

Notes:

Limitations and caveats

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

- The trial was terminated earlier than planned. It was sufficiently advanced to allow for meaningful analysis. - In many subjects, follow up phase was longer than the planned one. - Safety evaluations were not limited to the planned timepoints.

Notes: