



## Clinical trial results:

### **A Pivotal, Multicentre, Double-Blind, Double-Dummy, Randomised Trial on the Contraceptive Efficacy, Tolerability and Safety of LF111 (Drospirenone) Over 9 Cycles in Comparison With Desogestrel 0.075 mg Summary**

EudraCT number	2011-002396-42
Trial protocol	DE HU CZ AT ES SK
Global end of trial date	27 January 2014

#### **Results information**

Result version number	v1 (current)
This version publication date	11 July 2020
First version publication date	11 July 2020

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	CF111/302
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##### **Additional study identifiers**

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

Notes:

##### **Sponsors**

Sponsor organisation name	Laboratorios Leon Farma, S.A.
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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	10 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 January 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the contraceptive efficacy of LF111

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator:

According to the Guideline, active controlled studies should be performed to assess the adverse events, including vaginal bleeding events, and the comparator should, whenever possible, be chosen among market leading products with a similar mechanism of action and schedule of use. Desogestrel 0.075 mg (in a regimen of 28 active pills, marketed under trade names such as Cerazette® and Cerazet®) was chosen as the comparator in this study, because it is more effective at preventing ovulation than other POPs [6] and has been shown to inhibit ovulation in over 90% of cycles with a Pearl Index (PI) similar to the low-dose COCs.

Actual start date of recruitment	01 August 2012
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	Poland: 275
Country: Number of subjects enrolled	Slovakia: 57
Country: Number of subjects enrolled	Spain: 75
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Czech Republic: 327
Country: Number of subjects enrolled	Germany: 172
Country: Number of subjects enrolled	Hungary: 86
Country: Number of subjects enrolled	Romania: 217
Worldwide total number of subjects	1213
EEA total number of subjects	1213

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	1213
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Main criteria for inclusion: Woman without uncontrolled current diseases at risk of pregnancy, at the age of 18-45 years, systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg

### Period 1

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

Blinding implementation details:

During the trial, the subjects and all personnel involved in the conduct and interpretation of the trial, including the investigators, site personnel, and the sponsor's staff, were blinded to the medication codes. The randomisation schedule was to be filed securely by the CRO, in a manner such that blinding was properly maintained throughout the trial. Medication codes were not to be available until the completion of the trial and until after final data review (clinical data base lock).

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Test

Arm description:

Subjects who met the selection criteria were randomised in 5:2 ratio at Visit 1b to doubleblind and double-dummy treatment with either Test: DRSP 4.0 mg for 24 days followed by placebo for 4 days + placebo of desogestrel 0.075mg or Reference: desogestrel 0.075 mg for 28 days + placebo of Test for nine cycles.

Arm type	Experimental
Investigational medicinal product name	Drospirenone 4 mg
Investigational medicinal product code	LF111
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage Form: 28 film-coated tablets; Route of administration: Oral, once daily

<b>Arm title</b>	Reference
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Arm description:

1213 subjects were randomised in a ratio 5:2 to treatment with either Test (872 subjects) or Reference (341 subjects) medication.

Arm type	Active comparator
Investigational medicinal product name	Cerazette (desogestrel 0.075 mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage Form: 28 film-coated tablets; Route of administration: Oral, once daily

<b>Number of subjects in period 1<sup>[1]</sup></b>	Test	Reference
Started	858	333
Completed	688	250
Not completed	170	83
wish for pregnancy	4	1
ineligibility	5	3
Adverse event, non-fatal	82	44
at own subject's request	-	28
Pregnancy	4	1
other	13	3
at subject's own request	57	-
Protocol deviation	5	3

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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: Of 1213 subjects randomised, 1191 received IMP. 14 subjects randomised to the Test group and eight subjects randomised to the Reference group prematurely terminated the trial without receiving double-blind treatment

## Baseline characteristics

### Reporting groups

Reporting group title	Test
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Reporting group description:

Subjects who met the selection criteria were randomised in 5:2 ratio at Visit 1b to doubleblind and double-dummy treatment with either Test: DRSP 4.0 mg for 24 days followed by placebo for 4 days + placebo of desogestrel 0.075mg or Reference: desogestrel 0.075 mg for 28 days + placebo of Test for nine cycles.

Reporting group title	Reference
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Reporting group description:

1213 subjects were randomised in a ratio 5:2 to treatment with either Test (872 subjects) or Reference (341 subjects) medication.

Reporting group values	Test	Reference	Total
Number of subjects	858	333	1191
Age categorical Units: Subjects			
Adults (18-45 years)	858	333	1191
Gender categorical Units: Subjects			
Female	858	333	1191

## End points

### End points reporting groups

Reporting group title	Test
Reporting group description: Subjects who met the selection criteria were randomised in 5:2 ratio at Visit 1b to doubleblind and double-dummy treatment with either Test: DRSP 4.0 mg for 24 days followed by placebo for 4 days + placebo of desogestrel 0.075mg or Reference: desogestrel 0.075 mg for 28 days + placebo of Test for nine cycles.	
Reporting group title	Reference
Reporting group description: 1213 subjects were randomised in a ratio 5:2 to treatment with either Test (872 subjects) or Reference (341 subjects) medication.	
Subject analysis set title	Full Anaysis Set
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: Overall 1190 subjects (858 in the Test group and 332 in the Reference group) were exposed to IMP and had at least one post-baseline safety and at least one efficacy assessment	

### Primary: Overall Pearl Index (PI)

End point title	Overall Pearl Index (PI)
End point description: Overall Pearl Index was to be calculated as: number of pregnancies (M, U) * 1300/number of exposure cycles.	
End point type	Primary
End point timeframe: at the final evaluation	

End point values	Test	Reference	Full Anaysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	858	333	1190	
Units: n/a	858	333	1190	

### Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: Overall Pearl Index	
Comparison groups	Test v Reference v Full Anaysis Set

Number of subjects included in analysis	2381
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Pregnancy Ratio
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3154
upper limit	2.2671

### Secondary: Method failure PI

End point title	Method failure PI
End point description: Method failure PI was to be calculated as: Number of pregnancies (M) * 1300/Number of perfect medication cycles.	
End point type	Secondary
End point timeframe: at the final evaluation	

End point values	Test	Reference	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	858	333	1190	
Units: n/a	858	333	1190	

### Statistical analyses

No statistical analyses for this end point

### Secondary: PI after correction for additional contraception and sexual intercourse status

End point title	PI after correction for additional contraception and sexual intercourse status
End point description: PI after correction for additional contraception and for sexual activity was to be calculated as: Number of pregnancies (M,U) * 1300/Number of medication cycles (excluding those with back-up contraception and without sexual activity).	
End point type	Secondary
End point timeframe: at the final evaluation	



End point values	Test	Reference	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	858	333	1190	
Units: n/a	858	333	1190	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall pregnancy ratio

End point title	Overall pregnancy ratio
End point description:	
Overall pregnancy ratio was to be calculated as: Total number of pregnancies (M,U)/Total number of FAS subjects.	
End point type	Secondary
End point timeframe:	
at the final evaluation	

End point values	Test	Reference	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	858	333	1190	
Units: n/a	858	333	1190	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Method failure pregnancy ratio

End point title	Method failure pregnancy ratio
End point description:	
Method failure pregnancy ratio was to be calculated as: Total number of pregnancies (M)/Total number of FAS subjects.	
End point type	Secondary
End point timeframe:	
at the final evaluation	

End point values	Test	Reference	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	858	333	1190	
Units: n/a	858	333	1190	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Adverse events

End point title	Adverse events
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End point description:

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

End point type	Secondary
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End point timeframe:

All AEs, including SAEs, occurring within the period of observation for the clinical trial had to be recorded.

End point values	Test	Reference	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	858	333	1190	
Units: number of events	858	333	1190	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical laboratory evaluations

End point title	Clinical laboratory evaluations
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End point description:

Thyroid function, Haematology, Biochemistry, Urinalysis, Pregnancy tests

End point type	Secondary
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End point timeframe:

haematology, biochemistry, thyroid function: V1a, V3, V4 (electrolytes only) and V5 (or EDV); Serum pregnancy tests: V1a and V5 (or EDV), Urine pregnancy test: V2, V3, V4 and V5 and in any case during the trial when pregnancy was suspected

End point values	Test	Reference	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	858	333	1190	
Units: n/a	858	333	1190	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Vital signs

End point title	Vital signs
End point description: Vital signs parameters comprised systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, body height, weight and body mass index (BMI).	
End point type	Secondary
End point timeframe: Blood pressure and heart rate were to be measured at screening, V2, V3, V4 and V5 (or EDV).	

End point values	Test	Reference	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	858	333	1190	
Units: n/a	858	333	1190	

## Statistical analyses

No statistical analyses for this end point

### Secondary: 12-Lead electrocardiogram

End point title	12-Lead electrocardiogram
End point description: The following variables related to ECG were collected for a subset of 151 Test group and 56 Reference group subjects: summary (mean) heart rate, RR, PR and QRS duration, QT duration, QTcB – Bazett's correction formula and QTcF-Fridiricia's correction formula.	
End point type	Secondary
End point timeframe: Visit 1b and Visit 5/EDV	

End point values	Test	Reference	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	151	56	207	
Units: n/a	151	56	207	

## Statistical analyses

No statistical analyses for this end point

## Secondary: tolerability

End point title	tolerability
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End point description:

The tolerability assessments were based on the vaginal bleeding data, as reported in subjects' e-diaries on the daily basis. All diary records with less than 84 days were excluded from the period. Cycles without consecutively missing entries and with less than five non-consecutive missing entries only were used for the analysis.

End point type	Secondary
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End point timeframe:

Imputation was applied for single missing entries only. The maximum of the bleeding intensity recorded on the day before or the day after the missing entries were imputed.

End point values	Test	Reference	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	858	333	1190	
Units: n/a	858	333	1190	

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs, including SAEs, occurring within the period of observation for the clinical trial had to be recorded

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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### Reporting groups

Reporting group title	Test
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Reporting group description: -

Reporting group title	Reference
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Reporting group description: -

Serious adverse events	Test	Reference	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 858 (1.75%)	6 / 332 (1.81%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix neoplasm			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic adenoma			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypertension			

subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Nasal polyps			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood potassium increased			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 858 (0.12%)	1 / 332 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			

subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Tension headache			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	3 / 858 (0.35%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological infection			

subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
Hyperkalaemia			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	Test	Reference	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	332 / 858 (38.69%)	150 / 332 (45.18%)	
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
Anogenital warts			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Cervix neoplasm			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Fibroadenoma of breast			
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)	
occurrences (all)	2	0	
Hepatic adenoma			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Uterine leiomyoma			
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)	
occurrences (all)	2	0	
<b>Vascular disorders</b>			
Blood pressure fluctuation			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Hot flush			



subjects affected / exposed occurrences (all)	2 / 858 (0.23%) 2	1 / 332 (0.30%) 1	
Hypertension subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	1 / 332 (0.30%) 1	
Orthostatic hypotension subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	1 / 332 (0.30%) 1	
Varicose vein subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	2 / 332 (0.60%) 2	
Pregnancy, puerperium and perinatal conditions Ectopic pregnancy subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	1 / 332 (0.30%) 1	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	4 / 858 (0.47%) 4	0 / 332 (0.00%) 0	
Feeling abnormal subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	1 / 332 (0.30%) 1	
Generalised oedema subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	1 / 332 (0.30%) 2	
Inflammation subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Influenza like illness subjects affected / exposed occurrences (all)	7 / 858 (0.82%) 7	0 / 332 (0.00%) 0	
Irritability			

subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	1 / 332 (0.30%) 1	
Malaise subjects affected / exposed occurrences (all)	2 / 858 (0.23%) 2	0 / 332 (0.00%) 0	
Medical device discomfort subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Oedema subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	1 / 332 (0.30%) 1	
Oedema peripheral subjects affected / exposed occurrences (all)	3 / 858 (0.35%) 3	0 / 332 (0.00%) 0	
Spinal pain subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	1 / 332 (0.30%) 1	
Immune system disorders Allergic oedema subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	1 / 332 (0.30%) 1	
Hypersensitivity subjects affected / exposed occurrences (all)	2 / 858 (0.23%) 2	0 / 332 (0.00%) 0	
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	14 / 858 (1.63%) 17	5 / 332 (1.51%) 6	
Cervical dysplasia subjects affected / exposed occurrences (all)	26 / 858 (3.03%) 26	11 / 332 (3.31%) 11	
Dysmenorrhoea			

subjects affected / exposed	8 / 858 (0.93%)	2 / 332 (0.60%)
occurrences (all)	11	2
Menorrhagia		
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)
occurrences (all)	0	1
Ovarian cyst		
subjects affected / exposed	8 / 858 (0.93%)	2 / 332 (0.60%)
occurrences (all)	8	2
Metrorrhagia		
subjects affected / exposed	3 / 858 (0.35%)	1 / 332 (0.30%)
occurrences (all)	4	1
Dyspareunia		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Pelvic pain		
subjects affected / exposed	1 / 858 (0.12%)	1 / 332 (0.30%)
occurrences (all)	1	1
Premenstrual syndrome		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Uterine cervical laceration		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Uterine haemorrhage		
subjects affected / exposed	5 / 858 (0.58%)	5 / 332 (1.51%)
occurrences (all)	5	5
Uterine inflammation		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Vaginal discharge		
subjects affected / exposed	3 / 858 (0.35%)	0 / 332 (0.00%)
occurrences (all)	3	0
Vaginal haemorrhage		
subjects affected / exposed	32 / 858 (3.73%)	24 / 332 (7.23%)
occurrences (all)	39	26
vaginal inflammation		

subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)	
occurrences (all)	2	0	
Vulvovaginal dryness			
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)	
occurrences (all)	2	0	
Vulvovaginal pruritus			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	2 / 858 (0.23%)	1 / 332 (0.30%)	
occurrences (all)	2	1	
Epistaxis			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Nasal polyps			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)	
occurrences (all)	3	0	
Rhinitis allergic			
subjects affected / exposed	3 / 858 (0.35%)	0 / 332 (0.00%)	
occurrences (all)	3	0	
Rhinorrhoea			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Psychiatric disorders			

Affect lability		
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)
occurrences (all)	2	0
Affective disorder		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Anxiety		
subjects affected / exposed	3 / 858 (0.35%)	0 / 332 (0.00%)
occurrences (all)	5	0
Apathy		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Depressed mood		
subjects affected / exposed	3 / 858 (0.35%)	0 / 332 (0.00%)
occurrences (all)	3	0
Depression		
subjects affected / exposed	3 / 858 (0.35%)	3 / 332 (0.90%)
occurrences (all)	3	3
Insomnia		
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)
occurrences (all)	0	1
Libido decreased		
subjects affected / exposed	10 / 858 (1.17%)	5 / 332 (1.51%)
occurrences (all)	10	6
Libido disorder		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Loss of libido		
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)
occurrences (all)	0	1
Mood altered		
subjects affected / exposed	3 / 858 (0.35%)	1 / 332 (0.30%)
occurrences (all)	5	1
Mood swings		
subjects affected / exposed	5 / 858 (0.58%)	0 / 332 (0.00%)
occurrences (all)	5	0

Nervousness subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	4 / 858 (0.47%) 4	0 / 332 (0.00%) 0	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	3 / 858 (0.35%) 3	0 / 332 (0.00%) 0	
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	1 / 332 (0.30%) 1	
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Blood potassium increased subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Blood pressure systolic increased subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Blood thyroid stimulating hormone decreased subjects affected / exposed occurrences (all)	2 / 858 (0.23%) 2	0 / 332 (0.00%) 0	
Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	8 / 858 (0.93%) 8	2 / 332 (0.60%) 2	

Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 858 (0.58%)	0 / 332 (0.00%)	
occurrences (all)	5	0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Smear cervix abnormal			
subjects affected / exposed	1 / 858 (0.12%)	1 / 332 (0.30%)	
occurrences (all)	1	1	
Transaminases increased			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Ultrasound thyroid abnormal			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	4 / 858 (0.47%)	0 / 332 (0.00%)	
occurrences (all)	4	0	
Weight increased			
subjects affected / exposed	21 / 858 (2.45%)	6 / 332 (1.81%)	
occurrences (all)	21	6	
White blood cell count decreased			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
White blood cells urine			
subjects affected / exposed	3 / 858 (0.35%)	0 / 332 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Concussion			
subjects affected / exposed	1 / 858 (0.12%)	1 / 332 (0.30%)	
occurrences (all)	1	1	
Contusion			

subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Joint injury subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	1 / 332 (0.30%) 1	
Ligament rupture subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	1 / 332 (0.30%) 1	
Ligament sprain subjects affected / exposed occurrences (all)	4 / 858 (0.47%) 5	0 / 332 (0.00%) 0	
Post procedural haematoma subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Post vaccination syndrome subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Procedural pain subjects affected / exposed occurrences (all)	2 / 858 (0.23%) 2	0 / 332 (0.00%) 0	
Wrist fracture subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Congenital, familial and genetic disorders Gilbert's syndrome subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	2 / 858 (0.23%) 2	0 / 332 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Facial paresis	2 / 858 (0.23%) 2	1 / 332 (0.30%) 1	



subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	1 / 332 (0.30%) 1	
Headache subjects affected / exposed occurrences (all)	38 / 858 (4.43%) 75	17 / 332 (5.12%) 37	
Migraine subjects affected / exposed occurrences (all)	3 / 858 (0.35%) 3	4 / 332 (1.20%) 8	
Parosmia subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Psychomotor hyperactivity subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Tension headache subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 858 (0.00%) 0	1 / 332 (0.30%) 1	
Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Lymphadenitis subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	4 / 858 (0.47%) 5	2 / 332 (0.60%) 2	
Eye disorders Contact lens intolerance subjects affected / exposed occurrences (all)	1 / 858 (0.12%) 1	0 / 332 (0.00%) 0	
Gastrointestinal disorders			

Abdominal pain		
subjects affected / exposed	10 / 858 (1.17%)	4 / 332 (1.20%)
occurrences (all)	11	4
Abdominal pain lower		
subjects affected / exposed	2 / 858 (0.23%)	1 / 332 (0.30%)
occurrences (all)	2	1
Abdominal pain upper		
subjects affected / exposed	4 / 858 (0.47%)	0 / 332 (0.00%)
occurrences (all)	4	0
Anal haemorrhage		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Colitis		
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)
occurrences (all)	0	1
Constipation		
subjects affected / exposed	3 / 858 (0.35%)	1 / 332 (0.30%)
occurrences (all)	3	1
Diarrhoea		
subjects affected / exposed	15 / 858 (1.75%)	3 / 332 (0.90%)
occurrences (all)	18	3
Flatulence		
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)
occurrences (all)	0	1
Food poisoning		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Gastritis		
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)
occurrences (all)	2	0
Gastrointestinal disorder		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Gastrooesophageal reflux disease		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0

Haemorrhoids			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 858 (0.35%)	1 / 332 (0.30%)	
occurrences (all)	3	1	
Proctalgia			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	3 / 858 (0.35%)	1 / 332 (0.30%)	
occurrences (all)	6	1	
Umbilical hernia			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	5 / 858 (0.58%)	3 / 332 (0.90%)	
occurrences (all)	12	3	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Hepatocellular injury			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
acne			
subjects affected / exposed	27 / 858 (3.15%)	19 / 332 (5.72%)	
occurrences (all)	32	20	
Alopecia			
subjects affected / exposed	9 / 858 (1.05%)	4 / 332 (1.20%)	
occurrences (all)	10	5	
Dermatitis atopic			

subjects affected / exposed	0 / 858 (0.00%)	2 / 332 (0.60%)
occurrences (all)	0	2
Dry skin		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Eczema		
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)
occurrences (all)	0	1
Hirsutism		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Hyperhidrosis		
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)
occurrences (all)	2	0
Hypertrichosis		
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)
occurrences (all)	0	1
Intertrigo		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Neurodermatitis		
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)
occurrences (all)	0	1
Pruritus		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Psoriasis		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Rash		
subjects affected / exposed	4 / 858 (0.47%)	0 / 332 (0.00%)
occurrences (all)	4	0
Seborrhoea		
subjects affected / exposed	3 / 858 (0.35%)	1 / 332 (0.30%)
occurrences (all)	3	1
Skin disorder		

subjects affected / exposed occurrences (all)	2 / 858 (0.23%) 2	0 / 332 (0.00%) 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 858 (0.12%)	1 / 332 (0.30%)	
occurrences (all)	1	1	
Nephritis			
subjects affected / exposed	1 / 858 (0.12%)	1 / 332 (0.30%)	
occurrences (all)	1	1	
Nephrolithiasis			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Renal pain			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Endocrine disorders			
Hyperprolactinaemia			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Hyperthyroidism			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	3 / 858 (0.35%)	1 / 332 (0.30%)	
occurrences (all)	3	1	
Thyroiditis chronic			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Toxic nodular goitre			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 858 (0.12%)	1 / 332 (0.30%)	
occurrences (all)	1	1	
Back pain			

subjects affected / exposed	5 / 858 (0.58%)	2 / 332 (0.60%)	
occurrences (all)	5	2	
Bursitis			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Intervertebral disc disorder			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	3 / 858 (0.35%)	0 / 332 (0.00%)	
occurrences (all)	4	0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Acute Tonsillitis			
subjects affected / exposed	3 / 858 (0.35%)	1 / 332 (0.30%)	
occurrences (all)	3	1	
Appendicitis			
subjects affected / exposed	3 / 858 (0.35%)	0 / 332 (0.00%)	
occurrences (all)	3	0	
Bone abscess			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	4 / 858 (0.47%)	5 / 332 (1.51%)	
occurrences (all)	5	6	
Candida infection			
subjects affected / exposed	2 / 858 (0.23%)	2 / 332 (0.60%)	
occurrences (all)	2	2	

Cystitis		
subjects affected / exposed	14 / 858 (1.63%)	5 / 332 (1.51%)
occurrences (all)	15	6
Ear infection		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Endometritis		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Fungal infection		
subjects affected / exposed	1 / 858 (0.12%)	1 / 332 (0.30%)
occurrences (all)	1	1
Furuncle		
subjects affected / exposed	1 / 858 (0.12%)	1 / 332 (0.30%)
occurrences (all)	1	1
Gastroenteritis		
subjects affected / exposed	3 / 858 (0.35%)	2 / 332 (0.60%)
occurrences (all)	3	2
Gastrointestinal infection		
subjects affected / exposed	2 / 858 (0.23%)	2 / 332 (0.60%)
occurrences (all)	3	2
Gastrointestinal viral infection		
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)
occurrences (all)	2	0
Genital herpes		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Gingivitis		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Herpes simplex		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Herpes zoster		
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)
occurrences (all)	2	0

Influenza		
subjects affected / exposed	6 / 858 (0.70%)	7 / 332 (2.11%)
occurrences (all)	6	8
Laryngitis		
subjects affected / exposed	4 / 858 (0.47%)	2 / 332 (0.60%)
occurrences (all)	4	2
Nasopharyngitis		
subjects affected / exposed	29 / 858 (3.38%)	13 / 332 (3.92%)
occurrences (all)	32	15
Neurological infection		
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)
occurrences (all)	0	1
Oral herpes		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Otitis externa		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Parotitis		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	8 / 858 (0.93%)	3 / 332 (0.90%)
occurrences (all)	8	3
Pneumonia		
subjects affected / exposed	2 / 858 (0.23%)	1 / 332 (0.30%)
occurrences (all)	2	1
Pulpitis dental		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Respiratory tract infection		
subjects affected / exposed	1 / 858 (0.12%)	1 / 332 (0.30%)
occurrences (all)	1	1
Rhinitis		
subjects affected / exposed	3 / 858 (0.35%)	2 / 332 (0.60%)
occurrences (all)	3	3



Sinusitis		
subjects affected / exposed	4 / 858 (0.47%)	1 / 332 (0.30%)
occurrences (all)	4	1
Tonsillitis		
subjects affected / exposed	4 / 858 (0.47%)	1 / 332 (0.30%)
occurrences (all)	10	2
Tonsillitis streptococcal		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Tooth abscess		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Tooth infection		
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)
occurrences (all)	1	0
Upper respiratory tract infection		
subjects affected / exposed	5 / 858 (0.58%)	0 / 332 (0.00%)
occurrences (all)	5	0
Urinary tract infection		
subjects affected / exposed	5 / 858 (0.58%)	4 / 332 (1.20%)
occurrences (all)	7	4
Vaginal infection		
subjects affected / exposed	10 / 858 (1.17%)	4 / 332 (1.20%)
occurrences (all)	11	4
Bacterial vulvovaginitis		
subjects affected / exposed	8 / 858 (0.93%)	1 / 332 (0.30%)
occurrences (all)	8	1
Viral diarrhoea		
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)
occurrences (all)	0	1
Viral infection		
subjects affected / exposed	5 / 858 (0.58%)	1 / 332 (0.30%)
occurrences (all)	5	1
Viral upper respiratory tract infection		
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)
occurrences (all)	2	0

Vulval abscess			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Vulvitis			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	5 / 858 (0.58%)	6 / 332 (1.81%)	
occurrences (all)	5	5	
Vulvovaginal mycotic infection			
subjects affected / exposed	6 / 858 (0.70%)	0 / 332 (0.00%)	
occurrences (all)	6	0	
Vulvovaginitis			
subjects affected / exposed	3 / 858 (0.35%)	0 / 332 (0.00%)	
occurrences (all)	3	0	
Tendon rupture			
subjects affected / exposed	2 / 858 (0.23%)	0 / 332 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	0 / 858 (0.00%)	1 / 332 (0.30%)	
occurrences (all)	0	2	
Hyperkalaemia			
subjects affected / exposed	1 / 858 (0.12%)	0 / 332 (0.00%)	
occurrences (all)	1	0	
Increased appetite			
subjects affected / exposed	4 / 858 (0.47%)	1 / 332 (0.30%)	
occurrences (all)	4	1	
Obesity			
subjects affected / exposed	3 / 858 (0.35%)	0 / 332 (0.00%)	
occurrences (all)	4	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported