



## 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 |
|-----------------------|-----------|

##### **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.   |
| Sponsor organisation address | La Vallina s/n, Polígono Industrial de Navatejera, León, Spain, 24008             |
| Public contact               | Chief Scientific Officer, Chemo Research, S.L., +34 913021560, ecolli@exeltis.com |
| Scientific contact           | Chief Scientific Officer, Chemo Research, S.L., +34 913021560, ecolli@exeltis.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                       | 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 |
|------------------|-----------|

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 |
|-----------------------|------|

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.

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

## End points

### End points reporting groups

|  |                  |
|--|------------------|
| Reporting group title  | Test             |
| Reporting group description:<br>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:<br>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:<br>Full analysis set   |                  |
| Subject analysis set title   | Safety set       |
| Subject analysis set type  | Safety analysis  |
| Subject analysis set description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 |
|-----------------|----------------|

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 |
|----------------|-----------|

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 |
|-----------------|---------------------------------|

End point description:

Thyroid function, Haematology, Biochemistry, Urinalysis, Pregnancy tests

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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:<br>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:<br>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:<br>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:<br>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 |
|-----------------|--------------|

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 |
|----------------|-----------|

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 |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

|                       |      |
|-----------------------|------|
| Reporting group title | Test |
|-----------------------|------|

Reporting group description: -

|                       |           |
|-----------------------|-----------|
| Reporting group title | Reference |
|-----------------------|-----------|

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

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 858 (0.12%)<br>1   | 1 / 332 (0.30%)<br>1   |  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)  | 2 / 858 (0.23%)<br>2   | 0 / 332 (0.00%)<br>0   |  |
| Medical device discomfort<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 858 (0.12%)<br>1   | 0 / 332 (0.00%)<br>0   |  |
| Oedema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 858 (0.00%)<br>0   | 1 / 332 (0.30%)<br>1   |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)  | 3 / 858 (0.35%)<br>3   | 0 / 332 (0.00%)<br>0   |  |
| Spinal pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 858 (0.00%)<br>0   | 1 / 332 (0.30%)<br>1   |  |
| Immune system disorders<br>Allergic oedema<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 858 (0.00%)<br>0   | 1 / 332 (0.30%)<br>1   |  |
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)   | 2 / 858 (0.23%)<br>2   | 0 / 332 (0.00%)<br>0   |  |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)   | 1 / 858 (0.12%)<br>1   | 0 / 332 (0.00%)<br>0   |  |
| Reproductive system and breast<br>disorders<br>Breast pain<br>subjects affected / exposed<br>occurrences (all) | 14 / 858 (1.63%)<br>17 | 5 / 332 (1.51%)<br>6   |  |
| Cervical dysplasia<br>subjects affected / exposed<br>occurrences (all)   | 26 / 858 (3.03%)<br>26 | 11 / 332 (3.31%)<br>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<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Investigations  |                      |                      |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)          | 4 / 858 (0.47%)<br>4 | 0 / 332 (0.00%)<br>0 |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)        | 3 / 858 (0.35%)<br>3 | 0 / 332 (0.00%)<br>0 |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 858 (0.00%)<br>0 | 1 / 332 (0.30%)<br>1 |  |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all)      | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)       | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Blood potassium increased<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Blood pressure systolic increased<br>subjects affected / exposed<br>occurrences (all)           | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Blood thyroid stimulating hormone decreased<br>subjects affected / exposed<br>occurrences (all) | 2 / 858 (0.23%)<br>2 | 0 / 332 (0.00%)<br>0 |  |
| Blood thyroid stimulating hormone increased<br>subjects affected / exposed<br>occurrences (all) | 8 / 858 (0.93%)<br>8 | 2 / 332 (0.60%)<br>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<br>occurrences (all)   | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Joint injury<br>subjects affected / exposed<br>occurrences (all)   | 1 / 858 (0.12%)<br>1 | 1 / 332 (0.30%)<br>1 |  |
| Ligament rupture<br>subjects affected / exposed<br>occurrences (all)   | 0 / 858 (0.00%)<br>0 | 1 / 332 (0.30%)<br>1 |  |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)  | 4 / 858 (0.47%)<br>5 | 0 / 332 (0.00%)<br>0 |  |
| Post procedural haematoma<br>subjects affected / exposed<br>occurrences (all)  | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Post vaccination syndrome<br>subjects affected / exposed<br>occurrences (all)  | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)  | 2 / 858 (0.23%)<br>2 | 0 / 332 (0.00%)<br>0 |  |
| Wrist fracture<br>subjects affected / exposed<br>occurrences (all)   | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Congenital, familial and genetic disorders<br>Gilbert's syndrome<br>subjects affected / exposed<br>occurrences (all) | 1 / 858 (0.12%)<br>1 | 0 / 332 (0.00%)<br>0 |  |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                 | 2 / 858 (0.23%)<br>2 | 0 / 332 (0.00%)<br>0 |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                            | 2 / 858 (0.23%)<br>2 | 1 / 332 (0.30%)<br>1 |  |
| Facial paresis   |                      |                      |  |



|                                      |                  |                  |  |
|--------------------------------------|------------------|------------------|--|
| subjects affected / exposed          | 0 / 858 (0.00%)  | 1 / 332 (0.30%)  |  |
| occurrences (all)                    | 0                | 1                |  |
| Headache                             |                  |                  |  |
| subjects affected / exposed          | 38 / 858 (4.43%) | 17 / 332 (5.12%) |  |
| occurrences (all)                    | 75               | 37               |  |
| Migraine                             |                  |                  |  |
| subjects affected / exposed          | 3 / 858 (0.35%)  | 4 / 332 (1.20%)  |  |
| occurrences (all)                    | 3                | 8                |  |
| Parosmia                             |                  |                  |  |
| subjects affected / exposed          | 1 / 858 (0.12%)  | 0 / 332 (0.00%)  |  |
| occurrences (all)                    | 1                | 0                |  |
| Psychomotor hyperactivity            |                  |                  |  |
| subjects affected / exposed          | 1 / 858 (0.12%)  | 0 / 332 (0.00%)  |  |
| occurrences (all)                    | 1                | 0                |  |
| Tension headache                     |                  |                  |  |
| subjects affected / exposed          | 1 / 858 (0.12%)  | 0 / 332 (0.00%)  |  |
| occurrences (all)                    | 1                | 0                |  |
| Blood and lymphatic system disorders |                  |                  |  |
| Anaemia                              |                  |                  |  |
| subjects affected / exposed          | 0 / 858 (0.00%)  | 1 / 332 (0.30%)  |  |
| occurrences (all)                    | 0                | 1                |  |
| Iron deficiency anaemia              |                  |                  |  |
| subjects affected / exposed          | 1 / 858 (0.12%)  | 0 / 332 (0.00%)  |  |
| occurrences (all)                    | 1                | 0                |  |
| Lymphadenitis                        |                  |                  |  |
| subjects affected / exposed          | 1 / 858 (0.12%)  | 0 / 332 (0.00%)  |  |
| occurrences (all)                    | 1                | 0                |  |
| Ear and labyrinth disorders          |                  |                  |  |
| Vertigo                              |                  |                  |  |
| subjects affected / exposed          | 4 / 858 (0.47%)  | 2 / 332 (0.60%)  |  |
| occurrences (all)                    | 5                | 2                |  |
| Eye disorders                        |                  |                  |  |
| Contact lens intolerance             |                  |                  |  |
| subjects affected / exposed          | 1 / 858 (0.12%)  | 0 / 332 (0.00%)  |  |
| occurrences (all)                    | 1                | 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<br>occurrences (all) | 2 / 858 (0.23%)<br>2 | 0 / 332 (0.00%)<br>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