

**Clinical trial results:**

A PHASE III, MULTICENTRE, INTERNATIONAL, RANDOMISED, DOUBLE-BLIND, DOUBLE-DUMMY, PARALLEL-GROUP, PLACEBO AND ACTIVE COMPARATOR CONTROLLED CLINICAL TRIAL TO EVALUATE THE ANALGESIC EFFICACY AND SAFETY OF IBUPROFEN ARGININE/TRAMADOL 400/37.5 MG COMPARED WITH IBUPROFEN ARGININE 400 MG ALONE, TRAMADOL 50 MG ALONE AND PLACEBO IN PATIENTS WITH MODERATE TO SEVERE PAIN AFTER NON-ONCOLOGICAL ABDOMINAL HYSTERECTOMY

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-004081-21 |
| Trial protocol | ES |
| Global end of trial date | 21 April 2016 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 07 July 2022 |
| First version publication date | 07 July 2022 |

Trial information**Trial identification**

| | |
|-----------------------|---------------------|
| Sponsor protocol code | FMLD-IOTRA-20_FIIIB |
|-----------------------|---------------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | FARMALIDER S.A. |
| Sponsor organisation address | C/ La Granja Nº 1, Alcobendas (Madrid), Spain, 28108 |
| Public contact | Medical department, FARMALIDER, Medical department, FARMALIDER, 34 916612335, farmalider@farmalider.com |
| Scientific contact | Medical department, FARMALIDER, Medical department, FARMALIDER, 34 916612335, farmalider@farmalider.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 | 21 April 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 April 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 April 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the analgesic efficacy at multiple doses of the fixed combination of ibuprofen (arginine) and tramadol hydrochloride versus each ingredient separately and placebo, in oral administration, in patients with moderate to severe pain after partial or total non-oncological abdominal hysterectomy.

Protection of trial subjects:

The protocol and amendments were checked and approved by Clinical Research Ethics Committee of the Hospital de Getafe, Madrid as Reference CEIC and by the local CEICs of each of the participating centers. This study was conducted in accordance with the latest version of the Declaration of Helsinki (Fortaleza, 2013, www.wma.net), International Conference of Harmonisation Good Clinical Practice standards (GCP/ICH), and European and local legislation.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 27 January 2015 |
| 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 | Spain: 217 |
| Country: Number of subjects enrolled | Hungary: 159 |
| Worldwide total number of subjects | 376 |
| EEA total number of subjects | 376 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---------------------------|-----|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 376 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 533 patients were included in the study, of which 157 could not be randomized for different reasons, the most frequent being failure to achieve VAS \geq 4 cm after the post-surgical period according to the protocol. 376 patients were randomized into the 4 study groups.

Period 1

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

Blinding implementation details:

Due to the different pharmaceutical forms of the investigational products, two pharmaceutical forms of placebo, granules and drops, were necessary.

Arms

| | |
|--|------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Treatment 1 (Ibuprofen - Tramadol) |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Ibuprofen/ Tramadol |
| Investigational medicinal product code | |
| Other name | Experimental |
| Pharmaceutical forms | Granules for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Dose: 1 sachet

All treatments being administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| | |
|--|----------------------------|
| Investigational medicinal product name | Placebo B |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Granules for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Dose: 1 sachet

All treatments were administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| | |
|--|----------------------|
| Investigational medicinal product name | Placebo C |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops, solution |
| Routes of administration | Oral use |

Dosage and administration details:

Dose: 0,5 ml (20 drops)

All treatments were administered orally. The regimen of administration of the medication was 1 dose

every 6 hours from the time of randomisation.

| | |
|--|------------------------------------|
| Arm title | Treatment 2 (Ibuprofen (arginine)) |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Ibuprofen (arginine) |
| Investigational medicinal product code | |
| Other name | Reference A |
| Pharmaceutical forms | Granules for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Dose: 1 sachet ibuprofen (arginine)

All treatments being administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| | |
|--|----------------------------|
| Investigational medicinal product name | Placebo A |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Granules for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Dose: 1 sachet

All treatments being administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| | |
|--|----------------------|
| Investigational medicinal product name | Placebo C |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops, solution |
| Routes of administration | Oral use |

Dosage and administration details:

Dose: 0,5 ml (20 drops)

All treatments being administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| | |
|--|------------------------|
| Arm title | Treatment 3 (Tramadol) |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Tramadol |
| Investigational medicinal product code | |
| Other name | Reference B |
| Pharmaceutical forms | Oral drops, solution |
| Routes of administration | Oral use |

Dosage and administration details:

Dose: 0,5 ml (20 drops)

All treatments being administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| | |
|--|----------------------------|
| Investigational medicinal product name | Placebo B |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Granules for oral solution |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Dose: 1 sachet

All treatments were administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| | |
|--|-----------|
| Investigational medicinal product name | Placebo A |
|--|-----------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|----------------------------|
| Pharmaceutical forms | Granules for oral solution |
|----------------------|----------------------------|

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Dose: 1 sachet

All treatments being administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| | |
|------------------|-----------------------|
| Arm title | Treatment 4 (Placebo) |
|------------------|-----------------------|

| | |
|--------------------|--|
| Arm description: - | |
|--------------------|--|

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|-----------|
| Investigational medicinal product name | Placebo A |
|--|-----------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|----------------------------|
| Pharmaceutical forms | Granules for oral solution |
|----------------------|----------------------------|

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Dose: 1 sachet

All treatments being administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| | |
|--|-----------|
| Investigational medicinal product name | Placebo B |
|--|-----------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|----------------------------|
| Pharmaceutical forms | Granules for oral solution |
|----------------------|----------------------------|

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Dose: 1 sachet

All treatments were administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| | |
|--|-----------|
| Investigational medicinal product name | Placebo C |
|--|-----------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|----------------------|
| Pharmaceutical forms | Oral drops, solution |
|----------------------|----------------------|

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Dose: 0,5 ml (20 drops)

All treatments being administered orally. The regimen of administration of the medication was 1 dose every 6 hours from the time of randomisation.

| Number of subjects in period 1 | Treatment 1 (Ibuprofen - Tramadol) | Treatment 2 (Ibuprofen (arginine)) | Treatment 3 (Tramadol) |
|--------------------------------|--|--|---------------------------|
| | | | |
| Started | 91 | 94 | 98 |
| Completed | 74 | 59 | 57 |
| Not completed | 17 | 35 | 41 |
| Consent withdrawn by subject | 1 | 2 | 2 |
| Physician decision | - | - | - |
| Adverse event, non-fatal | 3 | 4 | 4 |
| Other reasons | 13 | 29 | 35 |

| Number of subjects in period 1 | Treatment 4 (Placebo) |
|--------------------------------|--------------------------|
| Started | 93 |
| Completed | 42 |
| Not completed | 51 |
| Consent withdrawn by subject | 4 |
| Physician decision | 1 |
| Adverse event, non-fatal | 1 |
| Other reasons | 45 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|--|---------------|-------|--|
| Number of subjects | 376 | 376 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 376 | 376 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 376 | 376 | |

End points

End points reporting groups

| | |
|--------------------------------|------------------------------------|
| Reporting group title | Treatment 1 (Ibuprofen - Tramadol) |
| Reporting group description: - | |
| Reporting group title | Treatment 2 (Ibuprofen (arginine)) |
| Reporting group description: - | |
| Reporting group title | Treatment 3 (Tramadol) |
| Reporting group description: - | |
| Reporting group title | Treatment 4 (Placebo) |
| Reporting group description: - | |

Primary: Pain intensity 24 hours after the start of the treatment.

| | |
|------------------------|---|
| End point title | Pain intensity 24 hours after the start of the treatment. |
| End point description: | The primary efficacy variable for this was the pain intensity score as measured by a visual analogue scale (VAS) and evaluated by the patient 24 hours after the first dose of the treatment. |
| End point type | Primary |
| End point timeframe: | Over 24 hours after first dose |

| End point values | Treatment 1 (Ibuprofen - Tramadol) | Treatment 2 (Ibuprofen (arginine)) | Treatment 3 (Tramadol) | Treatment 4 (Placebo) |
|-----------------------------|--|--|---------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 91 | 91 | 95 | 92 |
| Units: cm | | | | |
| median (standard error) | 2.9 (± 2.5) | 3.6 (± 2.7) | 4.1 (± 2.7) | 5.2 (± 3.1) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | ANCOVA analysis of pain intensity T1 and T2 |
| Comparison groups | Treatment 1 (Ibuprofen - Tramadol) v Treatment 2 (Ibuprofen (arginine)) |
| Number of subjects included in analysis | 182 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0804 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 0.1 |

| | |
|---|---|
| Statistical analysis title | ANCOVA analysis of pain intensity T 1 and T3 |
| Comparison groups | Treatment 1 (Ibuprofen - Tramadol) v Treatment 3 (Tramadol) |
| Number of subjects included in analysis | 186 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0036 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2 |
| upper limit | -0.4 |

| | |
|---|--|
| Statistical analysis title | ANCOVA analysis of pain intensity T1 and T4 |
| Comparison groups | Treatment 1 (Ibuprofen - Tramadol) v Treatment 4 (Placebo) |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3 |
| upper limit | -1.4 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE reporting requirements for all patients from randomisation to 30 days after last administered dose of study medication.

Adverse event reporting additional description:

Safety analysis was performed on 384 randomised patients.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------------------|
| Reporting group title | Treatment 1 (Ibuprofen - Tramadol) |
|-----------------------|------------------------------------|

Reporting group description: -

| | |
|-----------------------|------------------------------------|
| Reporting group title | Treatment 2 (Ibuprofen (arginine)) |
|-----------------------|------------------------------------|

Reporting group description: -

| | |
|-----------------------|------------------------|
| Reporting group title | Treatment 3 (Tramadol) |
|-----------------------|------------------------|

Reporting group description: -

| | |
|-----------------------|-----------------------|
| Reporting group title | Treatment 4 (Placebo) |
|-----------------------|-----------------------|

Reporting group description: -

| Serious adverse events | Treatment 1 (Ibuprofen - Tramadol) | Treatment 2 (Ibuprofen (arginine)) | Treatment 3 (Tramadol) |
|---|--|--|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 92 (3.26%) | 2 / 97 (2.06%) | 9 / 99 (9.09%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 97 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glioblastoma | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Endometrial stromal sarcoma | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix carcinoma stage 0 | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Borderline ovarian tumour | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Wound haemorrhage | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric injury | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suture-related complication | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |

| | | | |
|--|----------------|----------------|----------------|
| Abscess drainage | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 97 (1.03%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal wall haematoma | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 97 (1.03%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Vaginal haematoma | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Vulval abscess | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 97 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|--------------------------|--|--|
| Serious adverse events | Treatment 4 (Placebo) | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 96 (10.42%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Endometrial adenocarcinoma | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glioblastoma | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometrial stromal sarcoma | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervix carcinoma stage 0 | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Borderline ovarian tumour | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Wound haemorrhage | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureteric injury | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound dehiscence | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suture-related complication | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Abscess drainage | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal wall haematoma | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Vaginal haematoma | | | |
| subjects affected / exposed | 2 / 96 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Vulval abscess | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Treatment 1 (Ibuprofen - Tramadol) | Treatment 2 (Ibuprofen (arginine)) | Treatment 3 (Tramadol) |
|---|--|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 31 / 92 (33.70%) | 29 / 97 (29.90%) | 31 / 99 (31.31%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Benign gastrointestinal neoplasm subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Vascular disorders Hot flush subjects affected / exposed occurrences (all) Thrombosis subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 1 / 99 (1.01%) 1 |
| Surgical and medical procedures Protein C increased subjects affected / exposed occurrences (all) Removal of foreign body from throat subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 1 / 92 (1.09%) 1 | 1 / 97 (1.03%) 1 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 1 / 99 (1.01%) 1 |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) thoracic pain | 0 / 92 (0.00%) 0 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 1 / 97 (1.03%) 1 | 1 / 99 (1.01%) 1 0 / 99 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Malaise subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Discomfort subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 7 / 97 (7.22%) 7 | 3 / 99 (3.03%) 3 |
| Drug tolerance increased subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Social circumstances Tattoo subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 | 0 / 99 (0.00%) 0 |
| Vaginal discharge subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Vulvovaginal pruritus subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Catarrh subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Nasal congestion subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Cough | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 1 / 97 (1.03%) 1 | 1 / 99 (1.01%) 1 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Injury, poisoning and procedural complications Anaemia postoperative subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 | 1 / 99 (1.01%) 1 |
| Subcutaneous haematoma subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 | 0 / 99 (0.00%) 0 |
| Seroma subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Wound dehiscence subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Post procedural haematoma subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Wound secretion subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 2 / 97 (2.06%) 2 | 5 / 99 (5.05%) 5 |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 | 0 / 99 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 92 (4.35%) 4 | 1 / 97 (1.03%) 1 | 5 / 99 (5.05%) 6 |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Anaemia subjects affected / exposed occurrences (all) | 6 / 92 (6.52%) 6 | 5 / 97 (5.15%) 5 | 5 / 99 (5.05%) 5 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 | 0 / 99 (0.00%) 0 |
| Eye disorders Halo vision subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Gastrointestinal disorders Abdominal pain lower subjects affected / exposed occurrences (all) | 2 / 92 (2.17%) 2 | 1 / 97 (1.03%) 1 | 1 / 99 (1.01%) 1 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 | 1 / 99 (1.01%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 2 / 92 (2.17%) 2 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Incisional hernia subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Flatulence subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 3 / 97 (3.09%) 3 | 2 / 99 (2.02%) 2 |
| Nausea subjects affected / exposed occurrences (all) | 3 / 92 (3.26%) 3 | 4 / 97 (4.12%) 4 | 5 / 99 (5.05%) 5 |
| Gastrointestinal motility disorder subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Vomiting subjects affected / exposed occurrences (all) | 5 / 92 (5.43%) 5 | 1 / 97 (1.03%) 1 | 4 / 99 (4.04%) 4 |
| Diarrhoea | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 2 / 97 (2.06%) 2 | 0 / 99 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 1 / 97 (1.03%) 1 | 1 / 99 (1.01%) 1 |
| Abdominal wall haematoma subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 | 0 / 99 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis contact0 subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Ecchymosis subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Erythema subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 | 0 / 99 (0.00%) 0 |
| Decubitus ulcer subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Renal and urinary disorders | | | |
| Dysuria subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 2 / 99 (2.02%) 2 |
| Bladder spasm subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Incontinence subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Micturition urgency | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 | 1 / 99 (1.01%) 1 |
| Infections and infestations Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Cystitis subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Pharyngitis subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 1 / 99 (1.01%) 1 |
| Wound infection staphylococcal subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 97 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Postoperative wound infection subjects affected / exposed occurrences (all) | 2 / 92 (2.17%) 2 | 1 / 97 (1.03%) 1 | 1 / 99 (1.01%) 1 |
| Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all) | 0 / 92 (0.00%) 0 | 1 / 97 (1.03%) 1 | 0 / 99 (0.00%) 0 |

| | | | |
|---|--------------------------|--|--|
| Non-serious adverse events | Treatment 4 (Placebo) | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 23 / 96 (23.96%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Benign gastrointestinal neoplasm | | | |

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Thrombosis | | | |
| subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Surgical and medical procedures | | | |
| Protein C increased | | | |
| subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Removal of foreign body from throat | | | |
| subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Pain | | | |
| subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| thoracic pain | | | |
| subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Malaise | | | |
| subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Discomfort | | | |
| subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Pyrexia | | | |
| subjects affected / exposed occurrences (all) | 8 / 96 (8.33%) 8 | | |
| Drug tolerance increased | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Social circumstances Tattoo subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all) Vaginal discharge subjects affected / exposed occurrences (all) Vulvovaginal pruritus subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 0 / 96 (0.00%) 0 0 / 96 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders Catarrh subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 1 / 96 (1.04%) 1 1 / 96 (1.04%) 1 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Injury, poisoning and procedural complications Anaemia postoperative subjects affected / exposed occurrences (all) Subcutaneous haematoma | 0 / 96 (0.00%) 0 | | |

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Seroma subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Wound dehiscence subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Post procedural haematoma subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Wound secretion subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 3 / 96 (3.13%) 3 | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 2 / 96 (2.08%) 2 | | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Eye disorders Halo vision subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Gastrointestinal disorders | | | |

| | | | |
|--|---------------------|--|--|
| Abdominal pain lower subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Constipation subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Incisional hernia subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Flatulence subjects affected / exposed occurrences (all) | 2 / 96 (2.08%) 2 | | |
| Nausea subjects affected / exposed occurrences (all) | 5 / 96 (5.21%) 5 | | |
| Gastrointestinal motility disorder subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 96 (3.13%) 3 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | | |
| Abdominal wall haematoma subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders Dermatitis contact0 | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences (all) | 1 | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences (all) | 1 | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences (all) | 1 | | |
| Bladder spasm | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |
| Incontinence | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |
| Micturition urgency | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences (all) | 1 | | |
| Cystitis | | | |

| | | | |
|------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | | |
| occurrences (all) | 1 | | |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported