Clinical trial results:
A PHASE III, MULTICENTRE, INTERNATIONAL, RANDOMISED, DOUBLE-BLIND, DOUBLE-DUMMY, PARALLEL-GROUP, PLACEBO AND ACTIVE COMPARATORCONTROLLED 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 amedments 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≥ 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 pharmaceutcal 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	0 / 92 (0.00%)	0 / 97 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 92 (0.00%)	1 / 97 (1.03%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Thrombosis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 97 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Protein C increased			
subjects affected / exposed	0 / 92 (0.00%)	1 / 97 (1.03%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Removal of foreign body from throat			
subjects affected / exposed	1 / 92 (1.09%)	0 / 97 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 97 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 92 (0.00%)	1 / 97 (1.03%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
thoracic pain			

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

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

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

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

subjects affected / exposed	0 / 92 (0.00%)	0 / 97 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 92 (0.00%)	1 / 97 (1.03%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Infections and infestations			
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 97 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 97 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 97 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 97 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Wound infection staphylococcal			
subjects affected / exposed	1 / 92 (1.09%)	0 / 97 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Postoperative wound infection			
subjects affected / exposed	2 / 92 (2.17%)	1 / 97 (1.03%)	1 / 99 (1.01%)
occurrences (all)	2	1	1
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 97 (1.03%)	0 / 99 (0.00%)
occurrences (all)	0	1	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	0 / 96 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences (all)	0		
Thrombosis			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Protein C increased			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences (all)	0		
Removal of foreign body from throat			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences (all)	0		
thoracic pain			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences (all)	1		
Discomfort			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	8 / 96 (8.33%)		
occurrences (all)	8		
Drug tolerance increased			

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

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

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