

**Clinical trial results:****Phase II trial to evaluate the maintenance of ovulation inhibition with LF111 (drospirenone 4.0 mg 24/4 regimen) after scheduled 24-hour delays in pill intake.****Summary**

EudraCT number	2013-001513-33
Trial protocol	DE
Global end of trial date	17 March 2014

**Results information**

Result version number	v1 (current)
This version publication date	29 May 2020
First version publication date	29 May 2020

**Trial information****Trial identification**

Sponsor protocol code	CF111/204
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**Additional study identifiers**

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

Notes:

**Sponsors**

Sponsor organisation name	Laboratorios Leon Farma, S.A.
Sponsor organisation address	La Vallina s/n, Polígono Industrial de Navatejera, León, Spain, 28004
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Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	02 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 March 2014
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To demonstrate that ovulation inhibition with LF111 (drospirenone 4.0 mg 24/4 regimen) is maintained in spite of scheduled 24-hour delays in pill intake.

Protection of trial subjects:

N/A

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	21 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Germany: 130
Worldwide total number of subjects	130
EEA total number of subjects	130

Notes:

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**Subjects enrolled per age group**

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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)	130
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Healthy premenopausal females of any ethnic origin without regular intake of medicine, 18 to 35 years of age, inclusive. Smokers not older than 30 years, inclusive (up to 10 cigarettes daily). Subjects had to be in good physical and mental health as determined by vital signs, medical history, physical examination, gynaecological examination, etc.

### Pre-assignment

Screening details:

Screening phase: During this period the information and informed consent procedure and screening examinations were performed:

- Medical, surgical and gynaecological history including demographic data
- Physical and gynaecological examinations including cervix smear and TVUS
- Standard laboratory examinations of blood and urine for safety

### Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Blinding was not applicable because this was an open-label trial.

### Arms

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

Arm description:

Group A performed the following sequence:

- Cycle 1: DRSP 4.0 mg 24/4 regimen (regular intake scheme)
- Cycle 2: DRSP 4.0 mg 24/4 regimen (delayed intake scheme)

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:

once daily. Drospirenone 4.0 mg was to be taken by all subjects enrolled in this trial for a duration of 2 x 28 days

<b>Arm title</b>	Group B
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Arm description:

Group B performed the following sequence:

- Cycle 1: DRSP 4.0 mg 24/4 regimen (delayed intake scheme)
- Cycle 2: DRSP 4.0 mg 24/4 regimen (regular intake scheme)

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:

once daily. Drospirenone 4.0 mg was to be taken by all subjects enrolled in this trial for a duration of 2 x

<b>Number of subjects in period 1</b>	Group A	Group B
Started	65	65
Completed	58	63
Not completed	7	2
private reasons	-	1
Consent withdrawn by subject	2	-
Adverse event, non-fatal	2	1
Pregnancy	2	-
subject missed visit at Cycle 2 Day 27 and follow-	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Group A
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Reporting group description:

Group A performed the following sequence:

- Cycle 1: DRSP 4.0 mg 24/4 regimen (regular intake scheme)
- Cycle 2: DRSP 4.0 mg 24/4 regimen (delayed intake scheme)

Reporting group title	Group B
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Reporting group description:

Group B performed the following sequence:

- Cycle 1: DRSP 4.0 mg 24/4 regimen (delayed intake scheme)
- Cycle 2: DRSP 4.0 mg 24/4 regimen (regular intake scheme)

Reporting group values	Group A	Group B	Total
Number of subjects	65	65	130
Age categorical Units: Subjects			
Adults (18 to 35)	65	65	130
Gender categorical Units: Subjects			
Female	65	65	130

### Subject analysis sets

Subject analysis set title	Safety Saet
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The Safety Set consisted of all subjects who had been allocated to treatment and had at least one dose of IMP intake.

Subject analysis set title	Allocated to Treatment Set
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The Allocated to Treatment Set consisted of all subjects who signed the informed consent and had been allocated to treatment

Subject analysis set title	Full Anaysis Set
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Subject analysis set type	Full analysis
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Subject analysis set description:

The Full Analysis Set consisted of all subjects who were included in the Safety Set and had at least one study observation.

Subject analysis set title	Per Protocol Set
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Subject analysis set type	Per protocol
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Subject analysis set description:

The Per Protocol Set consisted of all subjects who were included in the Full Analysis Set and had no major protocol violation

Reporting group values	Safety Saet	Allocated to Treatment Set	Full Anaysis Set
Number of subjects	127	130	127

Age categorical Units: Subjects			
Adults (18 to 35)	127	130	127
Gender categorical Units: Subjects			
Female	127	130	127

<b>Reporting group values</b>	Per Protocol Set		
Number of subjects	127		
Age categorical Units: Subjects			
Adults (18 to 35)	127		
Gender categorical Units: Subjects			
Female	127		

## End points

### End points reporting groups

Reporting group title	Group A
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Reporting group description:

Group A performed the following sequence:

- Cycle 1: DRSP 4.0 mg 24/4 regimen (regular intake scheme)
- Cycle 2: DRSP 4.0 mg 24/4 regimen (delayed intake scheme)

Reporting group title	Group B
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Reporting group description:

Group B performed the following sequence:

- Cycle 1: DRSP 4.0 mg 24/4 regimen (delayed intake scheme)
- Cycle 2: DRSP 4.0 mg 24/4 regimen (regular intake scheme)

Subject analysis set title	Safety Saet
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The Safety Set consisted of all subjects who had been allocated to treatment and had at least one dose of IMP intake.

Subject analysis set title	Allocated to Treatment Set
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The Allocated to Treatment Set consisted of all subjects who signed the informed consent and had been allocated to treatment

Subject analysis set title	Full Anaysis Set
----------------------------	------------------

Subject analysis set type	Full analysis
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Subject analysis set description:

The Full Analysis Set consisted of all subjects who were included in the Safety Set and had at least one study observation.

Subject analysis set title	Per Protocol Set
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Subject analysis set type	Per protocol
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Subject analysis set description:

The Per Protocol Set consisted of all subjects who were included in the Full Analysis Set and had no major protocol violation

### Primary: Ovulation rate

End point title	Ovulation rate <sup>[1]</sup>
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End point description:

An ovulation was to be assumed if both of the following conditions were fulfilled:

- Ultrasound confirmation of a persisting or ruptured follicle > 13 mm
- Progesterone level > 16 nmol/L for at least five consecutive days

End point type	Primary
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End point timeframe:

Cycle 1 and Cycle 2

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: statistical analyses have not been performed

<b>End point values</b>	Group A	Group B	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	65	65	127	
Units: N/A	65	65	127	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Adverse events

End point title	Adverse events
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End point description:

End point type	Secondary
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End point timeframe:

All AEs, including SAEs, occurring within the period of observation for the clinical trial had to be recorded. The period of observation for the collection of AEs extended from the time when the subject gave informed consent until the date of final visit

<b>End point values</b>	Group A	Group B	Safety Saet	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	62	65	127	
Units: number of adverse events	60	64	124	

### Statistical analyses

No statistical analyses for this end point

### Secondary: bleeding pattern

End point title	bleeding pattern
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End point description:

Bleeding pattern was summarised based on the following defined tolerability endpoints:

- Number and rate of subjects with bleeding or spotting for each day of treatment, by cycle and by overall treatment period
- Number of days with bleeding or spotting per cycle
- Number of days with a certain spotting/bleeding intensity (spotting, slight, moderate, heavy) per cycle
- Number and length of bleeding/spotting episodes

End point type	Secondary
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End point timeframe:

From Cycle 1 Day 1 (i.e. start of IMP intake) to final visit (or EDV), the subjects recorded daily any vaginal bleeding with bleeding intensity in their diary.

<b>End point values</b>	Group A	Group B	Safety Saet	Full Anaysis Set
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	65	65	127	127
Units: n/m (%)	62	65	127	127

### Statistical analyses

No statistical analyses for this end point

### Secondary: clinical laboratory evaluation

End point title	clinical laboratory evaluation
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End point description:

safety laboratory values (haematology, biochemistry, liver function, clotting status, virology and urinalysis results)

End point type	Secondary
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End point timeframe:

screening and final examination

<b>End point values</b>	Group A	Group B	Safety Saet	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	65	65	127	
Units: various units	62	65	127	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Vital signs

End point title	Vital signs
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End point description:

Blood pressure and pulse was measured in sitting position after the subject had rested for at least 5 minutes. The measurements were performed at screening visit, Cycle 1 Day 12 ±1, Cycle 2 Day 12 ±1 and final visit (or EDV). Height was measured at screening visit only. Body weight was measured at screening visit and at final visit (or EDV), lightly dressed and without shoes.

End point type	Secondary
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End point timeframe:

screening, cycle 1, cycle 2, Final visit

<b>End point values</b>	Group A	Group B	Safety Saet	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	65	65	127	
Units: various units	62	65	127	

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The period of observation for the collection of AEs extended from the time when the subject gave informed consent until the date of final visit.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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### Reporting groups

Reporting group title	Group A
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Reporting group description: -

Reporting group title	Group B
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Reporting group description: -

<b>Serious adverse events</b>	Group A	Group B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	0 / 65 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

<b>Non-serious adverse events</b>	Group A	Group B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 62 (96.77%)	64 / 65 (98.46%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 62 (1.61%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Surgical and medical procedures			
Mole excision			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	

Tooth repair subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	3 / 65 (4.62%) 3	
General disorders and administration site conditions			
Chest discomfort subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Chest pain subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Fatigue subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 2	7 / 65 (10.77%) 7	
Injection site haematoma subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Pyrexia subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 2	0 / 65 (0.00%) 0	
Immune system disorders			
Mycotic allergy subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Social circumstances			
Tattoo subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Reproductive system and breast disorders			
Breast discomfort subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	3 / 65 (4.62%) 3	
Breast enlargement subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 2	0 / 65 (0.00%) 0	
Breast pain			

subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	1 / 65 (1.54%) 1	
Dysmenorrhoea subjects affected / exposed occurrences (all)	9 / 62 (14.52%) 11	11 / 65 (16.92%) 11	
Hydrometra subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
menorrhagia subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Ovarian cyst subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3	3 / 65 (4.62%) 3	
Vaginal discharge subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3	0 / 65 (0.00%) 0	
Vulvovaginal pruritus subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 2	2 / 65 (3.08%) 2	
Respiratory, thoracic and mediastinal disorders cough subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	2 / 65 (3.08%) 2	
Dysphonia subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Epistaxis subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 5	1 / 65 (1.54%) 1	
Psychiatric disorders			

Affective disorder			
subjects affected / exposed	3 / 62 (4.84%)	2 / 65 (3.08%)	
occurrences (all)	3	2	
Agitation			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Libido increased			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Loss of libido			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Mood altered			
subjects affected / exposed	2 / 62 (3.23%)	3 / 65 (4.62%)	
occurrences (all)	2	3	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	2 / 62 (3.23%)	2 / 65 (3.08%)	
occurrences (all)	2	2	
Blood cholesterol increased			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Blood potassium decreased			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Body temperature increased			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Glucose urine			

subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Lymphocyte count increased subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Nitrite urine present subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
Platelet count increased subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	1 / 65 (1.54%) 1	
Weight increased subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	1 / 65 (1.54%) 1	
Injury, poisoning and procedural complications			
Animal bite subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Arthropod bite subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
Contusion subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	2 / 65 (3.08%) 2	
Joint injection			

subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Limb injury subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	1 / 65 (1.54%) 1	
Radius fracture subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
Rib fracture subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Thermal burn subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	2 / 65 (3.08%) 2	
Cardiac disorders Cardiovascular disorder subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Tachycardia subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Nervous system disorders Cervicogenic headache subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Disturbance in attention subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Dizziness subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	2 / 65 (3.08%) 2	
Headache subjects affected / exposed occurrences (all)	26 / 62 (41.94%) 45	32 / 65 (49.23%) 52	
Hypoaesthesia			

subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Sciatica subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
Blood and lymphatic system disorders leukopenia subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 65 (1.54%) 1	
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
Ear and labyrinth disorders Auricular swelling subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
Vertigo subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 2	0 / 65 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3	2 / 65 (3.08%) 2	
Abdominal pain lower subjects affected / exposed occurrences (all)	9 / 62 (14.52%) 11	8 / 65 (12.31%) 10	
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	1 / 65 (1.54%) 1	
Stomatitis subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 65 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	1 / 65 (1.54%) 1	
Diarrhoea			

subjects affected / exposed	1 / 62 (1.61%)	2 / 65 (3.08%)	
occurrences (all)	1	2	
<b>Gastritis</b>			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
<b>Haematochezia</b>			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
<b>Nausea</b>			
subjects affected / exposed	4 / 62 (6.45%)	7 / 65 (10.77%)	
occurrences (all)	4	7	
<b>Toothache</b>			
subjects affected / exposed	1 / 62 (1.61%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
<b>Vomiting</b>			
subjects affected / exposed	2 / 62 (3.23%)	4 / 65 (6.15%)	
occurrences (all)	2	4	
<b>Skin and subcutaneous tissue disorders</b>			
<b>Acne</b>			
subjects affected / exposed	8 / 62 (12.90%)	7 / 65 (10.77%)	
occurrences (all)	9	7	
<b>Alopecia</b>			
subjects affected / exposed	1 / 62 (1.61%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
<b>Dry skin</b>			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
<b>Eczema</b>			
subjects affected / exposed	1 / 62 (1.61%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
<b>Paronychia</b>			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
<b>Rash</b>			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	

Renal and urinary disorders			
Albuminuria			
subjects affected / exposed	1 / 62 (1.61%)	2 / 65 (3.08%)	
occurrences (all)	1	2	
Bilirubinuria			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	1 / 62 (1.61%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Leukocyturia			
subjects affected / exposed	2 / 62 (3.23%)	1 / 65 (1.54%)	
occurrences (all)	2	1	
Pollakiuria			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Polyuria			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 62 (8.06%)	1 / 65 (1.54%)	
occurrences (all)	5	1	
Muscle spasms			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Spinal deformity			

subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Tenosynovitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	0 / 62 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Cystitis			
subjects affected / exposed	1 / 62 (1.61%)	5 / 65 (7.69%)	
occurrences (all)	1	5	
Echinococcosis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Gastrointestinal infection			
subjects affected / exposed	1 / 62 (1.61%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	27 / 62 (43.55%)	34 / 65 (52.31%)	
occurrences (all)	31	39	
Oral herpes			
subjects affected / exposed	4 / 62 (6.45%)	4 / 65 (6.15%)	
occurrences (all)	4	4	
Otitis externa			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Urethritis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences (all)	1	0	

Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3	1 / 65 (1.54%) 1	
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## **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