Clinical trial results:
Randomized Clinical Trial to Compare the Pregnancy Rates of Vaginally Applied Cyclogest® Pessary and Crinone® 8% Gel After In-vitro Fertilization

Summary

EudraCT number	2013-001105-81
Trial protocol	HU BE BG CZ
Global end of trial date	08 August 2014

Results information

Result version number	v1 (current)
This version publication date	26 March 2020
First version publication date	26 March 2020

Trial information

Trial identification

Sponsor protocol code	ACT-CYC-300-2013-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Actavis Group PTC ehf.
Sponsor organisation address	Reykjavikurvegur 76-78, Hafnarfjordur, Iceland, 220
Public contact	Reproductive Team, L.D. Collins & Co. Ltd., +44 (0) 1442 345067, enquiries@ldcollins.com
Scientific contact	Helen Saunders, Gedeon Richter Plc, +44 (0)22 884 0354, helen.saunders@preglem.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	05 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate non-inferiority in the achievement of pregnancy rate (fetal heart movement measured by TVUS) after 38 days of luteal phase support using Cyclogest® 400 mg bid compared to Crinone® 8% (90 mg) once daily.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The clinical study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, and in accordance with the national legal requirements as well as the principles of ICH-GCP. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 October 2013
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	Belgium: 21
Country: Number of subjects enrolled	Bulgaria: 100
Country: Number of subjects enrolled	Czech Republic: 255
Country: Number of subjects enrolled	Hungary: 152
Country: Number of subjects enrolled	Serbia: 240
Worldwide total number of subjects	768
EEA total number of subjects	528

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)	768
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Pre-menopausal woman (18 to 40 years old) undergoing fresh embryo transfer after in vitro fertilization, were enrolled in this multi-center, multi-national, open, randomized, two-parallel groups, non-inferiority study from October 2013 to August 2014. The study was conducted at 17 study sites in Belgium, Bulgaria, Czech Republic, Hungary and Serbia

Pre-assignment

Screening details:

A total of 812 women were enrolled in this study. Out of a total of 769 randomized patients, 385 patients (50,1%) were treated with Cyclogest® and 384 patients (49,9%) with Crinone®. 44 patients were enrolled but not treated of which 43 patients were screening failures and one patient was randomized but violated an exclusion criterion.

Period 1

Period 1 title	Baseline (Visit 1/ Day 0) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This trial was performed in an open label manner.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A: Cyclogest® 400 mg bid

Arm description:

Subjects were randomized to receive Cyclogest®, intravaginal 400mg pessaries (twice daily for a period of 10 weeks) from Visit 1 (Day 0). Patients self-administered the allocated investigational medicinal product (IMP) on each study day for up to 70 (±3) days (corresponding to the last scheduled visit), or until they terminated the study in case they did not become pregnant or until they discontinued on their own decision, or until they were withdrawn from the study by the investigator for other reasons. Embryo transfer was performed at Visit 2 (Day 2/ 3). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 3 (Day 18 - 19) by a serum pregnancy test. In case of negative serum pregnancy test at visit Day 18 (±1) or absence of pregnancy confirmed by transvaginal ultrasonography (TVUS) on Day 38 (+7), a final study assessment was to be performed at the respective visit or within 7 days after the scheduled visit. If positive, luteal support was continued up to Visit 5 (Week 10).

Arm type	Experimental
Investigational medicinal product name	Cyclogest® 400 mg bid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pessary
Routes of administration	Vaginal use

Dosage and administration details:

400 mg Cyclogest® pessaries were self-administered by the patients twice a day. Drug administration started in the evening of Day 0, preferably before going to bed, and ended in the morning of Day 70 (±3). Administrations were recommended at approximately 12 hours intervals, preferably always around the same time (e.g. if a patient was scheduled for first administration at 21:00, the subsequent drug administrations were to take place at 09:00 and 21:00) each day during the treatment period. In case a patient forgot to administer Cyclogest®, she had to administer it as soon as possible, unless it was nearly time (less than 2 hours) for the next dose. She was not allowed to use two doses together. The next dose had to be administered at the usual time. However, more than 2 pessaries per day should not have been used. The patient had to record this in her diary.

Arm title	Treatment B: Crinone® 8% (90mg) od

Arm description:

Subjects were randomized to receive Crinone® 8%, intra-vaginal micronized progesterone gel 90 mg, once daily from Visit 1 (Day 0). Patients self-administered the allocated investigational medicinal

product (IMP) on each study day for up to 70 (±3) days (corresponding to the last scheduled visit), or until they terminated the study in case they did not become pregnant or until they discontinued on their own decision, or until they were withdrawn from the study by the investigator for other reasons. Embryo transfer was performed at Visit 2 (Day 2/ 3). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 3 (Day 18 - 19) by a serum pregnancy test. If positive, luteal support was continued up to Visit 5 (Week 10). In case of negative serum pregnancy test at visit Day 18 (±1) or absence of pregnancy confirmed by transvaginal ultrasonography (TVUS) on Day 38 (+7), a final study assessment was to be performed at the respective visit or within 7 days after the scheduled visit.

Arm type	Active comparator
Investigational medicinal product name	Crinone® 8% (90mg) od
Investigational medicinal product code	
Other name	Crinone 8% w/w Progesterone Vaginal Gel, Micronized progesterone
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:

Crinone® 8% gel (90 mg) was self-administered by the patients once daily. Drug administration started in the evening of Day 0 and ended in the evening of Day 70 (±3). Crinone® was to be administered before going to bed each night during the treatment period and was always to be administered at approximately the same time. In case a patient forgot to administer Crinone®, she had to administer it as soon as possible, but no more than one applicator per day was to be used. The patient had to record this in her diary.

Number of subjects in period 1	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od
Started	385	383
Completed	360	364
Not completed	25	19
Consent withdrawn by subject	1	1
Adverse event, non-fatal	8	2
Other	7	13
Investigators decision	1	-
Lost to follow-up	5	2
Development of exclusion criterion	2	-
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A: Cyclogest® 400 mg bid

Reporting group description:

Subjects were randomized to receive Cyclogest®, intravaginal 400mg pessaries (twice daily for a period of 10 weeks) from Visit 1 (Day 0). Patients self-administered the allocated investigational medicinal product (IMP) on each study day for up to 70 (±3) days (corresponding to the last scheduled visit), or until they terminated the study in case they did not become pregnant or until they discontinued on their own decision, or until they were withdrawn from the study by the investigator for other reasons. Embryo transfer was performed at Visit 2 (Day 2/ 3). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 3 (Day 18 - 19) by a serum pregnancy test. In case of negative serum pregnancy test at visit Day 18 (±1) or absence of pregnancy confirmed by transvaginal ultrasonography (TVUS) on Day 38 (+7), a final study assessment was to be performed at the respective visit or within 7 days after the scheduled visit. If positive, luteal support was continued up to Visit 5 (Week 10).

Reporting group title	Treatment B: Crinone® 8% (90mg) od

Reporting group description:

Subjects were randomized to receive Crinone® 8%, intra-vaginal micronized progesterone gel 90 mg, once daily from Visit 1 (Day 0). Patients self-administered the allocated investigational medicinal product (IMP) on each study day for up to 70 (±3) days (corresponding to the last scheduled visit), or until they terminated the study in case they did not become pregnant or until they discontinued on their own decision, or until they were withdrawn from the study by the investigator for other reasons. Embryo transfer was performed at Visit 2 (Day 2/ 3). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 3 (Day 18 - 19) by a serum pregnancy test. If positive, luteal support was continued up to Visit 5 (Week 10). In case of negative serum pregnancy test at visit Day 18 (±1) or absence of pregnancy confirmed by transvaginal ultrasonography (TVUS) on Day 38 (+7), a final study assessment was to be performed at the respective visit or within 7 days after the scheduled visit.

Reporting group values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od	Total
Number of subjects	385	383	768
Age categorical			
Age (calculated from date of birth) at randomization between 18 and 40 years			
Units: Subjects			
≤35	273	268	541
>35	112	115	227
Age continuous			
Units: years			
arithmetic mean	32.8	33.2	
standard deviation	± 4.14	± 3.95	-
Gender categorical			
The study population consist of pre-menopausal woman.			
Units: Subjects			
Female	385	383	768
Male	0	0	0
Race			
Units: Subjects			
Caucasian/ White	382	383	765
Black	0	0	0
Asian	3	0	3
Hispanic	0	0	0
Other	0	0	0
Type of fertilization			
Units: Subjects			

Without ICSI	66	64	130
With ICSI	305	305	610
Missing	14	14	28
Embryo cleavage stage			
In case a patient has embryos from both stages, she will be counted towards.			
Units: Subjects			
2-4 cells	126	127	253
≥5 cells	245	242	487
Missing	14	14	28
Number of transferred embryos Units: Subjects			
1 Embryo	112	111	223
2 Embryo	200	195	395
3 Embryo	59	63	122
0 Embryo	14	14	28
Country Units: Subjects			
Belgium	12	9	21
Bulgaria	50	50	100
Czech Republic	127	128	255
Hungary	75	77	152
Serbia	121	119	240
Bleeding until Day 18			
Yes = Any bleeding prior to the assessment of pregnancy planned at Day 18 No = No bleeding prior to the assessment of pregnancy planned at Day 18			
Units: Subjects			
Yes	251	263	514
No	118	105	223
Missing	16	15	31
Bleeding until Day 38			
Yes = Any bleeding prior to the assessment of pregnancy planned at Day 38 No = No bleeding prior to the assessment of pregnancy planned at Day 18			
Units: Subjects			
Yes	272	273	545
No	96	93	189
Missing	17	17	34
Bleeding until Day 70			
Yes = Any bleeding prior to the assessment of pregnancy planned at Day 70 No = No bleeding prior to the assessment of pregnancy planned at Day 70			
Units: Subjects			
Yes	275	278	553
No	90	86	176
Missing	20	19	39
Body weight (kg) Units: kg			
arithmetic mean	64.34	64.61	
standard deviation	± 9.405	± 9.955	-
Height (cm) Units: cm			
arithmetic mean	167.4	167.5	
standard deviation	± 6.46	±	-

Body mass index (kg/m2) Units: kg/m2 arithmetic mean standard deviation	 22.95 ± 3.011	 23.00 ± 3.086	 -
Systolic blood pressure (mmHg) Units: mmHg arithmetic mean standard deviation	 116.4 ± 10.82	 116.8 ± 11.15	 -
Diastolic blood pressure (mmHg) Units: mmHg arithmetic mean standard deviation	 73.0 ±	 72.9 ± 7.81	 -
Pulse rate (/min) Units: /min arithmetic mean standard deviation	 75.4 ±	 74.9 ±	 -
Number of retrieved oocytes Units: number arithmetic mean standard deviation	 11.0 ±	 10.6 ± 5.72	 -

Subject analysis sets

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received at least one dose of medication

Reporting group values	FAS		
Number of subjects	768		
Age categorical			
Age (calculated from date of birth) at randomization between 18 and 40 years			
Units: Subjects			
≤35 >35			
Age continuous Units: years arithmetic mean standard deviation	 ±	 	
Gender categorical			
The study population consist of pre-menopausal woman.			
Units: Subjects			
Female Male			
Race Units: Subjects			
Caucasian/ White Black Asian Hispanic Other			

Type of fertilization Units: Subjects			
Without ICSI With ICSI Missing			
Embryo cleavage stage			
In case a patient has embryos from both stages, she will be counted towards.			
Units: Subjects			
2-4 cells ≥5 cells Missing			
Number of transferred embryos Units: Subjects			
1 Embryo 2 Embryo 3 Embryo 0 Embryo			
Country Units: Subjects			
Belgium Bulgaria Czech Republic Hungary Serbia			
Bleeding until Day 18			
Yes = Any bleeding prior to the assessment of pregnancy planned at Day 18 No = No bleeding prior to the assessment of pregnancy planned at Day 18			
Units: Subjects			
Yes No Missing			
Bleeding until Day 38			
Yes = Any bleeding prior to the assessment of pregnancy planned at Day 38 No = No bleeding prior to the assessment of pregnancy planned at Day 18			
Units: Subjects			
Yes No Missing			
Bleeding until Day 70			
Yes = Any bleeding prior to the assessment of pregnancy planned at Day 70 No = No bleeding prior to the assessment of pregnancy planned at Day 70			
Units: Subjects			
Yes No Missing			
Body weight (kg) Units: kg arithmetic mean standard deviation	 64.47 ± 9.687		
Height (cm) Units: cm			

arithmetic mean	167.4		
standard deviation	± 6.41		
Body mass index (kg/m2)			
Units: kg/m2			
arithmetic mean			
standard deviation	±		
Systolic blood pressure (mmHg)			
Units: mmHg			
arithmetic mean			
standard deviation	±		
Diastolic blood pressure (mmHg)			
Units: mmHg			
arithmetic mean	72.9		
standard deviation	± 7.73		
Pulse rate (/min)			
Units: /min			
arithmetic mean	75.1		
standard deviation	± 8.22		
Number of retrieved oocytes			
Units: number			
arithmetic mean	10.8		
standard deviation	± 5.84		

End points

End points reporting groups

Reporting group title	Treatment A: Cyclogest® 400 mg bid

Reporting group description:

Subjects were randomized to receive Cyclogest®, intravaginal 400mg pessaries (twice daily for a period of 10 weeks) from Visit 1 (Day 0). Patients self-administered the allocated investigational medicinal product (IMP) on each study day for up to 70 (±3) days (corresponding to the last scheduled visit), or until they terminated the study in case they did not become pregnant or until they discontinued on their own decision, or until they were withdrawn from the study by the investigator for other reasons. Embryo transfer was performed at Visit 2 (Day 2/ 3). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 3 (Day 18 - 19) by a serum pregnancy test. In case of negative serum pregnancy test at visit Day 18 (±1) or absence of pregnancy confirmed by transvaginal ultrasonography (TVUS) on Day 38 (+7), a final study assessment was to be performed at the respective visit or within 7 days after the scheduled visit. If positive, luteal support was continued up to Visit 5 (Week 10).

Reporting group title	Treatment B: Crinone® 8% (90mg) od

Reporting group description:

Subjects were randomized to receive Crinone® 8%, intra-vaginal micronized progesterone gel 90 mg, once daily from Visit 1 (Day 0). Patients self-administered the allocated investigational medicinal product (IMP) on each study day for up to 70 (±3) days (corresponding to the last scheduled visit), or until they terminated the study in case they did not become pregnant or until they discontinued on their own decision, or until they were withdrawn from the study by the investigator for other reasons. Embryo transfer was performed at Visit 2 (Day 2/ 3). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 3 (Day 18 - 19) by a serum pregnancy test. If positive, luteal support was continued up to Visit 5 (Week 10). In case of negative serum pregnancy test at visit Day 18 (±1) or absence of pregnancy confirmed by transvaginal ultrasonography (TVUS) on Day 38 (+7), a final study assessment was to be performed at the respective visit or within 7 days after the scheduled visit.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received at least one dose of medication

Primary: Clinical Pregnancy Rate at Visit 4 (Day 38): Full Analysis (FA)

End point title	Clinical Pregnancy Rate at Visit 4 (Day 38): Full Analysis (FA)

End point description:

The clinical pregnancy rate at Visit 4 was defined as the number of subjects with the presence of fetal heart beats at 5 weeks of pregnancy as determined by TVUS (transvaginal ultrasound). The primary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the 'Per Protocol' subject sample. Results are presented here for the Full Analysis subject sample which consisted of all subjects who received at least one dose of study drug and had a successful embryo transfer performed at Visit 2 (Day 2 or 3) or prematurely discontinued prior to embryo transfer at Visit 2 (Day 2 or 3) due to study drug-related issues.

End point type	Primary

End point timeframe:

At Visit 4 (Day 38)

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	366		
Units: number of subjects	368	366		

Statistical analyses

Statistical analysis title	Clinical Pregnancy Rate at Day 38: FA
Comparison groups	Treatment A: Cyclogest® 400 mg bid v Treatment B: Crinone® 8% (90mg) od
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Frequency difference
Point estimate	-1.6
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-8.6

Primary: Clinical Pregnancy Rate at Visit 4 (Day 38): Per Protocol (PP)

End point title	Clinical Pregnancy Rate at Visit 4 (Day 38): Per Protocol (PP)

End point description:

The clinical pregnancy rate at Visit 4 was defined as the number of subjects with the presence of fetal heart beats at 5 weeks of pregnancy as determined by TVUS (transvaginal ultrasound). The primary efficacy analysis was performed on the Full Analysis subject sample and repeated for the PP subject sample. Results are presented here for the PP subject sample which was defined through blind data review and consisted of all subjects who were included in the Full Analysis sample, did not present any major protocol deviations, and had a successful embryo transfer at Visit 2 (Day 2 or 3).

End point type	Primary

End point timeframe:

At Visit 4 (Day 38)

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357	356		
Units: number of subjects	357	356		

Statistical analyses

Statistical analysis title	Pregnancy Rate at Day 38: PP
Comparison groups	Treatment A: Cyclogest® 400 mg bid v Treatment B: Crinone® 8% (90mg) od

Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Frequency difference
Point estimate	-2.4
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-9.5

Notes:

[1] - Non-inferiority not shown.

Secondary: Clinical Pregnancy Rate at Visit 5 (Day 70): Full analysis (FA)

End point title	Clinical Pregnancy Rate at Visit 5 (Day 70): Full analysis (FA)

End point description:

The clinical pregnancy rate at Visit 5 was defined as the number of subjects with the presence of fetal heart beats at 10 weeks of pregnancy as determined by TVUS (transvaginal ultrasound). The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the Full Analysis subject sample which consisted of all subjects who received at least one dose of study drug and had a successful embryo transfer performed at Visit 2 (Day 2 or 3) or prematurely discontinued prior to embryo transfer at Visit 2 (Day 2 or 3) due to study drug-related issues.

End point type	Secondary

End point timeframe:

At Visit 5 (Day 70)

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	364		
Units: number of subjects	365	364		

Statistical analyses

Statistical analysis title	Pregnancy Rate at Day 70: FA
Comparison groups	Treatment A: Cyclogest® 400 mg bid v Treatment B: Crinone® 8% (90mg) od
Number of subjects included in analysis	729
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Frequency difference
Point estimate	-3.1
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-10.1

Notes:

[2] - Non - inferiority not shown.

Secondary: Clinical Pregnancy Rate at Visit 5 (Day 70): Per Protocol (PP)

End point title	Clinical Pregnancy Rate at Visit 5 (Day 70): Per Protocol (PP)

End point description:

The clinical pregnancy rate at Visit 5 was defined as the number of subjects with the presence of fetal heart beats at 10 weeks of pregnancy as determined by TVUS (transvaginal ultrasound). The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the PP subject sample which was defined through blind data review and consisted of all subjects who were included in the Full Analysis sample, did not present any major protocol deviations, and had a successful embryo transfer at Visit 2 (Day 2 or 3).

End point type	Secondary

End point timeframe:

At Visit 5 (Day 70)

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	355	355		
Units: number of subjects	355	355		

Statistical analyses

Statistical analysis title	Pregnancy Rate at Day 70: PP
Comparison groups	Treatment A: Cyclogest® 400 mg bid v Treatment B: Crinone® 8% (90mg) od
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Frequency difference
Point estimate	-3.4
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-10.5

Notes:

[3] - Non - inferiority not shown.

Secondary: Biochemical Pregnancy Rate at Visit 3 (Day 18): Full Analysis (FA)

End point title	Biochemical Pregnancy Rate at Visit 3 (Day 18): Full Analysis (FA)

End point description:

The biochemical pregnancy rate at Visit 3 was defined as the number of with the presence of fetal heart beats determined by TVUS (transvaginal ultrasound). The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the Full Analysis subject sample.

End point type	Secondary

End point timeframe:

At Visit 3 (Day 18)

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: number of subjects	369	368		

Statistical analyses

Statistical analysis title	Biochemical Pregnancy Rate at Day 18: FA
Comparison groups	Treatment A: Cyclogest® 400 mg bid v Treatment B: Crinone® 8% (90mg) od
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Frequency difference
Point estimate	-1.2
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-8.4

Secondary: Biochemical Pregnancy Rate at Visit 3 (Day 18): Per Protocol (PP)

End point title	Biochemical Pregnancy Rate at Visit 3 (Day 18): Per Protocol (PP)

End point description:

The biochemical pregnancy rate at Visit 3 was defined as the number of subjects with the presence of fetal heart beats determined by TVUS (transvaginal ultrasound). The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the PP subject sample.

End point type	Secondary

End point timeframe:

At Visit 3 (Day 18)

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357	356		
Units: number of subjects	357	356		

Statistical analyses

Statistical analysis title	Biochemical Pregnancy Rate at Day 18: PP
Comparison groups	Treatment A: Cyclogest® 400 mg bid v Treatment B: Crinone® 8% (90mg) od
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Frequency difference
Point estimate	-1.3
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-8.6

Secondary: Biochemical Pregnancy Rate at Visit 4 (Day 38): Full Analysis (FA)

End point title	Biochemical Pregnancy Rate at Visit 4 (Day 38): Full Analysis (FA)

End point description:

The biochemical pregnancy rate at Visit 4 was defined as the number of subjects with the presence of fetal heart beats determined by TVUS (transvaginal ultrasound). The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the Full Analysis subject sample.

End point type	Secondary

End point timeframe:

At Visit 4 (Day 38)

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	366		
Units: number of subjects	368	366		

Statistical analyses

Statistical analysis title	Biochemical Pregnancy Rate at Day 38: FA
Comparison groups	Treatment A: Cyclogest® 400 mg bid v Treatment B: Crinone® 8% (90mg) od
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Frequency difference
Point estimate	-2.1
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-9.3

Secondary: Biochemical Pregnancy Rate at Visit 4 (Day 38): Per Protocol (PP)

End point title	Biochemical Pregnancy Rate at Visit 4 (Day 38): Per Protocol (PP)

End point description:

The biochemical pregnancy rate at Visit 4 was defined as the number of subjects with the presence of fetal heart beats determined by TVUS (transvaginal ultrasound). The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the PP subject sample.

End point type	Secondary

End point timeframe:

At Visit 4 (Day 38)

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357	356		
Units: number of subjects	357	356		

Statistical analyses

Statistical analysis title	Biochemical Pregnancy Rate at Day 38: PP
Comparison groups	Treatment A: Cyclogest® 400 mg bid v Treatment B: Crinone® 8% (90mg) od
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Frequency difference
Point estimate	-2.9

Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-10.2

Notes:

[4] - Non - inferiority not shown.

Secondary: Abnormal Vaginal Discharge (Day 18): FA

End point title	Abnormal Vaginal Discharge (Day 18): FA

End point description:

The abnormal vaginal discharge at Day 18 was defined as number of days to document the subjects vaginal discharge either as 'normal', 'less than normal or no vaginal discharge', or 'increased'. The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the Full Analysis subject sample.

End point type	Secondary

End point timeframe:

Day 18

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: percentage of days				
arithmetic mean (standard deviation)				
Abnormal Days	37.31 (± 37.596)	46.05 (± 36.262)		
High Discharge Days	11.39 (± 23.218)	12.67 (± 21.957)		
Low Discharge Days	25.92 (± 36.266)	33.38 (± 37.609)		

Statistical analyses

No statistical analyses for this end point

Secondary: Abnormal Vaginal Discharge (Day 18): PP

End point title	Abnormal Vaginal Discharge (Day 18): PP

End point description:

The abnormal vaginal discharge at Day 18 was defined as number of days to document the subjects vaginal discharge either as 'normal', 'less than normal or no vaginal discharge', or 'increased'. The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the PP subject sample.

End point type	Secondary

End point timeframe:

Day 18

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	355	356		
Units: percentage of days				
arithmetic mean (standard deviation)				
Abnormal Days	37.76 (± 37.760)	45.84 (± 36.134)		
High Discharge Days	11.32 (± 23.021)	12.78 (± 21.967)		
Low Discharge Days	26.44 (± 36.632)	33.06 (± 37.458)		

Statistical analyses

No statistical analyses for this end point

Secondary: Abnormal Vaginal Discharge (Day 38): FA

End point title	Abnormal Vaginal Discharge (Day 38): FA

End point description:

The abnormal vaginal discharge at Day 38 was defined as number of days to document the subjects vaginal discharge either as 'normal', 'less than normal or no vaginal discharge', or 'increased'. The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the Full Analysis subject sample.

End point type	Secondary

End point timeframe:

Day 38

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	366		
Units: percentage of days				
arithmetic mean (standard deviation)				
Abnormal Days	37.26 (± 37.589)	46.30 (± 37.135)		
High Discharge Days	11.47 (± 23.076)	13.65 (± 23.835)		
Low Discharge Days	25.79 (± 36.202)	32.65 (± 38.194)		

Statistical analyses

No statistical analyses for this end point

Secondary: Abnormal Vaginal Discharge (Day 38): PP

End point title	Abnormal Vaginal Discharge (Day 38): PP

End point description:

The abnormal vaginal discharge at Day 38 was defined as number of days to document the subjects vaginal discharge either as 'normal', 'less than normal or no vaginal discharge', or 'increased'. The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the PP subject sample.

End point type	Secondary

End point timeframe:

Day 38

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	355	356		
Units: percentage of days				
arithmetic mean (standard deviation)				
Abnormal Days	37.73 (± 37.740)	46.05 (± 37.046)		
High Discharge Days	11.42 (± 22.871)	13.69 (± 23.776)		
Low Discharge Days	26.32 (± 36.559)	32.36 (± 38.090)		

Statistical analyses

No statistical analyses for this end point

Secondary: Abnormal Vaginal Discharge (Day 70): FA

End point title	Abnormal Vaginal Discharge (Day 70): FA

End point description:

The abnormal vaginal discharge at Day 70 was defined as number of days to document the subjects vaginal discharge either as 'normal', 'less than normal or no vaginal discharge', or 'increased'. The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the Full Analysis subject sample.

End point type	Secondary

End point timeframe:

Day 70

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	363	365		
Units: percentage of days				
arithmetic mean (standard deviation)				
Abnormal Days	37.28 (± 37.988)	46.29 (± 37.758)		
High Discharge Days	11.44 (± 23.380)	13.74 (± 24.327)		
Low Discharge Days	25.84 (± 36.482)	32.54 (± 38.458)		

Statistical analyses

No statistical analyses for this end point

Secondary: Abnormal Vaginal Discharge (Day 70): PP

End point title	Abnormal Vaginal Discharge (Day 70): PP

End point description:

The abnormal vaginal discharge at Day 70 was defined as number of days to document the subjects vaginal discharge either as 'normal', 'less than normal or no vaginal discharge', or 'increased'. The secondary efficacy analysis was performed on the Full Analysis (FA) subject sample and repeated for the PP subject sample. Results are presented here for the PP subject sample

End point type	Secondary

End point timeframe:

Day 70

End point values	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	356		
Units: percentage of days				
arithmetic mean (standard deviation)				
Abnormal Days	37.68 (± 38.136)	45.90 (± 37.713)		
High Discharge Days	11.32 (± 23.164)	13.75 (± 24.261)		
Low Discharge Days	26.36 (± 36.813)	32.15 (± 38.345)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the date of informed consent signed (Day -6 to -2) until last follow-up visit.

Adverse event reporting additional description:

The Safety subject sample consisted of all subjects who were allocated to treatment and received at least one administration of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Treatment A: Cyclogest® 400 mg bid

Reporting group description:

Multiple intra-vaginal or rectal dose (twice daily for a period of 10 weeks) of 400 mg Cyclogest® (pessary) as therapeutic indication for premenstrual syndrome and puerperal depression.

Reporting group title	Treatment B: Crinone® 8% (90mg) od

Reporting group description:

Treatment of infertility due to inadequate luteal phase. For use during in-vitro fertilisation, where infertility is mainly due to tubal, idiopathic or endometriosis linked sterility associated with normal ovulatory cycles.

Serious adverse events	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 385 (1.56%)	13 / 383 (3.39%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Post procedural hemorrhage			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Trisomy 18			

subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Selective abortion			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholin’s cyst removal			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	3 / 385 (0.78%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	1 / 385 (0.26%)	5 / 383 (1.31%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adnexal torsion			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment A: Cyclogest® 400 mg bid	Treatment B: Crinone® 8% (90mg) od	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	162 / 385 (42.08%)	158 / 383 (41.25%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal neoplasm			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Vascular disorders			
Hot flush			
subjects affected / exposed	16 / 385 (4.16%)	9 / 383 (2.35%)	
occurrences (all)	162	158	
Haemorrhage			
subjects affected / exposed	5 / 385 (1.30%)	6 / 383 (1.57%)	
occurrences (all)	162	158	
Deep vein thrombosis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Exsanguination			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Surgical and medical procedures			
Bartholin's cyst removal			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Selective abortion			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Pregnancy, puerperium and perinatal conditions			

Ectopic pregnancy			
subjects affected / exposed	4 / 385 (1.04%)	3 / 383 (0.78%)	
occurrences (all)	162	158	
Abortion missed			
subjects affected / exposed	5 / 385 (1.30%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Vomiting in pregnancy			
subjects affected / exposed	4 / 385 (1.04%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Abortion spontaneous			
subjects affected / exposed	1 / 385 (0.26%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Abortion			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Abortion incomplete			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Blighted OVUM			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Imminent Abortion			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	40 / 385 (10.39%)	39 / 383 (10.18%)	
occurrences (all)	162	158	
Malaise			
subjects affected / exposed	8 / 385 (2.08%)	6 / 383 (1.57%)	
occurrences (all)	162	158	
Pyrexia			
subjects affected / exposed	2 / 385 (0.52%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Secretion discharge			

subjects affected / exposed	1 / 385 (0.26%)	3 / 383 (0.78%)	
occurrences (all)	162	158	
Swelling			
subjects affected / exposed	2 / 385 (0.52%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Asthenia			
subjects affected / exposed	3 / 385 (0.78%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Feeling cold			
subjects affected / exposed	2 / 385 (0.52%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Feeling of body temperature change			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Irritability			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Pain			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Application site pruritus			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Discomfort			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Feeling hot			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Influenza like illness			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	

Reproductive system and breast disorders			
Breast discomfort			
subjects affected / exposed	29 / 385 (7.53%)	28 / 383 (7.31%)	
occurrences (all)	162	158	
Breast tenderness			
subjects affected / exposed	22 / 385 (5.71%)	23 / 383 (6.01%)	
occurrences (all)	162	158	
Vaginal haemorrhage			
subjects affected / exposed	16 / 385 (4.16%)	12 / 383 (3.13%)	
occurrences (all)	162	158	
Ovarian hyperstimulation syndrome			
subjects affected / exposed	8 / 385 (2.08%)	14 / 383 (3.66%)	
occurrences (all)	162	158	
Pelvic pain			
subjects affected / exposed	16 / 385 (4.16%)	5 / 383 (1.31%)	
occurrences (all)	162	158	
Metrorrhagia			
subjects affected / exposed	12 / 385 (3.12%)	8 / 383 (2.09%)	
occurrences (all)	162	158	
Ovarian enlargement			
subjects affected / exposed	4 / 385 (1.04%)	5 / 383 (1.31%)	
occurrences (all)	162	158	
Breast pain			
subjects affected / exposed	4 / 385 (1.04%)	4 / 383 (1.04%)	
occurrences (all)	162	158	
Vaginal discharge			
subjects affected / exposed	0 / 385 (0.00%)	6 / 383 (1.57%)	
occurrences (all)	162	158	
Vulvovaginal pruritus			
subjects affected / exposed	2 / 385 (0.52%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Breast enlargement			
subjects affected / exposed	1 / 385 (0.26%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Uterine haemorrhage			

subjects affected / exposed	1 / 385 (0.26%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Uterine spasm			
subjects affected / exposed	1 / 385 (0.26%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Adnexal torsion			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Ovarian cyst			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Pruritus genital			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Uterine pain			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Psychiatric disorders			
Mood swings			
subjects affected / exposed	13 / 385 (3.38%)	7 / 383 (1.83%)	
occurrences (all)	162	158	
Mood altered			
subjects affected / exposed	10 / 385 (2.60%)	9 / 383 (2.35%)	
occurrences (all)	162	158	
Abnormal dreams			
subjects affected / exposed	6 / 385 (1.56%)	11 / 383 (2.87%)	
occurrences (all)	162	158	
Somatoform disorder pregnancy			
subjects affected / exposed	4 / 385 (1.04%)	9 / 383 (2.35%)	
occurrences (all)	162	158	
Anxiety			

subjects affected / exposed	3 / 385 (0.78%)	3 / 383 (0.78%)	
occurrences (all)	162	158	
Fear			
subjects affected / exposed	3 / 385 (0.78%)	3 / 383 (0.78%)	
occurrences (all)	162	158	
Self esteem decreased			
subjects affected / exposed	2 / 385 (0.52%)	4 / 383 (1.04%)	
occurrences (all)	162	158	
Insomnia			
subjects affected / exposed	3 / 385 (0.78%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Decreased activity			
subjects affected / exposed	2 / 385 (0.52%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Depression			
subjects affected / exposed	0 / 385 (0.00%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Emotional disorder			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Impatience			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Mental disorder			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Stress			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Investigations			
Weight increased			
subjects affected / exposed	8 / 385 (2.08%)	6 / 383 (1.57%)	
occurrences (all)	162	158	
Laboratory test abnormal			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	

Menstruation normal			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Transaminases increased			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Urine output decreased			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	11 / 385 (2.86%)	4 / 383 (1.04%)	
occurrences (all)	162	158	
Post procedural haemorrhage			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Congenital, familial and genetic disorders			
Trisomy 18			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Nervous system disorders			
Somnolence			
subjects affected / exposed	45 / 385 (11.69%)	27 / 383 (7.05%)	
occurrences (all)	162	158	
Headache			
subjects affected / exposed	23 / 385 (5.97%)	24 / 383 (6.27%)	
occurrences (all)	162	158	
Dizziness			
subjects affected / exposed	14 / 385 (3.64%)	11 / 383 (2.87%)	
occurrences (all)	162	158	
Lethargy			
subjects affected / exposed	2 / 385 (0.52%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Dysgeusia			
subjects affected / exposed	2 / 385 (0.52%)	0 / 383 (0.00%)	
occurrences (all)	162	158	

Migraine			
subjects affected / exposed	0 / 385 (0.00%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Paraesthesia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Poor quality sleep			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Syncope			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Vertigo positional			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	39 / 385 (10.13%)	40 / 383 (10.44%)	
occurrences (all)	162	158	
Abdominal pain			
subjects affected / exposed	33 / 385 (8.57%)	37 / 383 (9.66%)	
occurrences (all)	162	158	
Constipation			
subjects affected / exposed	21 / 385 (5.45%)	22 / 383 (5.74%)	
occurrences (all)	162	158	
Nausea			
subjects affected / exposed	14 / 385 (3.64%)	21 / 383 (5.48%)	
occurrences (all)	162	158	
Abdominal pain upper			
subjects affected / exposed	12 / 385 (3.12%)	6 / 383 (1.57%)	
occurrences (all)	162	158	
Diarrhoea			

subjects affected / exposed	11 / 385 (2.86%)	7 / 383 (1.83%)	
occurrences (all)	162	158	
Vomiting			
subjects affected / exposed	4 / 385 (1.04%)	9 / 383 (2.35%)	
occurrences (all)	162	158	
Flatulence			
subjects affected / exposed	5 / 385 (1.30%)	6 / 383 (1.57%)	
occurrences (all)	162	158	
Gastric Dilatation			
subjects affected / exposed	6 / 385 (1.56%)	3 / 383 (0.78%)	
occurrences (all)	162	158	
Abdominal pain lower			
subjects affected / exposed	6 / 385 (1.56%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Toothache			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Abdominal discomfort			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Abdominal rigidity			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Abdominal tenderness			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Duodenal ulcer			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Intestinal congestion			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 385 (1.04%)	2 / 383 (0.52%)	
occurrences (all)	162	158	
Alopecia			
subjects affected / exposed	5 / 385 (1.30%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Pruritus			
subjects affected / exposed	3 / 385 (0.78%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Hyperhidrosis			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Night sweats			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	3 / 385 (0.78%)	3 / 383 (0.78%)	
occurrences (all)	162	158	
Urinary retention			
subjects affected / exposed	2 / 385 (0.52%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Dysuria			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Incontinence			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Nephritis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Renal pain			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Urinary incontinence			

subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 385 (1.30%)	3 / 383 (0.78%)	
occurrences (all)	162	158	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 385 (0.78%)	5 / 383 (1.31%)	
occurrences (all)	162	158	
Vaginal infection			
subjects affected / exposed	2 / 385 (0.52%)	3 / 383 (0.78%)	
occurrences (all)	162	158	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 385 (0.00%)	3 / 383 (0.78%)	
occurrences (all)	162	158	
Fungal infection			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Influenza			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Sinusitis			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Viral infection			
subjects affected / exposed	1 / 385 (0.26%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Gastroenteritis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 383 (0.26%)	
occurrences (all)	162	158	
Nasopharyngitis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 383 (0.00%)	
occurrences (all)	162	158	
Metabolism and nutrition disorders			

Hyponatraemia subjects affected / exposed occurrences (all)	0 / 385 (0.00%) 162	1 / 383 (0.26%) 158	

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