Clinical trial results:
A Randomized, Open-label, Two-arm, Multicenter Study Comparing the Efficacy, Safety and Tolerability of Oral Dydrogesterone 30 mg Daily Versus Crinone 8% Intravaginal Progesterone Gel 90 mg Daily for Luteal Support in In-Vitro Fertilization (LOTUS II)

Summary

EudraCT number	2012-002993-29
Trial protocol	BE
Global end of trial date	26 May 2017

Results information

Result version number	v1 (current)
This version publication date	18 July 2019
First version publication date	18 July 2019

Trial information

Trial identification

Sponsor protocol code	M13-625

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02491437
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbott Laboratories GmbH
Sponsor organisation address	Freundallee 9A, Hannover, Germany, 30173
Public contact	Senior Global Medical Director, Abbott Laboratories GmbH, claire.pexman-fieth@abbott.com
Scientific contact	Senior Global Medical Director, Abbott Laboratories GmbH, claire.pexman-fieth@abbott.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	26 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of oral dydrogesterone 10 milligrams (mg) three times daily (TID) versus micronized progesterone as vaginal gel 90 mg once daily for luteal support in in vitro fertilization (IVF). The primary efficacy endpoint was the presence of fetal heart beats at 12 weeks of gestation (10 weeks of pregnancy) determined by transvaginal ultrasound.

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice and the applicable national regulations to assure that the rights, safety, and well-being of the participating study subjects were protected, consistent with the ethical principles that have their origin in the Declaration of Helsinki. All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 August 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	Australia: 5
Country: Number of subjects enrolled	Belgium: 177
Country: Number of subjects enrolled	China: 239
Country: Number of subjects enrolled	Germany: 166
Country: Number of subjects enrolled	Hong Kong: 17
Country: Number of subjects enrolled	India: 211
Country: Number of subjects enrolled	Russian Federation: 81
Country: Number of subjects enrolled	Singapore: 19
Country: Number of subjects enrolled	Thailand: 27
Country: Number of subjects enrolled	Ukraine: 92
Worldwide total number of subjects	1034
EEA total number of subjects	343

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)	1034
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Premenopausal females, aged > 18 years < 42 years were enrolled in this randomized, open-label, multicenter study from August 2015. The study was conducted at 37 sites in Australia, Belgium, China, Germany, Hong-Kong, India, Russia, Singapore, Thailand and Ukraine. The study completed in May 2017.

Pre-assignment

Screening details:

Subjects had to have a documented history of infertility, with a clinically indicated protocol for induction of IVF with a fresh embryo. 4 subjects who were randomized did not receive treatment with study drug.

Period 1

Period 1 title	Randomized through Treatment Start
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Duphaston

Arm description:

Subjects were randomized to receive Duphaston, oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1). Embryo transfer was performed at Visit 3 (Day 3 to 6). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 4 (Day 17 to 20) by a routine pregnancy test. If positive, luteal support was continued up to Visit 6 (Week 10).

Arm type	Experimental
Investigational medicinal product name	Duphaston
Investigational medicinal product code	
Other name	Oral Dydrogesterone
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Duphaston was supplied as micronized, film-coated 10.0 mg tablets in blister strips of aluminium foil and polyvinylchloride film. Subjects received oral dydrogesterone 10 mg tablets TID from Day 1 to Week 10 (if pregnancy was confirmed at Visit 4).

Arm title	Crinone

Arm description:

Subjects were randomized to receive Crinone 8%, intravaginal micronized progesterone gel 90 mg, once daily from Visit 2 (Day 1). Embryo transfer was performed at Visit 3 (Day 3 to 6). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 4 (Day 17 to 20) by a routine pregnancy test. If positive, luteal support was continued up to Visit 6 (Week 10).

Arm type	Active comparator
Investigational medicinal product name	Crinone
Investigational medicinal product code	
Other name	Micronized progesterone
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:

Crinone 8% was supplied as a vaginal gel contained in single use, one-piece polyethylene vaginal applicators. Each applicator delivered 1.125 grams of Crinone gel containing 90 mg (8% gel) of micronized progesterone and subjects administered one applicator daily from Day 1 to Week 10 (if pregnancy was confirmed at Visit 4).

Number of subjects in period 1	Duphaston	Crinone
Started	520	514
Completed	518	512
Not completed	2	2
No randomized study drug taken	2	2

Period 2

Period 2 title	Treatment through Trial Completion
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Duphaston

Arm description:

Subjects were randomized to receive Duphaston, oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1). Embryo transfer was performed at Visit 3 (Day 3 to 6). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 4 (Day 17 to 20) by a routine pregnancy test. If positive, luteal support was continued up to Visit 6 (Week 10).

Arm type	Experimental
Investigational medicinal product name	Duphaston
Investigational medicinal product code	
Other name	Oral Dydrogesterone
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Duphaston was supplied as micronized, film-coated 10.0 mg tablets in blister strips of aluminium foil and polyvinylchloride film. Subjects received oral dydrogesterone 10 mg tablets TID from Day 1 to Week 10 (if pregnancy was confirmed at Visit 4).

Arm title	Crinone

Arm description:

Subjects were randomized to receive Crinone 8%, intravaginal micronized progesterone gel 90 mg, once daily from Visit 2 (Day 1). Embryo transfer was performed at Visit 3 (Day 3 to 6). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 4 (Day 17 to 20) by a routine pregnancy test. If positive, luteal support was continued up to Visit 6 (Week 10).

Arm type	Active comparator
Investigational medicinal product name	Crinone
Investigational medicinal product code	
Other name	Micronized progesterone
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:

Crinone 8% was supplied as a vaginal gel contained in single use, one-piece polyethylene vaginal applicators. Each applicator delivered 1.125 grams of Crinone gel containing 90 mg (8% gel) of

micronized progesterone and subjects administered one applicator daily from Day 1 to Week 10 (if pregnancy was confirmed at Visit 4).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Worldwide number enrolled is based on the subjects who were randomized and allocated to treatment. Baseline characteristics is based on subjects who received at least one administration of study drug. 4 subjects who were randomized did not receive study drug.

Number of subjects in period 2[2]	Duphaston	Crinone
Started	518	512
Pregnancies at Week 2 (Visit 4)	234	214
Pregnancies at Week 10 (Visit 6)	191	171
Giving Live Birth	170	159
Completed	168	157
Not completed	350	355
Consent withdrawn by subject	13	5
Administrative	3	5
Adverse event, non-fatal	65	58
Lost to follow-up	6	4
Pregnancy not confirmed after 2 weeks (Day 17-20)	253	272
Protocol deviation	10	11

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Number of subjects starting Period 1 is based on those randomized and allocated to treatment. Number of subjects starting Period 2 is based on those who received at least one administration of study drug. The baseline demographics table presents data for the Safety subject sample (ie, subjects receiving treatment); therefore Period 2 is the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Duphaston
Reporting group description:	
Subjects were randomized to receive Duphaston, oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1). Embryo transfer was performed at Visit 3 (Day 3 to 6). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 4 (Day 17 to 20) by a routine pregnancy test. If positive, luteal support was continued up to Visit 6 (Week 10).	
Reporting group title	Crinone
Reporting group description:	
Subjects were randomized to receive Crinone 8%, intravaginal micronized progesterone gel 90 mg, once daily from Visit 2 (Day 1). Embryo transfer was performed at Visit 3 (Day 3 to 6). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 4 (Day 17 to 20) by a routine pregnancy test. If positive, luteal support was continued up to Visit 6 (Week 10).	

Reporting group values	Duphaston	Crinone	Total
Number of subjects	518	512	1030
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	31.8	31.6	
standard deviation	± 4.5	± 4.6	-
Gender categorical Units: Subjects			
Female	518	512	1030
Male	0	0	0
Ethnicity Units: Subjects			
Hispanic	4	5	9
Not Hispanic	514	507	1021
Race Units: Subjects			
Asian	260	254	514
Black	1	0	1
White	251	253	504
Other	6	5	11

End points

End points reporting groups

Reporting group title	Duphaston
Reporting group description:	
Subjects were randomized to receive Duphaston, oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1). Embryo transfer was performed at Visit 3 (Day 3 to 6). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 4 (Day 17 to 20) by a routine pregnancy test. If positive, luteal support was continued up to Visit 6 (Week 10).	
Reporting group title	Crinone
Reporting group description:	
Subjects were randomized to receive Crinone 8%, intravaginal micronized progesterone gel 90 mg, once daily from Visit 2 (Day 1). Embryo transfer was performed at Visit 3 (Day 3 to 6). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 4 (Day 17 to 20) by a routine pregnancy test. If positive, luteal support was continued up to Visit 6 (Week 10).	
Reporting group title	Duphaston
Reporting group description:	
Subjects were randomized to receive Duphaston, oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1). Embryo transfer was performed at Visit 3 (Day 3 to 6). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 4 (Day 17 to 20) by a routine pregnancy test. If positive, luteal support was continued up to Visit 6 (Week 10).	
Reporting group title	Crinone
Reporting group description:	
Subjects were randomized to receive Crinone 8%, intravaginal micronized progesterone gel 90 mg, once daily from Visit 2 (Day 1). Embryo transfer was performed at Visit 3 (Day 3 to 6). Pregnancy was confirmed 2 weeks after embryo transfer at Visit 4 (Day 17 to 20) by a routine pregnancy test. If positive, luteal support was continued up to Visit 6 (Week 10).	

Primary: Pregnancy Rate at Visit 6 (Week 10): Per Protocol (PP) Subject Sample

End point title	Pregnancy Rate at Visit 6 (Week 10): Per Protocol (PP) Subject Sample
End point description:	
The pregnancy rate at Visit 6 was defined as the percentage of subjects with the presence of fetal heart beats at 12 weeks of gestation (10 weeks of pregnancy) as determined by transvaginal ultrasound. The primary efficacy analysis was performed on the PP subject sample (in line with the objective of non-inferiority) and repeated for the Full Analysis (FA) 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 FA sample, did not present any major protocol deviations, and had a successful embryo transfer at Visit 3 (Day 3 to 6).	
End point type	Primary
End point timeframe:	
At Visit 6 (Week 10)	

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	490	481		
Units: percentage of subjects				
number (confidence interval 95%)	36.7 (32.5 to 41.2)	34.7 (30.5 to 39.2)		

Statistical analyses

Statistical analysis title	Non-inferiority: Pregnancy Rate at Visit 6

Statistical analysis description:

Analysis of difference (non-inferiority) between treatments (Duphaston – Crinone) for Pregnancy Rate at Visit 6 in the PP subject sample, performed using Cochran-Mantel-Haenszel test, stratified for country and age groups (older or younger than 35 years).

Comparison groups	Duphaston v Crinone
Number of subjects included in analysis	971
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference (%)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	8

Notes:

[1] - In order to declare non-inferiority, the lower bound of the two-sided 95% confidence interval (CI) for the difference in ongoing pregnancy rates between Crinone and Duphaston had to exclude a difference greater than 10% in favor of Duphaston.

Primary: Pregnancy Rate at Visit 6 (Week 10): FA Subject Sample

End point title	Pregnancy Rate at Visit 6 (Week 10): FA Subject Sample

End point description:

The pregnancy rate at Visit 6 was defined as the percentage of subjects with the presence of fetal heart beats at 12 weeks of gestation (10 weeks of pregnancy) as determined by transvaginal ultrasound. The primary efficacy analysis was performed on the PP subject sample (in line with the objective of non-inferiority) and repeated for the FA subject sample. Results are presented here for the FA 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 3 (Day 3 to 6) or prematurely discontinued prior to embryo transfer at Visit 3 (Day 3 to 6) due to study drug-related issues.

End point type	Primary

End point timeframe:

At Visit 6 (Week 10)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	494	489		
Units: percentage of subjects				
number (confidence interval 95%)	38.7 (34.4 to 43.1)	35.0 (30.7 to 39.4)		

Statistical analyses

Statistical analysis title	Non-inferiority: Pregnancy Rate at Visit 6

Statistical analysis description:

Analysis of difference (non-inferiority) between treatments (Duphaston – Crinone) for Pregnancy Rate at Visit 6 in the FA subject sample, performed using Cochran-Mantel-Haenszel test, stratified for country and age groups (older or younger than 35 years).

Comparison groups	Duphaston v Crinone
Number of subjects included in analysis	983
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference (%)
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	9.7

Notes:

[2] - In order to declare non-inferiority, the lower bound of the two-sided 95% CI for the difference in ongoing pregnancy rates between Crinone and Duphaston had to exclude a difference greater than 10% in favor of Duphaston.

Secondary: Pregnancy Rate at Visit 4 (Week 2)

End point title	Pregnancy Rate at Visit 4 (Week 2)

End point description:

A routine pregnancy test (serum beta human chorionic gonadotropin) was performed 2 weeks after embryo transfer to confirm the subject's pregnancy. The pregnancy rate at Visit 4 (Day 17 to 20) was calculated as the percentage of subjects who had a positive pregnancy test at Visit 4. Analysis was performed using the FA subject sample which consisted of all subjects who had received at least one dose of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or prematurely discontinued prior to embryo transfer at Visit 3 due to study drug-related issues.

End point type	Secondary

End point timeframe:

At Visit 4 (Day 17 to 20)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	494	489		
Units: percentage of subjetcs				
number (confidence interval 95%)	47.4 (42.9 to 51.9)	43.8 (39.3 to 48.3)		

Statistical analyses

Statistical analysis title	Non-inferiority: Pregnancy Rate at Visit 4

Statistical analysis description:

Analysis of difference (non-inferiority) between treatments (Duphaston – Crinone) for Pregnancy Rate at Visit 4, performed using Cochran-Mantel-Haenszel test, stratified for country and age groups (older or younger than 35 years).

Comparison groups	Duphaston v Crinone
Number of subjects included in analysis	983
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference (%)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	9.8

Secondary: Pregnancy Rate at Visit 5 (Week 6)

End point title	Pregnancy Rate at Visit 5 (Week 6)

End point description:

Ongoing pregnancy at Visit 5 (Week 6) was confirmed based on clinical evidence. The pregnancy rate at Visit 5 was calculated as the percentage of subjects who had pregnancy confirmed at Visit 5. Analysis was performed using the FA subject sample which consisted of all subjects who had received at least one dose of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or prematurely discontinued prior to embryo transfer at Visit 3 due to study drug-related issues.

End point type	Secondary

End point timeframe:

At Visit 5 (Week 6)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	494	489		
Units: percentage of subjects				
number (confidence interval 95%)	40.7 (36.3 to 45.2)	36.8 (32.5 to 41.3)		

Statistical analyses

Statistical analysis title	Non-inferiority: Pregnancy Rate at Visit 5

Statistical analysis description:

Analysis of difference (non-inferiority) between treatments (Duphaston – Crinone) for Pregnancy Rate at Visit 5, performed using Cochran-Mantel-Haenszel test, stratified for country and age groups (older or younger than 35 years).

Comparison groups	Duphaston v Crinone
Number of subjects included in analysis	983
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference (%)
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	9.9

Secondary: Abortion (Miscarriage) Rate

End point title	Abortion (Miscarriage) Rate

End point description:

A pregnancy outcome was defined as an abortion if the pregnancy was ongoing at Visit 5 (Week 6) and gestational age was ≤ 22 weeks. The abortion rate was calculated as the percentage of subjects who had an abortion during the study. Analysis was performed using the FA subject sample which consisted of all subjects who had received at least one dose of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or prematurely discontinued prior to embryo transfer at Visit 3 due to study drug-related issues.

End point type	Secondary

End point timeframe:

From Visit 5 (Week 6) up to 22 weeks of gestation (20 weeks of pregnancy)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	494	489		
Units: percentage of subjects				
number (confidence interval 95%)	3.0 (1.7 to 5.0)	2.5 (1.3 to 4.3)		

Statistical analyses

Statistical analysis title	Non-inferiority: Abortion (Miscarriage) Rate

Statistical analysis description:

Analysis of difference (non-inferiority) between treatments (Crinone - Duphaston) for Abortion Rate, performed using Cochran-Mantel-Haenszel test, stratified for country and age groups (older or younger than 35 years).

Comparison groups	Duphaston v Crinone
Number of subjects included in analysis	983
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference (%)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	1.5

Secondary: Preterm Birth Rate

End point title	Preterm Birth Rate

End point description:

Preterm birth was defined as a pregnancy outcome with gestational age > 22 weeks and < 37 weeks. Pregnancy outcomes with gestational age ≥ 37 weeks were considered as birth. The preterm birth rate was calculated as the percentage of subjects who had preterm birth during the study. Analysis was performed using the FA subject sample which consisted of all subjects who had received at least one dose of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or prematurely discontinued prior to embryo transfer at Visit 3 due to study drug-related issues.

End point type	Secondary

End point timeframe:

From 22 weeks up to 37 weeks of gestation (from 20 weeks up to 35 weeks of pregnancy)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	494	489		
Units: percentage of subjects				
number (confidence interval 95%)	7.5 (5.3 to 10.2)	6.1 (4.2 to 8.6)		

Statistical analyses

Statistical analysis title	Non-inferiority: Preterm Birth Rate

Statistical analysis description:

Analysis of difference (non-inferiority) between treatments (Crinone - Duphaston) for Preterm Birth Rate, performed using Cochran-Mantel-Haenszel test, stratified for country and age groups (older or younger than 35 years).

Comparison groups	Duphaston v Crinone

Number of subjects included in analysis	983
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference (%)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	1.8

Secondary: Live Birth Rate

End point title	Live Birth Rate

End point description:

The live birth rate (sum of preterm births and births) was calculated as the percentage of subjects who had a live birth during the study. Analysis was performed using the FA subject sample which consisted of all subjects who had received at least one dose of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or prematurely discontinued prior to embryo transfer at Visit 3 due to study drug-related issues.

End point type	Secondary

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	494	489		
Units: percentage of subjects				
number (confidence interval 95%)	34.4 (30.2 to 38.8)	32.5 (28.4 to 36.9)		

Statistical analyses

Statistical analysis title	Non-inferiority: Live Birth Rate

Statistical analysis description:

Analysis of difference (non-inferiority) between treatments (Duphaston – Crinone) for Live Birth Rate, performed using Cochran-Mantel-Haenszel test, stratified for country and age groups (older or younger than 35 years).

Comparison groups	Duphaston v Crinone
Number of subjects included in analysis	983
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference (%)
Point estimate	1.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	7.8

Secondary: Healthy Newborn Rate

End point title	Healthy Newborn Rate

End point description:

The healthy newborn rate was calculated as the percentage of subjects who gave birth to a healthy newborn during the study. Subjects who gave birth to more than one healthy newborn were counted only once. Analysis was performed using the FA subject sample which consisted of all subjects who had received at least one dose of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or prematurely discontinued prior to embryo transfer at Visit 3 due to study drug-related issues.

End point type	Secondary

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	494	489		
Units: percentage of subjects				
number (confidence interval 95%)	32.2 (28.1 to 36.5)	31.3 (27.2 to 35.6)		

Statistical analyses

Statistical analysis title	Non-inferiority: Healthy Newborn Rate

Statistical analysis description:

Analysis of difference (non-inferiority) between treatments (Duphaston – Crinone) for Healthy Newborn Rate, performed using Cochran-Mantel-Haenszel test, stratified for country and age groups (older or younger than 35 years).

Comparison groups	Duphaston v Crinone
Number of subjects included in analysis	983
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference (%)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	6.7

Secondary: Mean Gestational Age

End point title	Mean Gestational Age

End point description:

After successful delivery (Visit 9), the time of delivery (gestational age) was obtained. The gestational age (weeks) was derived as:
(date of birth - date of embryo transfer + 1 day) / 7 + 2 weeks.
Results are based on the number of newborns in each reporting group for the FA subject sample with data available for analysis. Note: Subjects with biochemical pregnancy were not included in the analysis.

End point type	Secondary

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	178		
Units: weeks				
arithmetic mean (standard deviation)	34.932 (± 8.767)	35.260 (± 8.941)		

Statistical analyses

No statistical analyses for this end point

Secondary: Newborn Status: Healthy Status, Gender, Abnormal Findings and Malformations

End point title	Newborn Status: Healthy Status, Gender, Abnormal Findings and Malformations

End point description:

After successful delivery (Visit 9), healthy newborn status (Yes or No) and gender were recorded. In addition, a physical examination of the newborn was performed and any abnormal findings and malformations were recorded. Percentages for each of the indicated parameters are based on the number of newborns in each reporting group for the FA subject sample with data available for analysis. Note: A subject could have more than one newborn. 'n' in category title indicates number of newborns analysed for each individual parameter.

End point type	Secondary

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	188		
Units: percentage of newborns				
number (not applicable)				
Heathy Newborn: Yes (n=205, 188)	92.7	93.1		
Heathy Newborn: No (n=205, 188)	7.3	6.9		
Gender: Male (n=205, 188)	51.2	50.5		
Gender: Female (n=205, 188)	48.8	49.5		
Abnormal Physical Examination (n=204, 185)	7.8	6.5		
Malformations (n=205, 185)	3.4	3.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Newborn Status: Height, Weight and Head Circumference

End point title	Newborn Status: Height, Weight and Head Circumference

End point description:

After successful delivery (Visit 9), the height, weight and head circumference of the newborn were recorded. Results for each of the indicated parameters are based on the number of newborns in each reporting group for the FA subject sample with data available for analysis. Note: A subject could have more than one newborn. 'n' in category title indicates number of newborns analysed for each individual parameter.

End point type	Secondary

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	188		
Units: centimetres (cm) or grams (g)				
arithmetic mean (standard deviation)				
Height (cm) (n=200, 177)	48.8 (± 4.0)	48.8 (± 3.9)		
Weight (g) (n=203, 184)	2934.3 (± 684.2)	2963.3 (± 719.2)		
Head Circumference (cm) (n=188, 173)	33.6 (± 2.5)	33.9 (± 2.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Newborn Status: Mean APGAR (standing for Appearance, Pulse, Grimace, Activity, and Respiration) Score

End point title	Newborn Status: Mean APGAR (standing for Appearance, Pulse, Grimace, Activity, and Respiration) Score

End point description:

After successful delivery (Visit 9), the newborn APGAR score at 1 minute and 5 minutes postpartal were obtained. Results are based on the number of newborns in each reporting group for the FA subject sample with data available for analysis. Note: A subject could have more than one newborn. 'n' in category title indicates number of newborns analysed for each individual parameter.

End point type	Secondary

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer)

End point values	Duphaston	Crinone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	176		
Units: units on a scale				
arithmetic mean (standard deviation)				
1 Minute Postpartal (n=198, 176)	8.7 (± 1.2)	8.5 (± 1.4)		
5 Minutes Postpartal (n=197, 176)	9.3 (± 1.1)	9.3 (± 0.9)		

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 start of treatment (Day 1) to the follow-up phone call at Visit 10 (30 days after delivery).

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	18.1

Reporting groups

Reporting group title	Duphaston - Maternal

Reporting group description:

Reporting group represents the Safety subject sample (ie, maternal subjects) who received Duphaston oral dydrogesterone 10 mg tablets TID (30 mg daily).

Reporting group title	Crinone - Maternal

Reporting group description:

Reporting group represents the Safety subject sample (ie, maternal subjects) who received Crinone 8%, intravaginal micronized progesterone gel 90 mg, once daily.

Reporting group title	Duphaston - Fetus/Newborn

Reporting group description:

Reporting group represents the fetus/newborns arising from the Duphaston reporting group. The mothers of the fetus/newborns received Duphaston oral dydrogesterone 10 mg tablets TID (30 mg daily).

Reporting group title	Crinone - Fetus/Newborn

Reporting group description:

Reporting group represents the fetus/newborns arising from the Crinone reporting group. The mothers of the fetus/newborns received Crinone 8%, intravaginal micronized progesterone gel 90 mg, once daily.

Serious adverse events	Duphaston - Maternal	Crinone - Maternal	Duphaston - Fetus/Newborn
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 518 (13.71%)	67 / 512 (13.09%)	28 / 221 (12.67%)
number of deaths (all causes)	0	0	4
number of deaths resulting from adverse events	0	0	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	3 / 518 (0.58%)	1 / 512 (0.20%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Selective abortion			
subjects affected / exposed	1 / 518 (0.19%)	2 / 512 (0.39%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Caesarean section			
subjects affected / exposed	0 / 518 (0.00%)	2 / 512 (0.39%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion threatened			
subjects affected / exposed	6 / 518 (1.16%)	7 / 512 (1.37%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			
subjects affected / exposed	6 / 518 (1.16%)	6 / 512 (1.17%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Imminent abortion			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Ectopic pregnancy			
subjects affected / exposed	6 / 518 (1.16%)	8 / 512 (1.56%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cervical incompetence			
subjects affected / exposed	1 / 518 (0.19%)	1 / 512 (0.20%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ruptured ectopic pregnancy			
subjects affected / exposed	1 / 518 (0.19%)	1 / 512 (0.20%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperemesis gravidarum			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Premature labour			
subjects affected / exposed	6 / 518 (1.16%)	2 / 512 (0.39%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Premature delivery			
subjects affected / exposed	4 / 518 (0.77%)	2 / 512 (0.39%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Premature rupture of membranes			
subjects affected / exposed	2 / 518 (0.39%)	1 / 512 (0.20%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Threatened labour			
subjects affected / exposed	1 / 518 (0.19%)	2 / 512 (0.39%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion missed			
subjects affected / exposed	12 / 518 (2.32%)	2 / 512 (0.39%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion			

subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Abortion complete			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Abortion late			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Premature baby			
subjects affected / exposed	7 / 518 (1.35%)	6 / 512 (1.17%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foetal death			
subjects affected / exposed	1 / 518 (0.19%)	4 / 512 (0.78%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stillbirth			
subjects affected / exposed	1 / 518 (0.19%)	1 / 512 (0.20%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pre-eclampsia			
subjects affected / exposed	0 / 518 (0.00%)	4 / 512 (0.78%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HELLP syndrome			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Placenta praevia			

subjects affected / exposed	2 / 518 (0.39%)	1 / 512 (0.20%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasa praevia			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Haemorrhage in pregnancy			
subjects affected / exposed	0 / 518 (0.00%)	2 / 512 (0.39%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Placenta praevia haemorrhage			
subjects affected / exposed	1 / 518 (0.19%)	1 / 512 (0.20%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blighted ovum			
subjects affected / exposed	1 / 518 (0.19%)	1 / 512 (0.20%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gestational diabetes			
subjects affected / exposed	1 / 518 (0.19%)	1 / 512 (0.20%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oligohydramnios			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Retained placenta or membranes			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Postpartum haemorrhage			

subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Low birth weight baby			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	6 / 221 (2.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Foetal distress syndrome			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foetal acidosis			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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
Foetal growth restriction			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	11 / 518 (2.12%)	14 / 512 (2.73%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adnexal torsion			
subjects affected / exposed	1 / 518 (0.19%)	1 / 512 (0.20%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	2 / 518 (0.39%)	2 / 512 (0.39%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			

subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Respiratory, thoracic and mediastinal disorders			
Neonatal respiratory distress syndrome			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	5 / 221 (2.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Apnoea neonatal			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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
Neonatal respiratory failure			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	2 / 221 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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
Investigations			
Foetal monitoring abnormal			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Foetal heart rate abnormal			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	5 / 221 (2.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart disease congenital			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	2 / 221 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patent ductus arteriosus			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amniotic band syndrome			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital hand malformation			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital cystic kidney disease			

subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal dysplasia			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital central nervous system anomaly			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital aortic anomaly			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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
Intestinal malrotation			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystic lymphangioma			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kinematic imbalances due to suboccipital strain			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Turner's syndrome			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac disorders			

Bradycardia			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	3 / 221 (1.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia neonatal			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	2 / 221 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral circulatory failure			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
VIIth nerve paralysis			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	2 / 221 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain injury			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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
Hydrocephalus			

subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Abdominal pain lower			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Abdominal pain upper			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Abdominal distension			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Volvulus			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Necrotising colitis			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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

Large intestine perforation			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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			
Hydronephrosis			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Renal colic			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Pyelonephritis			
subjects affected / exposed	0 / 518 (0.00%)	1 / 512 (0.20%)	0 / 221 (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
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 518 (0.19%)	0 / 512 (0.00%)	0 / 221 (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
Neonatal pneumonia			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis neonatal			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	4 / 221 (1.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Neonatal infection			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 518 (0.00%)	0 / 512 (0.00%)	0 / 221 (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	Crinone - Fetus/Newborn		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 201 (11.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Selective abortion			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Caesarean section			

subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion threatened			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abortion spontaneous			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Imminent abortion			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ectopic pregnancy			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical incompetence			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ruptured ectopic pregnancy			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperemesis gravidarum			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Premature labour			

subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Premature delivery			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Premature rupture of membranes			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Threatened labour			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abortion missed			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abortion			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abortion complete			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abortion late			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Premature baby			

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foetal death				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stillbirth				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pre-eclampsia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HELLP syndrome				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Placenta praevia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vasa praevia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage in pregnancy				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Placenta praevia haemorrhage				

subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blighted ovum			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gestational diabetes			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oligohydramnios			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retained placenta or membranes			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postpartum haemorrhage			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Low birth weight baby			
subjects affected / exposed	3 / 201 (1.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Foetal distress syndrome			
subjects affected / exposed	3 / 201 (1.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Foetal acidosis			

subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foetal growth restriction				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Ovarian hyperstimulation syndrome				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Adnexal torsion				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vaginal haemorrhage				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uterine haemorrhage				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Neonatal respiratory distress syndrome				
subjects affected / exposed	5 / 201 (2.49%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Apnoea neonatal				

subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neonatal respiratory failure			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Foetal monitoring abnormal			
subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foetal heart rate abnormal			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	7 / 201 (3.48%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Heart disease congenital			
subjects affected / exposed	4 / 201 (1.99%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Patent ductus arteriosus			
subjects affected / exposed	4 / 201 (1.99%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Amniotic band syndrome			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital hand malformation			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital cystic kidney disease			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal dysplasia			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital central nervous system anomaly			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Congenital aortic anomaly				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal malrotation				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystic lymphangioma				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Kinematic imbalances due to suboccipital strain				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Turner's syndrome				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Bradycardia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia neonatal				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Myocardial ischaemia			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral circulatory failure			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
VIIth nerve paralysis			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain injury			
subjects affected / exposed	2 / 201 (1.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal distension				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Volvulus				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Necrotising colitis				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Hydronephrosis				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal colic				

subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neonatal pneumonia			
subjects affected / exposed	7 / 201 (3.48%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Sepsis neonatal			
subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neonatal infection			
subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Duphaston - Maternal	Crinone - Maternal	Duphaston - Fetus/Newborn
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 518 (9.65%)	35 / 512 (6.84%)	0 / 221 (0.00%)
Pregnancy, puerperium and perinatal conditions			
Vaginal haemorrhage			
subjects affected / exposed	50 / 518 (9.65%)	35 / 512 (6.84%)	0 / 221 (0.00%)
occurrences (all)	50	35	0

Non-serious adverse events	Crinone - Fetus/Newborn		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 201 (0.00%)		
Pregnancy, puerperium and perinatal conditions			
Vaginal haemorrhage			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2015	An updated version of the Investigator's Brochure was released in January 2015. The clinical trial protocol was updated to reflect that the reference safety information for the expectedness assessment was the Investigator's Brochure and not the Summary of Product Characteristics (SPC) for Duphaston issued on 29 April 2011, which was mentioned in the protocol. For the comparative study drug, Crinone 8% intravaginal gel 90 mg, the reference safety information was the current SPC issued in the United Kingdom.
07 September 2015	The following main changes were included: • Inclusion Criterion #8: the wording for the negative pregnancy test was changed to reflect that it was not the only method used to confirm that the subject was not pregnant: most of the IVF centers did not routinely perform a serum or urine pregnancy test before they started the downregulation process with either gonadotropin agonists or antagonists; for them, the vaginal exam, which was performed prior to any IVF-related procedures, was the basis for further treatment decisions/options. • The protocol was adjusted to the current more frequently used long (downregulation/ovarian stimulation) protocol by increasing the screening and enrollment phase from 14 to 40 days prior to the oocyte retrieval/randomization visit. • Due to the delay in the start of recruitment, the study dates and duration were updated. • Wording was added to explain the expectedness of early miscarriages before presence of fetal heart beats at 12 weeks of gestation (10 weeks of pregnancy), to explain AE/serious AE reporting of pregnancy, and to include definitions of biochemical pregnancy and miscarriage. • The fasting requirement for some laboratory tests was changed to "if possible fasting," as the Investigators informed that many subjects were not fasting when they went to the study sites, particularly for the end of treatment at Week 10, when subjects were pregnant. • The timing of posttreatment visits was adapted to the visit days in the study flow chart.
04 January 2016	For subject eligibility (Inclusion Criterion #5), a selection of hormones, including luteinizing hormone (LH), prolactin (PRL), testosterone, and thyrotropin (TSH), had to be within the normal limits for the clinical laboratory, or considered not clinically significant by the Investigator within 6 months prior to screening. During the study progress it became clear that most of the Asian IVF centers participating in this study were not routinely performing this hormone testing prior to any IVF cycles. Therefore, the assessment of some hormone values (follicle-stimulating hormone, estradiol, LH, PRL, testosterone, and TSH) was added as a requirement at screening for those subjects who did not have available values prior to screening. Wording of Inclusion Criteria #4 and #5, the flow chart of study assessments, and some other sections in the protocol were updated accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported