Clinical trial results:
Multi-center, randomized, comparator-controlled, single-blind, parallel-group study to investigate the pharmacodynamics, pharmacokinetics and safety of an intrauterine system (BAY 987443) with three different release rates of indomethacin and one release rate of levonorgestrel, as compared with Jaydess, in a combined proof-of-concept and dose finding study in healthy pre-menopausal women treated for 90 days

Summary

EudraCT number	2018-000128-33
Trial protocol	DE GB
Global end of trial date	01 August 2019

Results information

Result version number	v1 (current)
This version publication date	03 July 2020
First version publication date	03 July 2020

Trial information

Trial identification

Sponsor protocol code	BAY98-7443/17700

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03562624
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	01 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effects of BAY98-7443 on the number of uterine bleeding and spotting days during the treatment period

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. 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	22 June 2018
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	United Kingdom: 6
Country: Number of subjects enrolled	Germany: 168
Worldwide total number of subjects	174
EEA total number of subjects	174

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)	174

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

318 healthy female subjects were screened in 6 centers in Germany and 1 center in UK, the first subject first visit was on 22/Jun/2018 and last subject last visit was on 25/Jun/2019

Pre-assignment

Screening details:

Of the 318 screened subjects, 144 screen failures were recorded and 174 subjects were randomized. Of the randomized subjects, 167 subjects completed the pre-treatment cycle and were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BAY98-7443 (low IND dose)

Arm description:

Combi intrauterine system (IUS) Treatment, 13.5 mg LNG (Levonorgestrel) with 6.5 mg IND (Indomethacin)

Arm type	Experimental
Investigational medicinal product name	Low dose Combi IUS
Investigational medicinal product code	BAY98-7443
Other name	
Pharmaceutical forms	Intrauterine delivery system
Routes of administration	Intrauterine use

Dosage and administration details:

During the 90-day treatment period, 4.10 to 4.60 mg IND (geometric mean: 4.36 mg) were released during the complete period of use (average daily in vivo IND release rate 49.4 µg/d). 0.500 to 1.10 mg LNG (geometric mean: 0.762 mg) were released during the complete period of use (average daily in vivo LNG release rate 8.63 µg/d).

Arm title	BAY98-7443 (middle IND dose)

Arm description:

Combi IUS Treatment, 13.5 mg LNG with 12.5 mg IND

Arm type	Experimental
Investigational medicinal product name	Middle dose Combi IUS
Investigational medicinal product code	BAY98-7443
Other name	
Pharmaceutical forms	Intrauterine delivery system
Routes of administration	Intrauterine use

Dosage and administration details:

During the 90-day treatment period, 8.90 to 10.4 mg IND (geometric mean: 9.82 mg) were released during the complete period of use (average daily in vivo IND release rate 112 µg/d). 0.600 to 1.00 mg LNG (geometric mean: 0.768 mg) were released during the complete period of use (average daily in vivo LNG release rate 8.72 µg/d).

Arm title	BAY98-7443 (high IND dose)

Arm description:

Combi IUS Treatment, 13.5 mg LNG with 15.4 mg IND

Arm type	Experimental

Investigational medicinal product name	High dose Combi IUS
Investigational medicinal product code	BAY98-7443
Other name	
Pharmaceutical forms	Intrauterine delivery system
Routes of administration	Intrauterine use

Dosage and administration details:

There was no IND left in the devices removed at the end of the 90-day treatment period, which means that they released all IND prior to the end of the study period. Based on the IND plasma concentrations it can be assumed that the devices run empty of IND shortly after 41 days after insertion on average. 0.400 to 1.40 mg LNG (geometric mean: 0.713 mg) were released during the complete period of use (average daily in vivo LNG release rate 8.10 µg/d).

Arm title	Jaydess

Arm description:

Marketed comparator IUS, 13.5 mg LNG

Arm type	Active comparator
Investigational medicinal product name	Jaydess
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intrauterine delivery system
Routes of administration	Intrauterine use

Dosage and administration details:

During the 90-day treatment period, 0.600 to 1.00 mg LNG (geometric mean: 0.787 mg) were released during the complete period of use (average daily in vivo LNG release rate 8.93 µg/d).

Number of subjects in period 1[1]	BAY98-7443 (low IND dose)	BAY98-7443 (middle IND dose)	BAY98-7443 (high IND dose)
Started	42	40	45
Completed	41	40	41
Not completed	1	0	4
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	1	-	3

Number of subjects in period 1[1]	Jaydess
Started	40
Completed	37
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	2

Notes:

[1] - 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: Only 167 subjects out of 174 randomized subjects completed pre-treatment cycle and were treated

Baseline characteristics

Reporting groups	
Reporting group title	BAY98-7443 (low IND dose)
Reporting group description:	
Combi intrauterine system (IUS) Treatment, 13.5 mg LNG (Levonorgestrel) with 6.5 mg IND (Indomethacin)	
Reporting group title	BAY98-7443 (middle IND dose)
Reporting group description:	
Combi IUS Treatment, 13.5 mg LNG with 12.5 mg IND	
Reporting group title	BAY98-7443 (high IND dose)
Reporting group description:	
Combi IUS Treatment, 13.5 mg LNG with 15.4 mg IND	
Reporting group title	Jaydess
Reporting group description:	
Marketed comparator IUS, 13.5 mg LNG	

Reporting group values	BAY98-7443 (low IND dose)	BAY98-7443 (middle IND dose)	BAY98-7443 (high IND dose)
Number of subjects	42	40	45
Age categorical Units: Subjects			
Adults (18-64 years)	42	40	45
Age continuous Units: years			
arithmetic mean	33.0	32.4	35.2
standard deviation	± 7.7	± 6.9	± 5.3
Gender categorical Units: Subjects			
Female	42	40	45

Reporting group values	Jaydess	Total	
Number of subjects	40	167	
Age categorical Units: Subjects			
Adults (18-64 years)	40	167	
Age continuous Units: years			
arithmetic mean	32.8		
standard deviation	± 5.6	-	
Gender categorical Units: Subjects			
Female	40	167	

End points

End points reporting groups

Reporting group title	BAY98-7443 (low IND dose)
Reporting group description:	
Combi intrauterine system (IUS) Treatment, 13.5 mg LNG (Levonorgestrel) with 6.5 mg IND (Indomethacin)	
Reporting group title	BAY98-7443 (middle IND dose)
Reporting group description:	
Combi IUS Treatment, 13.5 mg LNG with 12.5 mg IND	
Reporting group title	BAY98-7443 (high IND dose)
Reporting group description:	
Combi IUS Treatment, 13.5 mg LNG with 15.4 mg IND	
Reporting group title	Jaydess
Reporting group description:	
Marketed comparator IUS, 13.5 mg LNG	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received study medication were included in the SAF. This was the set used for the safety analysis	
Subject analysis set title	Pharmacodynamic analysis set (PDS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects from the SAF without major deviations from the study protocol and with evaluable endpoints for the primary PD variable were included in the valid for PD analysis set. This was the set used for the primary analysis	

Primary: Mean number of uterine bleeding/spotting (B/S) days during treatment

End point title	Mean number of uterine bleeding/spotting (B/S) days during treatment[1]
End point description:	
<1> Spotting: less than associated with normal menstruation relative to the experience of subjects with no need for sanitary protection (except for panty liners) Bleeding: 1) Light: less than associated with normal menstruation relative to the experience of subjects with need for sanitary protection 2) Normal: like normal menstruation relative to the experience of subjects 3) Heavy: more than normal menstruation relative to the experience of subjects. <2> It is the Credible interval rather than the Confidence interval that was calculated for the mean number of each arm, but due to system restriction, credible interval cannot be selected	
End point type	Primary
End point timeframe:	
From Day 0 after insertion of the IUS until the end of treatment (just prior to time of removal) on Day 89	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: The statistical analysis is in the Attachment	

End point values	BAY98-7443 (low IND dose)	BAY98-7443 (middle IND dose)	BAY98-7443 (high IND dose)	Jaydess
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	40	41	37
Units: days				
number (confidence interval 90%)	27.98 (22.71 to 33.26)	34.83 (29.77 to 39.94)	33.55 (29.61 to 37.39)	41.29 (37.75 to 44.82)

Attachments (see zip file)	Statistical analysis for primary endpoint/Study

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects showing endometrial histology typical for an intrauterine LNG application in biopsies taken during treatment

End point title	Number of subjects showing endometrial histology typical for an intrauterine LNG application in biopsies taken during treatment

End point description:

3 expert pathologists who neither knew the treatment group of the subject nor the time point of the biopsy (pre-treatment, treatment) assessed the biopsies (e.g. applying standardized criteria derived from Blaustein standard pathology textbook, as well as other criteria for secretory-type effects caused by exogenous progestins after intrauterine application). Each expert pathologist assessed the slides without knowledge of the assessment of the other 2 readers. The assessment was mainly based on criteria such as glandular architecture, glandular epithelium, gland secretion, gland mitosis, decidual changes to stroma, and similarity to an endometrium with typical LNG effects

End point type	Secondary

End point timeframe:

On Day 89

End point values	BAY98-7443 (low IND dose)	BAY98-7443 (middle IND dose)	BAY98-7443 (high IND dose)	Jaydess
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	38	40	37
Units: Subjects	37	38	39	35

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events (TEAE)

End point title	Number of subjects with treatment-emergent adverse events (TEAE)

End point description:

End point type	Secondary

End point timeframe:

From first administration of study medication (i.e. insertion of IUS) up to end of follow-up

End point values	BAY98-7443 (low IND dose)	BAY98-7443 (middle IND dose)	BAY98-7443 (high IND dose)	Jaydess
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	45	40
Units: Subjects	37	39	44	38

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first administration of study medication (i.e. insertion of IUS) up to the end of follow-up	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	BAY98-7443 (low IND dose)
Reporting group description:	
Combi intrauterine system (IUS) Treatment, 13.5 mg LNG (Levonorgestrel) with 6.5 mg IND (Indomethacin)	
Reporting group title	BAY98-7443 (middle IND dose)
Reporting group description:	
Combi IUS Treatment, 13.5 mg LNG with 12.5 mg IND	
Reporting group title	BAY98-7443 (high IND dose)
Reporting group description:	
Combi IUS Treatment, 13.5 mg LNG with 15.4 mg IND	
Reporting group title	Jaydess
Reporting group description:	
Marketed comparator IUS, 13.5 mg LNG	

Serious adverse events	BAY98-7443 (low IND dose)	BAY98-7443 (middle IND dose)	BAY98-7443 (high IND dose)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Varicose vein			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Jaydess		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			

Varicose vein			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BAY98-7443 (low IND dose)	BAY98-7443 (middle IND dose)	BAY98-7443 (high IND dose)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 42 (88.10%)	39 / 40 (97.50%)	44 / 45 (97.78%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign breast neoplasm			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Intraductal papilloma of breast			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	2 / 45 (4.44%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Catheter site related reaction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Malaise			

subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Oedema peripheral			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 42 (2.38%)	3 / 40 (7.50%)	2 / 45 (4.44%)
occurrences (all)	1	3	3
Thirst			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Breast cyst			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Breast oedema			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Breast pain			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	1	1	0
Breast tenderness			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Cervical cyst			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Dysmenorrhoea			
subjects affected / exposed	3 / 42 (7.14%)	4 / 40 (10.00%)	1 / 45 (2.22%)
occurrences (all)	4	6	1
Menorrhagia			

subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Ovarian cyst			
subjects affected / exposed	6 / 42 (14.29%)	3 / 40 (7.50%)	5 / 45 (11.11%)
occurrences (all)	7	3	5
Pelvic pain			
subjects affected / exposed	4 / 42 (9.52%)	10 / 40 (25.00%)	17 / 45 (37.78%)
occurrences (all)	8	18	23
Uterine disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Vaginal discharge			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal discomfort			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	1 / 45 (2.22%)
occurrences (all)	1	1	1
Vulvovaginal dryness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Breast discomfort			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	3	0
Adnexa uteri cyst			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Vulvovaginal pruritus			
subjects affected / exposed	0 / 42 (0.00%)	2 / 40 (5.00%)	0 / 45 (0.00%)
occurrences (all)	0	2	0
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Pelvic discomfort			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Premenstrual pain			

subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal burning sensation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 42 (4.76%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	2	0	0
Dysphonia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 42 (4.76%)	2 / 40 (5.00%)	1 / 45 (2.22%)
occurrences (all)	2	2	1
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Depressed mood			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Libido decreased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Loss of libido			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Mood altered			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	3
Mood swings			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Product issues			

Device expulsion			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	3
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Blood urine present			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	2
Weight decreased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	2 / 45 (4.44%)
occurrences (all)	0	1	2
White blood cell count increased			

subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Nitrite urine present			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Platelet count increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Ultrasound uterus abnormal			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Burns second degree			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Muscle strain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Post procedural haemorrhage			
subjects affected / exposed	5 / 42 (11.90%)	5 / 40 (12.50%)	25 / 45 (55.56%)
occurrences (all)	5	5	32
Thermal burn			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	9 / 42 (21.43%)	5 / 40 (12.50%)	3 / 45 (6.67%)
occurrences (all)	13	10	3
Skin abrasion			

subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Post-traumatic pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Procedural nausea			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	2	0
Procedural dizziness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Post-traumatic neck syndrome			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Unintentional medical device removal			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 42 (0.00%)	2 / 40 (5.00%)	0 / 45 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 42 (4.76%)	3 / 40 (7.50%)	1 / 45 (2.22%)
occurrences (all)	2	3	1
Headache			
subjects affected / exposed	8 / 42 (19.05%)	12 / 40 (30.00%)	10 / 45 (22.22%)
occurrences (all)	10	31	15
Sciatica			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Lymphadenitis			

subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	2	1	0
Abdominal pain			
subjects affected / exposed	4 / 42 (9.52%)	2 / 40 (5.00%)	0 / 45 (0.00%)
occurrences (all)	5	4	0
Abdominal pain lower			
subjects affected / exposed	9 / 42 (21.43%)	5 / 40 (12.50%)	3 / 45 (6.67%)
occurrences (all)	17	9	4
Abdominal pain upper			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Abnormal faeces			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	2
Nausea			

subjects affected / exposed	2 / 42 (4.76%)	6 / 40 (15.00%)	6 / 45 (13.33%)
occurrences (all)	2	8	7
Toothache			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	2 / 45 (4.44%)
occurrences (all)	1	1	2
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	4 / 45 (8.89%)
occurrences (all)	0	0	4
Alopecia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Seborrhoea			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Skin disorder			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			

Bilirubinuria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	6 / 45 (13.33%)
occurrences (all)	0	0	6
Ketonuria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	5 / 45 (11.11%)
occurrences (all)	0	0	5
Renal pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Leukocyturia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	4 / 42 (9.52%)	2 / 40 (5.00%)	0 / 45 (0.00%)
occurrences (all)	5	4	0
Metatarsalgia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 42 (0.00%)	3 / 40 (7.50%)	0 / 45 (0.00%)
occurrences (all)	0	5	0
Neck pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			

subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Myosclerosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	3 / 42 (7.14%)	4 / 40 (10.00%)	0 / 45 (0.00%)
occurrences (all)	3	4	0
Bacteriuria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	4 / 45 (8.89%)
occurrences (all)	0	0	4
Bronchitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	2
Conjunctivitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	2 / 45 (4.44%)
occurrences (all)	1	0	2
Genital herpes			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	2 / 42 (4.76%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	14 / 42 (33.33%)	20 / 40 (50.00%)	20 / 45 (44.44%)
occurrences (all)	14	23	25

Otitis media			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	2 / 42 (4.76%)	1 / 40 (2.50%)	1 / 45 (2.22%)
occurrences (all)	2	1	1
Sinusitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	2
Vaginal infection			
subjects affected / exposed	0 / 42 (0.00%)	2 / 40 (5.00%)	1 / 45 (2.22%)
occurrences (all)	0	3	1
Vulval abscess			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	1	1	0
Vulvovaginitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Pharyngotonsillitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	2	0
Salpingo-oophoritis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0

Alveolar osteitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Candida infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	3
Decreased appetite			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	1 / 45 (2.22%)
occurrences (all)	1	0	1

Non-serious adverse events	Jaydess		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 40 (95.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign breast neoplasm			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Intraductal papilloma of breast			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			

Catheter site related reaction subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Chest pain subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Fatigue subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Malaise subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Pyrexia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Thirst subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Reproductive system and breast disorders Breast cyst subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Breast oedema subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Breast pain subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Breast tenderness			

subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Cervical cyst				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Dysmenorrhoea				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Menorrhagia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Ovarian cyst				
subjects affected / exposed	5 / 40 (12.50%)			
occurrences (all)	5			
Pelvic pain				
subjects affected / exposed	11 / 40 (27.50%)			
occurrences (all)	19			
Uterine disorder				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Vaginal discharge				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Vulvovaginal discomfort				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Vulvovaginal dryness				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Breast discomfort				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Adnexa uteri cyst				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Vulvovaginal pruritus				

subjects affected / exposed occurrences (all) Haemorrhagic ovarian cyst subjects affected / exposed occurrences (all) Pelvic discomfort subjects affected / exposed occurrences (all) Premenstrual pain subjects affected / exposed occurrences (all) Vulvovaginal burning sensation subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0 2 / 40 (5.00%) 3 0 / 40 (0.00%) 0 1 / 40 (2.50%) 1 1 / 40 (2.50%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0 1 / 40 (2.50%) 1 1 / 40 (2.50%) 2		
Psychiatric disorders Affective disorder subjects affected / exposed occurrences (all) Depressed mood subjects affected / exposed occurrences (all) Libido decreased subjects affected / exposed occurrences (all) Loss of libido	0 / 40 (0.00%) 0 1 / 40 (2.50%) 1 1 / 40 (2.50%) 1		

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Mood altered			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Product issues			
Device expulsion			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Blood urine present			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Neutrophil count increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Platelet count decreased			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Nitrite urine present			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Platelet count increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Ultrasound uterus abnormal			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Burns second degree			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Muscle strain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Post procedural haemorrhage			
subjects affected / exposed	14 / 40 (35.00%)		
occurrences (all)	15		
Thermal burn			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	7		
Skin abrasion			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Post-traumatic pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Procedural nausea			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Procedural dizziness			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Unintentional medical device removal			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Headache			

subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	20		
Sciatica			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Lymphadenitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Eye disorders			
Blepharospasm			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	21		
Abdominal pain lower			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Abnormal faeces			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Toothache			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Alopecia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Dermatitis contact			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Seborrhoea			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Skin disorder			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Bilirubinuria			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Ketonuria			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Renal pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Leukocyturia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Metatarsalgia			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Muscle tightness			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Myosclerosis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Bacteriuria			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Gastrointestinal infection			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		

Genital herpes				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	18 / 40 (45.00%)			
occurrences (all)	22			
Otitis media				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Tonsillitis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Vaginal infection				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Vulval abscess				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Vulvovaginal candidiasis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Vulvovaginitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			

Pharyngotonsillitis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Salpingo-oophoritis subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Alveolar osteitis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Oral herpes subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Candida infection subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Decreased appetite subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2018	This amendment was issued due to a request of the Ethics Committee and included the addition of anti-HBc IgM and anti-HBc IgG to the exclusion criterion relating to the presence of an active viral infection as well as the inclusion of reactions after local anesthetics to the exclusion criterion relating to history of skin reactions, other allergic-type reactions and known hypersensitivity
23 October 2018	Modifications due to this amendment included the removal of a withdrawal criterion upon request of the Medicine and Healthcare Products Regulatory Agency, the implementation of IUS expulsion reporting requirements to clarify AE reporting, the generalization of IUS removal instructions, the alignment with Jaydess Summary of Product Characteristics and contraception guidance to reduce risk of pregnancy, the clarification of provision of contraception instructions due to a request of the relevant UK Ethics Committee, the clarification of procedures performed for additional pre-treatment cycles, the update of the fetal risk profile for Combi IUS, the clarification of expected number of evaluable subjects and subgroup assignment, the clarification of IUS insertion relative to Cycle Days, and the clarification of criteria for classification of dropouts

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

When interpreting the results for the arm "BAY98-7443 (high IND dose)" over the 90-day reference period, the fact that the depletion of the high dose indomethacin drug reservoir prior to the end of the 90-day treatment period must be considered

Notes: