Clinical trial results:
A randomized, placebo-controlled, double-blind, parallel-group, multi-center, exploratory dose-response study to assess the efficacy and safety of different oral doses of BAY1128688 in women with symptomatic endometriosis over a 12-week treatment period

Summary

EudraCT number	2017-000244-18
Trial protocol	GB ES HU FI CZ AT DE BE DK NL PL IT
Global end of trial date	22 October 2018

Results information

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

Trial information

Trial identification

Sponsor protocol code	BAY1128688/17472

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03373422
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	22 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to explore the dose response relationship of different doses of BAY1128688 compared to placebo in the treatment of endometriosis-related symptoms over a 12-week 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	30 November 2017
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	Austria: 5
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 33
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	121
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in 13 countries worldwide between 30 NOV 2017 (first subject first visit) and 22 OCT 2018 (last subject last visit).

Pre-assignment

Screening details:

Overall 230 subjects were screened of which 89 (39%) were screening failures. 141 subjects entered the pre-treatment period and were randomized, 20 randomized subjects dropped out before receiving the first dose of the study drug, therefore, 121 subjects were treated (enrolled).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Tablet identical in appearance to BAY1128688; one tablet in the morning and one tablet in the evening

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo, for 12 weeks

Arm title	BAY1128688 3 mg once daily (OD)

Arm description:

Subjects received one 3 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening

Arm type	Experimental
Investigational medicinal product name	BAY1128688
Investigational medicinal product code	BAY1128688
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 mg once daily (OD),
Plus one placebo OD. Oral, 12 weeks (84 days)

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo, for 12 weeks

Arm title	BAY1128688 10 mg OD

Arm description:

Subjects received one 10 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening

Arm type	Experimental
Investigational medicinal product name	BAY1128688
Investigational medicinal product code	BAY1128688
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg once daily (OD),
Plus one placebo OD. Oral, 12 weeks (84 days)

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo, for 12 weeks

Arm title	BAY1128688 30 mg OD

Arm description:

Subjects received one 30 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening

Arm type	Experimental
Investigational medicinal product name	BAY1128688
Investigational medicinal product code	BAY1128688
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30 mg once daily (OD),
Plus one placebo OD. Oral, 12 weeks (84 days)

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo, for 12 weeks

Arm title	BAY1128688 30 mg twice daily (BID)

Arm description:

Subjects received one 30 mg BAY1128688 tablet in the morning and one 30 mg BAY1128688 tablet in the evening

Arm type	Experimental
Investigational medicinal product name	BAY1128688
Investigational medicinal product code	BAY1128688
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30 mg twice daily (BID), 12 weeks (84 days)

Arm title	BAY1128688 60 mg BID

Arm description:

Subjects received one 60 mg BAY1128688 tablet in the morning and one 60 mg BAY1128688 tablet in the evening

Arm type	Experimental
Investigational medicinal product name	BAY1128688
Investigational medicinal product code	BAY1128688
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg twice daily (BID), 12 weeks (84 days)

Number of subjects in period 1	Placebo	BAY1128688 3 mg once daily (OD)	BAY1128688 10 mg OD
Started	31	11	31
Included in PPS	26	11	27
Completed	12	4	14
Not completed	19	7	17
Consent withdrawn by subject	1	-	-
Physician decision	-	-	-
Adverse Event	-	-	1
Study Terminated by Sponsor	17	6	16
Lack of efficacy	1	1	-
Protocol deviation	-	-	-

Number of subjects in period 1	BAY1128688 30 mg OD	BAY1128688 30 mg twice daily (BID)	BAY1128688 60 mg BID
Started	10	11	27
Included in PPS	9	11	20
Completed	5	4	11
Not completed	5	7	16
Consent withdrawn by subject	-	-	2
Physician decision	-	-	1
Adverse Event	-	2	1
Study Terminated by Sponsor	5	5	11
Lack of efficacy	-	-	-
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Tablet identical in appearance to BAY1128688; one tablet in the morning and one tablet in the evening	
Reporting group title	BAY1128688 3 mg once daily (OD)
Reporting group description:	
Subjects received one 3 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening	
Reporting group title	BAY1128688 10 mg OD
Reporting group description:	
Subjects received one 10 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening	
Reporting group title	BAY1128688 30 mg OD
Reporting group description:	
Subjects received one 30 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening	
Reporting group title	BAY1128688 30 mg twice daily (BID)
Reporting group description:	
Subjects received one 30 mg BAY1128688 tablet in the morning and one 30 mg BAY1128688 tablet in the evening	
Reporting group title	BAY1128688 60 mg BID
Reporting group description:	
Subjects received one 60 mg BAY1128688 tablet in the morning and one 60 mg BAY1128688 tablet in the evening	

Reporting group values	Placebo	BAY1128688 3 mg once daily (OD)	BAY1128688 10 mg OD
Number of subjects	31	11	31
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	31.39	32.45	32.65
standard deviation	± 5.70	± 9.22	± 6.07
Gender Categorical			
Units: Subjects			
Female	31	11	31
Male	0	0	0

Reporting group values	BAY1128688 30 mg OD	BAY1128688 30 mg twice daily (BID)	BAY1128688 60 mg BID
Number of subjects	10	11	27
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	32.90	33.45	31.33
standard deviation	± 4.93	± 5.43	± 7.33

Gender Categorical Units: Subjects			
Female	10	11	27
Male	0	0	0

Reporting group values	Total		
Number of subjects	121		
Age Categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	-		
Gender Categorical Units: Subjects			
Female	121		
Male	0		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Tablet identical in appearance to BAY1128688; one tablet in the morning and one tablet in the evening	
Reporting group title	BAY1128688 3 mg once daily (OD)
Reporting group description:	
Subjects received one 3 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening	
Reporting group title	BAY1128688 10 mg OD
Reporting group description:	
Subjects received one 10 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening	
Reporting group title	BAY1128688 30 mg OD
Reporting group description:	
Subjects received one 30 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening	
Reporting group title	BAY1128688 30 mg twice daily (BID)
Reporting group description:	
Subjects received one 30 mg BAY1128688 tablet in the morning and one 30 mg BAY1128688 tablet in the evening	
Reporting group title	BAY1128688 60 mg BID
Reporting group description:	
Subjects received one 60 mg BAY1128688 tablet in the morning and one 60 mg BAY1128688 tablet in the evening	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects treated with at least one dose of study drug	
Subject analysis set title	Per-protocol set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
All randomized subjects without validity findings affecting the primary efficacy analysis	

Primary: Absolute change in mean pain of the 7 days with worst endometriosis-associated pelvic pain (EAPP) from baseline to end of treatment

End point title	Absolute change in mean pain of the 7 days with worst endometriosis-associated pelvic pain (EAPP) from baseline to end of treatment[1]
End point description:	
This endpoint was analyzed with PPS	
End point type	Primary
End point timeframe:	
From baseline to end of treatment (last 28 days of the treatment period, Days 57 - 84)	

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Placebo	BAY1128688 3 mg once daily (OD)	BAY1128688 10 mg OD	BAY1128688 30 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11[2]	5[3]	11[4]	5[5]
Units: scores				
arithmetic mean (standard deviation)	-2.03 (± 2.45)	-1.51 (± 1.74)	-2.14 (± 1.79)	-3.74 (± 1.56)

Notes:

[2] - PPS

[3] - PPS

[4] - PPS

[5] - PPS

End point values	BAY1128688 30 mg twice daily (BID)	BAY1128688 60 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[6]	8[7]		
Units: scores				
arithmetic mean (standard deviation)	-2.40 (± 1.23)	-2.29 (± 1.58)		

Notes:

[6] - PPS

[7] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of treatment-emergent adverse events

End point title	Incidence of treatment-emergent adverse events

End point description:

End point type	Secondary

End point timeframe:

From start of the study drug until the end of the follow-up period

End point values	Placebo	BAY1128688 3 mg once daily (OD)	BAY1128688 10 mg OD	BAY1128688 30 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	11	31	10
Units: Subjects	20	5	10	9

End point values	BAY1128688 30 mg twice daily (BID)	BAY1128688 60 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	27		
Units: Subjects	6	21		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of the study drug until the end of the follow-up period	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Tablet identical in appearance to BAY1128688; one tablet in the morning and one tablet in the evening	
Reporting group title	BAY1128688 3 mg once daily (OD)
Reporting group description:	
Subjects received one 3 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening	
Reporting group title	BAY1128688 10 mg OD
Reporting group description:	
Subjects received one 10 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening	
Reporting group title	BAY1128688 60 mg BID
Reporting group description:	
Subjects received one 60 mg BAY1128688 tablet in the morning and one 60 mg BAY1128688 tablet in the evening	
Reporting group title	BAY1128688 30 mg OD
Reporting group description:	
Subjects received one 30 mg BAY1128688 tablet in the morning, and one placebo tablet in the evening	
Reporting group title	BAY1128688 30 mg twice daily (BID)
Reporting group description:	
Subjects received one 30 mg BAY1128688 tablet in the morning and one 30 mg BAY1128688 tablet in the evening	

Serious adverse events	Placebo	BAY1128688 3 mg once daily (OD)	BAY1128688 10 mg OD
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 31 (3.23%)	1 / 11 (9.09%)	0 / 31 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (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
Surgical and medical procedures			
Endometriosis ablation			

subjects affected / exposed	1 / 31 (3.23%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Peritoneal haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (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
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (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
Drug-induced liver injury			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (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	BAY1128688 60 mg BID	BAY1128688 30 mg OD	BAY1128688 30 mg twice daily (BID)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)	2 / 10 (20.00%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Endometriosis ablation			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (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
Gastrointestinal disorders			
Peritoneal haemorrhage			

subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (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
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	BAY1128688 3 mg once daily (OD)	BAY1128688 10 mg OD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 31 (64.52%)	5 / 11 (45.45%)	10 / 31 (32.26%)
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Crying			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	2	0	1
Influenza like illness			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1

Swelling			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Breast pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Endometriosis			
subjects affected / exposed	3 / 31 (9.68%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	4	1	0
Metrorrhagia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Ovarian cyst			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Pelvic pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Premenstrual syndrome			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Uterine haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Vaginal haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal pruritus			

subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Pelvic fluid collection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Pneumonitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Mood swings			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Panic attack			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Feeling guilty			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			

subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Serum ferritin decreased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	2 / 31 (6.45%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0
Headache			
subjects affected / exposed	4 / 31 (12.90%)	1 / 11 (9.09%)	4 / 31 (12.90%)
occurrences (all)	9	1	6
Migraine			

subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Trigeminal neuralgia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Eye disorders			
Episcleritis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			

subjects affected / exposed	2 / 31 (6.45%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 31 (3.23%)	1 / 11 (9.09%)	2 / 31 (6.45%)
occurrences (all)	1	1	2
Vomiting			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Ocular icterus			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Solar urticaria			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Polyuria			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Influenza			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	4 / 31 (12.90%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	4	0	1
Otitis externa			

subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Vulvovaginitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Myringitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 31 (0.00%)	0 / 11 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	BAY1128688 60 mg BID	BAY1128688 30 mg OD	BAY1128688 30 mg twice daily (BID)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 27 (77.78%)	8 / 10 (80.00%)	6 / 11 (54.55%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

Crying			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Swelling			
subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Breast pain			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	2 / 27 (7.41%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Endometriosis			
subjects affected / exposed	4 / 27 (14.81%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
Metrorrhagia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Ovarian cyst			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Premenstrual syndrome			

subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Uterine haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pruritus			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pelvic fluid collection			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Pneumonitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Mood swings			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Panic attack			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Feeling guilty			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 27 (3.70%)	2 / 10 (20.00%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	2 / 27 (7.41%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Serum ferritin decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
subjects affected / exposed	2 / 27 (7.41%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	7 / 27 (25.93%)	1 / 10 (10.00%)	2 / 11 (18.18%)
occurrences (all)	7	1	3
Migraine			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Trigeminal neuralgia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	2 / 27 (7.41%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Eye disorders			
Episcleritis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

Abdominal pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	3 / 27 (11.11%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	3	0	1
Vomiting			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Hepatobiliary disorders			
Ocular icterus			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Eczema			

subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Solar urticaria			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Polyuria			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Influenza			

subjects affected / exposed	1 / 27 (3.70%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 27 (7.41%)	2 / 10 (20.00%)	1 / 11 (9.09%)
occurrences (all)	5	2	1
Otitis externa			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vulvovaginitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Myringitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 27 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2018	All local amendments (1-8) were caused by the requests from the local regulatory authorities or ethics committees. Only one global amendment was submitted to Health Authorities. Amendment 9, dated 16 FEB 2018, was global. The protocol was amended mainly to implement the changes that had been made via local amendments, to ensure harmonization of study procedures. The following key modifications were made: Patients with copper IUDs could be included in the study, if IUD had been used for at least 6 months before study entry. Total sexual abstinence was added as an alternative method of contraception. Frequency of pregnancy testing was increased (with a maximum interval of 14 days). New exclusion criterion was introduced to exclude patients in custody.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 July 2018	Study BAY1128688/17472 (AKRENDO 1) was terminated early on 20 July 2018 due to hepatotoxicity	-

Notes:

Limitations and caveats

None reported