Clinical trial results:
Multicenter, open-label, randomized, controlled parallel-group study to assess discontinuation rates, bleeding patterns, user satisfaction and adverse event profile of LCS12 in comparison to etonogestrel subdermal implant over 12 months of use in women 18 to 35 years of age

Summary

EudraCT number	2010-023911-32
Trial protocol	SE FI GB NO
Global end of trial date	30 April 2015

Results information

Result version number	v1
This version publication date	12 May 2016
First version publication date	12 May 2016

Trial information

Trial identification

Sponsor protocol code	BAY86-5028/13363

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01397097
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, D-51368, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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	30 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that discontinuation rates in women (ages 18-35 years inclusive) using Levonorgestrel intrauterine delivery system with 12 microgram levonorgestrel per day initial in vitro release rate (LCS12) were not higher than those seen in women using Etonogestrel (ENG) subdermal implant over a period of 12 months. The objective of the 2year extension phase was to evaluate safety of LCS12 during the intended duration of use, that is, for up to 3 years.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 148
Country: Number of subjects enrolled	Sweden: 124
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Finland: 362
Country: Number of subjects enrolled	France: 67
Country: Number of subjects enrolled	Australia: 40
Worldwide total number of subjects	766
EEA total number of subjects	726

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)	766
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 38 study centers in 6 countries Sweden, Finland, France, United Kingdom, Norway, and Australia, between 15 September 2011 (first subject first visit) and 30 April 2015 (last subject last visit).

Pre-assignment

Screening details:

Overall 952 subjects were screened, of them 766 enrolled and randomized to treatment LCS12 group (385) or ENG implant group (381) in 1-year comparative treatment phase. Of the 382 subjects assigned to LCS12 treatment in the first year, 283 subjects entered the optional 2-year extension phase.

Period 1

Period 1 title	Treatment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	LCS12 (BAY86-5028)

Arm description:

Subjects received LCS12 for 12 months with an optional extension phase for further 24 months.

Arm type	Experimental
Investigational medicinal product name	Levonorgestrel (LNG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intrauterine delivery system
Routes of administration	Intrauterine use

Dosage and administration details:

Subjects received LCS12 for 12 months with an optional extension phase for further 24 months.

Arm title	Etonogestrel (ENG)

Arm description:

Subjects received 68 mg etonorgestrel implant for subdermal use at initial release rate 60 – 70 mcg/day for 12 months with an optional extension phase for further 24 months under standard care.

Arm type	Experimental
Investigational medicinal product name	Etonogestrel (ENG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Subdermal use

Dosage and administration details:

Subjects received 68 mg etonorgestrel implant for subdermal use at initial release rate 60 – 70 mcg/day for 12 months with an optional extension phase for further 24 months under standard care.

Number of subjects in period 1	LCS12 (BAY86-5028)	Etonogestrel (ENG)
Started	385	381
Treated	381	381
Completed	304	279
Not completed	81	102
Insertion failure	4	-
Consent withdrawn by subject	5	4
Protocol violation	1	-
Wish for pregnancy	3	4
Death	1	-
Other	-	1
Pregnancy	3	-
Adverse event	54	83
Lost to follow-up	10	10

Period 2

Period 2 title	Extension phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LCS12 (BAY86-5028)

Arm description:

Subjects received LCS12 for 12 months with an optional extension phase for further 24 months.

Arm type	Experimental
Investigational medicinal product name	Levonorgestrel (LNG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intrauterine delivery system
Routes of administration	Intrauterine use

Dosage and administration details:

Subjects received LCS12 for 12 months with an optional extension phase for further 24 months.

Number of subjects in period 2	LCS12 (BAY86-5028)
Started	283
Completed	199
Not completed	84
Consent withdrawn by subject	10
Wish for pregnancy	18
Other	9
Pregnancy	1
Adverse event	41
Lost to follow-up	5

Baseline characteristics

Reporting groups	
Reporting group title	LCS12 (BAY86-5028)
Reporting group description:	
Subjects received LCS12 for 12 months with an optional extension phase for further 24 months.	
Reporting group title	Etonogestrel (ENG)
Reporting group description:	
Subjects received 68 mg etonorgestrel implant for subdermal use at initial release rate 60 – 70 mcg/day for 12 months with an optional extension phase for further 24 months under standard care.	

Reporting group values	LCS12 (BAY86-5028)	Etonogestrel (ENG)	Total
Number of subjects	385	381	766
Age categorical Units: Subjects			
Adults (18-64 years)	385	381	766
Gender categorical Units: Subjects			
Female	385	381	766

End points

End points reporting groups

Reporting group title	LCS12 (BAY86-5028)
Reporting group description:	
Subjects received LCS12 for 12 months with an optional extension phase for further 24 months.	
Reporting group title	Etonogestrel (ENG)
Reporting group description:	
Subjects received 68 mg etonorgestrel implant for subdermal use at initial release rate 60 – 70 mcg/day for 12 months with an optional extension phase for further 24 months under standard care.	
Reporting group title	LCS12 (BAY86-5028)
Reporting group description:	
Subjects received LCS12 for 12 months with an optional extension phase for further 24 months.	
Subject analysis set title	Safety analysis set (SAF) Treatment Phase
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF included all subjects who had successful or unsuccessful attempt of LCS12 or ENG sub-dermal implant insertion.	
Subject analysis set title	Safety analysis set (SAF) - Overall Study
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF included subjects who attempted at least one successful or unsuccessful insertion of LCS12 during the overall study.	
Subject analysis set title	Full analysis set (FAS)-Treatment Phase
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS included all randomized subjects who received treatment (had a successful LCS12/ENG sub-dermal implant insertion).	
Subject analysis set title	Full analysis set (FAS) - Overall Study
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS included all randomized subjects who received treatment (i.e., had a successful LCS12 insertion) during overall study.	
Subject analysis set title	LCS12
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received LCS12 for 36 months.	
Subject analysis set title	ENG – Treatment Phase
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received 68 mg ENG implant for subdermal use at initial release rate 60 – 70 mcg/day for 12 months.	
Subject analysis set title	LCS12 – Treatment phase 1 Year
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received LCS12 for until end of first year of treatment.	
Subject analysis set title	LCS12 – Treatment phase 2 Year
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received LCS12 from start of 2nd year until end of 2nd year.	
Subject analysis set title	LCS12 – Treatment phase 3 Year
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received LCS12 from start of 3rd year until end of 3rd year.

Primary: Discontinuation Rate at 12 Month

End point title	Discontinuation Rate at 12 Month[1]

End point description:

Discontinuation rate was the number and percentage of subjects who discontinued the study drug during the 12-month comparative treatment phase.

End point type	Primary

End point timeframe:

Month 12

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	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	378[2]	381[3]		
Units: Percentage of subjects				
number (not applicable)	19.58	26.77		

Notes:

[2] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

[3] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation Rates for any Reason and for Specific Reasons - Treatment Phase

End point title	Discontinuation Rates for any Reason and for Specific Reasons - Treatment Phase

End point description:

Discontinuation rate was the number and percentage of subjects who discontinued the study drug during the treatment phase. The reasons of discontinuation were recorded and analysed over a period.

End point type	Secondary

End point timeframe:

Month 12

End point values	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	378[4]	381[5]		
Units: Percentage of subjects				
number (not applicable)				
Any reason	19.6	26.8		
Wish for pregnancy	0.8	1		
Any reason except-wish for pregnancy	18.8	25.7		
LCS12 expulsion	0.8	0		

Perforations (LCS12 group)	0	0		
Adverse events	14.3	21.8		
ENG subdermal implant site infection or expulsion	0	0		
Deeply inserted ENG subdermal implant	0	0		
Female genital bleeding pattern alterations	4.2	11.5		

Notes:

[4] - FAS (Treatment Phase) with evaluable subjects for this outcome measure.

[5] - FAS (Treatment Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Discontinuation Rate by Kaplan-Meier Analysis – Treatment Phase

End point title	Overall Discontinuation Rate by Kaplan-Meier Analysis – Treatment Phase

End point description:

Overall discontinuation rates were analyzed by Kaplan-Meier analyses and presented as half yearly drop-out rates.

End point type	Secondary

End point timeframe:

At first half year, second half year and third half year

End point values	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	378[6]	381[7]		
Units: Percentage of subjects				
number (not applicable)				
First half year	9.52	14.7		
Second half year	10.82	14.15		
Third half year	0.47	0		

Notes:

[6] - FAS (Treatment phase) with evaluable subjects for this outcome measure.

[7] - FAS (Treatment phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation Rates by Reason During Overall Phase

End point title	Discontinuation Rates by Reason During Overall Phase

End point description:

Discontinuation rate was the number and percentage of subjects who discontinued the study drug during the overall phase. The reasons of discontinuation were recorded and analysed over a period.

End point type	Secondary

End point timeframe:

From start of treatment until 36 months

End point values	LCS12			
Subject group type	Subject analysis set			
Number of subjects analysed	378[8]			
Units: Percentage of subjects				
number (not applicable)				
Any reason	41.8			
Wish for pregnancy	5.6			
Any reason except-wish for pregnancy	36.2			
Pregnancy	1.1			
Adverse events	25.1			
LCS12 expulsion	1.3			
Perforations	0			
Female genital bleeding pattern alterations	8.5			

Notes:

[8] - FAS (Overall study) with evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation Rates by Reason and Parity During Overall Phase

End point title	Discontinuation Rates by Reason and Parity During Overall Phase

End point description:

Discontinuation rate was the number and percentage of subjects who discontinued the study drug during the overall phase. The reasons of discontinuation were recorded and analysed over a period. Parity determined as nulliparous if the number of birth is 0 and parous if the number of birth is 1, 2, 3…n, including vaginal delivery and Cesarean section. The reasons of discontinuation were recorded and analysed over a period in nulliparous and parous.

End point type	Secondary

End point timeframe:

From start of treatment until month 36

End point values	LCS12			
Subject group type	Subject analysis set			
Number of subjects analysed	378[9]			
Units: Percentage of subjects				
number (not applicable)				
Nulliparous: Any reason (n=290)	43.1			
Nulliparous: Wish for pregnancy (n=290)	5.5			
Nulliparous: Except-wish for pregnancy (n=290)	37.6			
Nulliparous: Pregnancy (n=290)	0.7			
Nulliparous: LCS12 expulsion (n=290)	1.4			

Nulliparous: Perforations (n=290)	0			
Nulliparous: Adverse events (n=290)	26.6			
Parous: Any reason (n=88)	37.5			
Parous: Wish for pregnancy (n=88)	5.7			
Parous: Except-wish for pregnancy (n=88)	31.8			
Parous: Pregnancy (n=88)	2.3			
Parous: LCS12 expulsion (n=88)	1.1			
Parous: Perforations (n=88)	0			
Parous: Adverse events (n=88)	20.5			

Notes:

[9] - FAS (Overall study) with evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation Rates by Reason and Year During Overall Phase

End point title	Discontinuation Rates by Reason and Year During Overall Phase

End point description:

Discontinuation rate was the number and percentage of subjects who discontinued the study drug during the overall phase. The reasons of discontinuation were recorded and analysed over a period.

End point type	Secondary

End point timeframe:

From start of treatment until month 36

End point values	LCS12 – Treatment phase 1 Year	LCS12 – Treatment phase 2 Year	LCS12 – Treatment phase 3 Year	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	378[10]	294[11]	233[12]	
Units: Percentage of subjects				
number (not applicable)				
Any reason	19	17.7	14.6	
Wish for pregnancy	0.8	3.1	3.9	
Any reason except-wish for pregnancy	18.3	14.6	10.7	
Pregnancy	0.5	0.3	0.4	
Adverse events	14.3	9.2	6	
LCS12 expulsion	0.8	0.7	0	
Perforations	0	0	0	
Female genital bleeding pattern alterations	4.2	3.4	2.6	

Notes:

[10] - FAS (Overall study) with evaluable subjects of the respective treatment year for this measure.

[11] - FAS (Overall study) with evaluable subjects of the respective treatment year for this measure.

[12] - FAS (Overall study) with evaluable subjects of the respective treatment year for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Satisfaction Rate in Year 1

End point title	Overall Satisfaction Rate in Year 1

End point description:

Satisfaction was to be assessed by the subject based on a 5-point Likert item, using the following question: How satisfied are you with the birth control method used during the study? 1. Very satisfied 2. Satisfied 3. Neither satisfied nor dissatisfied 4. Dissatisfied 5. Very dissatisfied. The overall satisfaction rate is the percentage of subjects selecting "1. Very satisfied" or "2. Satisfied" for the above question. Here, in the below table, number of subjects (n) signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

At 6 and 12 months

End point values	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365[13]	369[14]		
Units: Percentage of subjects				
number (not applicable)				
Month 6 (M6): Very satisfied (n=365,369)	44.1	46.9		
M6: Satisfied (n=365,369)	38.6	24.4		
M6: Neither satisfied nor dissatisfied (n=365,369)	9	14.4		
M6: Dissatisfied (n=365,369)	6.8	9.8		
M6: Very dissatisfied (n=365,369)	1.4	4.6		
Month 12 (M12): Very satisfied (n=327,319)	53.8	49.5		
M12: Satisfied (n=327,319)	32.7	26.3		
M12: Neither satisfied nor dissatisfied(n=327,319)	6.7	10.3		
M12: Dissatisfied (n=327,319)	5.8	11.9		
M12: Very dissatisfied (n=327,319)	0.9	1.9		

Notes:

[13] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

[14] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: User Satisfaction – Acceptability of the Administration of Study Treatment

End point title	User Satisfaction – Acceptability of the Administration of Study Treatment

End point description:

The degree of user satisfaction was assessed at the end-of-study visit using an eight item questionnaire. One of the items assessed was acceptability of study treatment which was categorized into the following: acceptable without inconvenience/discomfort (I/D), acceptable with some I/D, not acceptable with moderate I/D, and not acceptable with extreme I/D. Here, in the below table, number of subjects (n) signifies evaluable subjects for the respective category. Here, in the below table, number of subjects (n) signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

month 6 and 12

End point values	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358[15]	366[16]		
Units: Subject				
M6: Acceptable without I/D (n=331, 318)	81	201		
M6: Acceptable with some I/D (n=331, 318)	203	109		
M6: Not acceptable with moderate I/D (n=331, 318)	16	3		
M6: Not acceptable with extreme I/D (n=331, 318)	31	5		
M12: Acceptable without I/D (n=357, 366)	93	210		
M12: Acceptable with some I/D (n=357, 366)	204	136		
M12: Not acceptable with moderate I/D (n=357, 366)	27	14		
M12: Not acceptable with extreme I/D (n=357, 366)	33	6		

Notes:

[15] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

[16] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: User Satisfaction – Choices Upon Completion of the Study

End point title	User Satisfaction – Choices Upon Completion of the Study

End point description:

At visit month 6 and month 12 the choices upon completion of the study has been asked from the subjects using six item questionnaire. Questionnaires for the continuation of the study treatment was categorized into the following: continue with study treatment, use a different hormonal contraceptive, discontinue use of all contraceptives, continue with study treatment, and use different hormonal contraceptives. Here, in the below table, number of subjects (n) signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

Month 6 and 12

End point values	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357[17]	366[18]		
Units: Subject				
M6 m: Continue with study treatment (n=329, 317)	252	236		
M6: Different hormonal Contraceptive (n=329, 317)	18	13		
M6: Different Contraceptive method (n=329, 317)	8	15		
M6: Discontinue of all Contraceptive (n=329, 317)	0	3		
M6: Undecided (n=329, 317)	51	50		
M12: Continue with study treatment (n=357, 366)	251	214		
M12: Different hormonal Contraceptive (n=357, 366)	34	58		
M12: Different Contraceptive method (n=357, 366)	30	56		
M12: Discontinue of all Contraceptive (n=357, 366)	5	5		
M12: No need Contraceptive this time (n=357, 366)	8	12		
M12: Undecided (n=357, 366)	29	21		

Notes:

[17] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

[18] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: User Satisfaction – Amount of Menstrual Bleeding

End point title	User Satisfaction – Amount of Menstrual Bleeding

End point description:

The degree of user satisfaction was assessed at the end-of-study visit using an eight item questionnaire. One of the items assessed was acceptability of study treatment which was categorized into the following: acceptable without inconvenience/discomfort (I/D), acceptable with some I/D, not acceptable with moderate I/D, and not acceptable with extreme I/D. Here, in the below table, number of subjects (n) signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

Month 6 and 12

End point values	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357[19]	365[20]		
Units: Subject				
M6: Decreased (n= 331, 317)	254	201		
M6: Not Changed (n= 331, 317)	61	73		
M6: Increased (n= 331, 317)	16	43		
M12: Decreased (n= 357, 365)	203	147		

M12: Not Changed (n= 357, 365)	121	142		
M12: Increased (n= 357, 365)	33	76		

Notes:

[19] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

[20] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: User Satisfaction – Satisfaction With Menstrual Bleeding Pattern

End point title	User Satisfaction – Satisfaction With Menstrual Bleeding Pattern

End point description:

The degree of user satisfaction with menstrual bleeding absence was assessed at the end-of-study visit using four item questionnaire. Questionnaires for this assessment were categorized into very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied and not applicable. Here, in the below table, number of subjects (n) signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

Month 6 and 12

End point values	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358[21]	366[22]		
Units: Subjects				
M6: Very satisfied (n=331, 318)	87	66		
M6: Somewhat satisfied (n=331, 318)	123	66		
M6: Neither satisfied nor dissatisfied (n=331,318)	64	54		
M6: Dissatisfied (n=331, 318)	30	55		
M6: Very dissatisfied (n=331, 318)	9	23		
M6: Not applicable (n=331, 318)	18	54		
M12: Very satisfied (n=358, 366)	119	75		
M12: Somewhat satisfied (n=358, 366)	99	48		
M12: Neither satisfied nor dissatisfied(n=358,366)	69	68		
M12: Dissatisfied (n=358, 366)	35	67		
M12: Very dissatisfied (n=358, 366)	21	50		
M12: Not applicable (n=358, 366)	15	58		

Notes:

[21] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

[22] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: User Satisfaction – Frequency of Experiencing Unexpected Bleeding

End point title	User Satisfaction – Frequency of Experiencing Unexpected

	Bleeding

End point description:

The degree of user satisfaction with menstrual bleeding absence was assessed at the end-of-study visit using four item questionnaire. Questionnaires for this assessment were categorized into never, seldom, often and very often. Here, in the below table, number of subjects (n) signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

Month 6 and 12

End point values	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358[23]	366[24]		
Units: Subjects				
M6: Never (n=331, 317)	111	111		
M6: Seldom (n=331, 317)	170	110		
M6: Often (n=331, 317)	40	67		
M6: Very often (n=331, 317)	10	29		
M12: Never (n=358, 366)	158	119		
M12: Seldom (n=358, 366)	150	116		
M12: Often (n=358, 366)	34	81		
M12: Very often (n=358, 366)	16	50		

Notes:

[23] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

[24] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: User Satisfaction – Satisfaction With Menstrual Bleeding Absence

End point title	User Satisfaction – Satisfaction With Menstrual Bleeding Absence

End point description:

The degree of user satisfaction with menstrual bleeding absence was assessed at the end-of-study visit using four item questionnaire. Questionnaires for this assessment were categorized into very satisfied, somewhat satisfied, neither satisfied nor dissatisfied and dissatisfied. Here, in the below table, number of subjects (n) signifies evaluable subjects for the respective category. '99999' in the posting indicates that data were not calculated.

End point type	Secondary

End point timeframe:

Month 6 and 12

End point values	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141[25]	193[26]		
Units: Subjects				
M6: Very satisfied (n=117,189)	86	136		
M6: Somewhat satisfied (n=117,189)	21	33		
M6: Neither satisfied nor dissatisfied (n=117,189)	10	17		
M6: Dissatisfied (n=117,189)	0	3		
M12: Very satisfied (n=141,193)	111	150		
M12: Somewhat satisfied (n=141,193)	18	29		
M12: Neither satisfied nor dissatisfied(n=141,193)	11	12		
M12: Dissatisfied (n=141,193)	0	2		
M12: Very dissatisfied (n=141,193)	1	0		

Notes:

[25] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

[26] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Contraceptive Efficacy: Pearl Index (PI)- Treatment Phase

End point title	Contraceptive Efficacy: Pearl Index (PI)- Treatment Phase

End point description:

The Pearl Index was defined as the number of pregnancies per 100 woman years (WYs). Given the assumption that the number of pregnancies follows a Poisson distribution, the Pearl Index thus is the mean of this distribution.

End point type	Secondary

End point timeframe:

Month 12

End point values	LCS12 (BAY86-5028)	Etonogestrel (ENG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	378[27]	381[28]		
Units: pregnancies per 100 women years				
arithmetic mean (confidence interval 95%)	0.9 (0.19 to 2.63)	0 (0 to 1.18)		

Notes:

[27] - FAS (Treatment Phase) included evaluable subjects for this outcome measure.

[28] - FAS (Treatment Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Contraceptive Efficacy: Pearl Index-Overall Study, first year, Second year, Third year, Up to Second year, Up to Third year and Overall of the treatment

End point title	Contraceptive Efficacy: Pearl Index-Overall Study, first year, Second year, Third year, Up to Second year, Up to Third year and Overall of the treatment

End point description:

The Pearl Index was defined as the number of pregnancies per 100 woman years (WYs). Given the assumption that the number of pregnancies follows a Poisson distribution, the Pearl Index thus is the mean of this distribution. Here, in the below table, number of subjects (n) signifies evaluable subjects for the respective category.

End point type	Secondary

End point timeframe:

From start of study treatment up to Month 36

End point values	LCS12			
Subject group type	Subject analysis set			
Number of subjects analysed	378[29]			
Units: Pregnancies per 100 women years				
arithmetic mean (confidence interval 95%)				
Year 1 (n=378)	0.92 (0.19 to 2.7)			
Year 2 (n=295)	0.39 (0.01 to 2.15)			
Year 3 (n=237)	0.98 (0.12 to 3.53)			
2 Years (n=378)	0.68 (0.19 to 1.75)			
3 Years (n=378)	0.76 (0.28 to 1.65)			
Overall (n=378)	0.76 (0.28 to 1.65)			

Notes:

[29] - FAS (overall study) with evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: LNG Residual Content Analysis

End point title	LNG Residual Content Analysis

End point description:

The residual LNG content was determined in the used LCS12 which was collected from the subjects who prematurely discontinued study treatment in order to determine the performance of LCS12. Subjects who were discontinued from the study between 11 days and 609 days were reported for this outcome measure.

End point type	Secondary

End point timeframe:

Between 11 days and 609 days and after 609 days

End point values	LCS12			
Subject group type	Subject analysis set			
Number of subjects analysed	81[30]			
Units: milligram				
number (not applicable)				
Immediate after insertion	13.7			
After 609 days	9.5			

Notes:

[30] - FAS (Overall study) with evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to Month 12 for the subjects in comparative treatment phase and up to Year 3 for the subjects in extension phase

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	LCS12

Reporting group description:

Subjects received LCS12 for 36 months.

Reporting group title	ENG - Treatment Phase

Reporting group description:

Subjects received 68 mg ENG implant for sub-dermal use at initial release rate 60 - 70 microgram per day (mcg/day) for 12 months.

Reporting group title	LCS12 - Treatment phase 1 Year

Reporting group description:

Subjects received LCS12 for until end of first year of treatment.

Reporting group title	LCS12 - Treatment phase 2 Year

Reporting group description:

Subjects received LCS12 from start of 2nd year until end of 2nd year.

Reporting group title	LCS12 - Treatment phase 3 Year

Reporting group description:

Subjects received LCS12 from start of 3rd year until end of 3rd year.

Serious adverse events	LCS12	ENG - Treatment Phase	LCS12 - Treatment phase 1 Year
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 382 (4.71%)	9 / 381 (2.36%)	8 / 382 (2.09%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events		0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian adenoma			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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
Dislocation of vertebra			
subjects affected / exposed	0 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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
Tendon rupture			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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
Pelvic fracture			
subjects affected / exposed	0 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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
Urinary retention postoperative			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	1 / 382 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abdominoplasty			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	1 / 382 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroidectomy			

subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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
Pregnancy, puerperium and perinatal conditions			
Ruptured ectopic pregnancy			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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
Biochemical pregnancy			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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
Pregnancy of unknown location			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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
Ectopic pregnancy with contraceptive device			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	1 / 382 (0.26%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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
Cholelithiasis			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	1 / 382 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Tracheomalacia			
subjects affected / exposed	0 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	1 / 382 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	1 / 382 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	1 / 382 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prognathism			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	1 / 382 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	2 / 382 (0.52%)	1 / 381 (0.26%)	1 / 382 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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
Diverticulitis			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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
Peritonsillar abscess			
subjects affected / exposed	0 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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
Pneumonia			
subjects affected / exposed	0 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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 / 382 (0.00%)	1 / 381 (0.26%)	0 / 382 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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
Pneumococcal sepsis			
subjects affected / exposed	1 / 382 (0.26%)	0 / 381 (0.00%)	0 / 382 (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

Serious adverse events	LCS12 - Treatment phase 2 Year	LCS12 - Treatment phase 3 Year	

Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 293 (1.37%)	7 / 234 (2.99%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian adenoma			
subjects affected / exposed	0 / 293 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dislocation of vertebra			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 293 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary retention postoperative			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abdominoplasty			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroidectomy			
subjects affected / exposed	1 / 293 (0.34%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ruptured ectopic pregnancy			
subjects affected / exposed	0 / 293 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biochemical pregnancy			
subjects affected / exposed	1 / 293 (0.34%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy of unknown location			
subjects affected / exposed	0 / 293 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy with contraceptive device			

subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	1 / 293 (0.34%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Tracheomalacia			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			

subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prognathism			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 293 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LCS12	ENG - Treatment Phase	LCS12 - Treatment phase 1 Year
Total subjects affected by non-serious adverse events			
subjects affected / exposed	298 / 382 (78.01%)	186 / 381 (48.82%)	270 / 382 (70.68%)
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	57 / 382 (14.92%)	6 / 381 (1.57%)	51 / 382 (13.35%)
occurrences (all)	57	6	51
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 382 (11.52%)	42 / 381 (11.02%)	41 / 382 (10.73%)
occurrences (all)	72	56	68
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	30 / 382 (7.85%)	7 / 381 (1.84%)	26 / 382 (6.81%)
occurrences (all)	41	7	36
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	64 / 382 (16.75%)	27 / 381 (7.09%)	21 / 382 (5.50%)
occurrences (all)	80	27	23
Dysmenorrhoea			
subjects affected / exposed	137 / 382 (35.86%)	29 / 381 (7.61%)	128 / 382 (33.51%)
occurrences (all)	170	30	151
Uterine spasm			
subjects affected / exposed	61 / 382 (15.97%)	0 / 381 (0.00%)	61 / 382 (15.97%)
occurrences (all)	66	0	66

Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	59 / 382 (15.45%)	59 / 381 (15.49%)	49 / 382 (12.83%)
occurrences (all)	66	61	54
Infections and infestations			
Influenza			
subjects affected / exposed	18 / 382 (4.71%)	24 / 381 (6.30%)	15 / 382 (3.93%)
occurrences (all)	26	27	22
Nasopharyngitis			
subjects affected / exposed	29 / 382 (7.59%)	32 / 381 (8.40%)	26 / 382 (6.81%)
occurrences (all)	33	39	29
Urinary tract infection			
subjects affected / exposed	40 / 382 (10.47%)	15 / 381 (3.94%)	25 / 382 (6.54%)
occurrences (all)	59	22	31
Viral upper respiratory tract infection			
subjects affected / exposed	22 / 382 (5.76%)	11 / 381 (2.89%)	17 / 382 (4.45%)
occurrences (all)	35	15	22
Vulvovaginal candidiasis			
subjects affected / exposed	30 / 382 (7.85%)	10 / 381 (2.62%)	19 / 382 (4.97%)
occurrences (all)	41	12	27

Non-serious adverse events	LCS12 - Treatment phase 2 Year	LCS12 - Treatment phase 3 Year	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 293 (25.60%)	55 / 234 (23.50%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 293 (0.00%)	6 / 234 (2.56%)	
occurrences (all)	0	6	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 293 (0.34%)	3 / 234 (1.28%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	4 / 293 (1.37%)	1 / 234 (0.43%)	
occurrences (all)	4	1	
Reproductive system and breast disorders			

Cervical dysplasia			
subjects affected / exposed	32 / 293 (10.92%)	20 / 234 (8.55%)	
occurrences (all)	34	23	
Dysmenorrhoea			
subjects affected / exposed	14 / 293 (4.78%)	4 / 234 (1.71%)	
occurrences (all)	14	5	
Uterine spasm			
subjects affected / exposed	0 / 293 (0.00%)	0 / 234 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	8 / 293 (2.73%)	4 / 234 (1.71%)	
occurrences (all)	8	4	
Infections and infestations			
Influenza			
subjects affected / exposed	3 / 293 (1.02%)	1 / 234 (0.43%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	2 / 293 (0.68%)	2 / 234 (0.85%)	
occurrences (all)	2	2	
Urinary tract infection			
subjects affected / exposed	11 / 293 (3.75%)	10 / 234 (4.27%)	
occurrences (all)	11	17	
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 293 (2.05%)	6 / 234 (2.56%)	
occurrences (all)	6	7	
Vulvovaginal candidiasis			
subjects affected / exposed	7 / 293 (2.39%)	7 / 234 (2.99%)	
occurrences (all)	7	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2011	1. LCS12 extension phase was to continue up to 3 years, and was not to be ended if a marketing authorization was received. Phase between the screening visit and randomization visit was reduced to 8 weeks from the originally planned 12 weeks 2. Date of birth was removed from the population characteristics to be displayed; only age was used 3. Cervical smear: results evaluated with other systems corresponding to the Bethesda system were accepted 4. It was emphasized that the investigators had to be experienced with Intrauterine device (IUD)/ Intra-uterine delivery system (IUS) insertion, and that they must have attended the LCS12 insertion training given by the sponsor 5. The need to use back up contraception if switching from progestin only oral contraception or hormone releasing IUS to the study drug was added 6. The text describing the use of a condom or another barrier method for contraception at least 7 days before LCS12 removal was reworded. Instructions were included for both prematurely discontinuing subjects and for subjects who complete the study 7. Perforations were to be reported as serious adverse events 8. As the use of progestogen containing contraceptives may have an effect on peripheral insulin resistance and glucose tolerance, guidance on monitoring blood glucose concentration was added 9. A clarification was made regarding the reporting of pregnancies occurring after the end-of-study (EOS): In the LCS12 group, all pregnancies reported up to 12 months after EOS were followed up for the final outcome of the mother and fetus/child 10. Further clarification of the definition of dysmenorrhea as an AE was included 11. As women with presence or history of venous or arterial thrombotic/thromboembolic events were not allowed in the study, the sentence about making women with history of thromboembolic disorder aware of a possible reoccurrence was removed 12. Minor changes implemented to the text due to grammatical or typographical errors.

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.

Decimal places were automatically truncated if last decimal equals zero.

Notes: