Clinical trial results:
Multi-center, single-arm study to assess the safety, efficacy, discontinuation rate and pharmacokinetics of the low-dose levonorgestrel intrauterine contraceptive system (LCS12) in post-menarcheal female adolescents under 18 years of age for 1 year, and an optional 2-year extension phase

Summary

EudraCT number	2011-002065-37
Trial protocol	SE FI NL AT BE DE DK NO
Global end of trial date	28 May 2015

Results information

Result version number	v2 (current)
This version publication date	04 September 2016
First version publication date	02 July 2016
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY86-5028/14371

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01434160
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000606-PIP01-09
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the safety of the low-dose levonorgestrel (LNG) (12 microgram [mcg]/24 hour [h]) intrauterine contraceptive system (LCS12) in adolescents over 1 year of treatment, including the insertion and removal procedures.
The objective of the 2-year extension phase was to evaluate safety and efficacy 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 representatives. Participating subjects and/or their legally authorized representatives 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	26 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	Belgium: 64
Country: Number of subjects enrolled	Germany: 64
Country: Number of subjects enrolled	Austria: 63
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	Finland: 23
Country: Number of subjects enrolled	Netherlands: 55
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Sweden: 14
Worldwide total number of subjects	304
EEA total number of subjects	304

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)	302
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 36 study centers for 1 year treatment phase and 34 study centers for 2 year extension phase in 8 countries, from 26 September 2011 (first subject first visit) to 28 May 2015 (last subject last visit).

Pre-assignment

Screening details:

Overall 343 subjects were enrolled in the study, of which 304 were assigned to treatment. Thirty nine (39) subjects were excluded at screening, of which 26 were screening failures, 5 were withdrew consent, 4 were lost to follow-up, 2 due to adverse events, and 2 for other reasons.

Period 1

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

Arms

Arm title	Levonorgestrel (BAY86-5028)

Arm description:

Subjects received levonorgestrel (LNG) intrauterine contraceptive system with an initial in vitro release rate of 12 microgram LNG/day (LCS12) for up to 12 months.

Arm type	Experimental
Investigational medicinal product name	Levonorgestrel
Investigational medicinal product code	BAY86-5028
Other name	
Pharmaceutical forms	Intrauterine delivery system
Routes of administration	Intrauterine use

Dosage and administration details:

The total LNG content in LCS12 was 13.5 mg. LCS12 was inserted into the uterus and could remain in place for up to 12 months.

Number of subjects in period 1	Levonorgestrel (BAY86-5028)
Started	304
Completed	253
Not completed	51
Insertion failure	1
Protocol violation	2
Adverse event, non-fatal	40
Death	1
Other, unspecified	4
Lost to follow-up	3

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

Arms

Arm title	Levonorgestrel (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
Investigational medicinal product code	BAY86-5028
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	Levonorgestrel (BAY86-5028)
Started	220
Completed	173
Not completed	47
Consent withdrawn by subject	2
Protocol violation	1
Wish for pregnancy	3
Adverse event, non-fatal	25
Other, unspecified	14
Pregnancy	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Phase
Reporting group description:	
Subjects received LCS12 for 12 months with optional extension of 24 months.	

Reporting group values	Treatment Phase	Total	
Number of subjects	304	304	
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	16.2		
standard deviation	± 1	-	
Gender Categorical Units: Subjects			
Female	304	304	
Male	0	0	

End points

End points reporting groups

Reporting group title	Levonorgestrel (BAY86-5028)
Reporting group description:	
Subjects received levonorgestrel (LNG) intrauterine contraceptive system with an initial in vitro release rate of 12 microgram LNG/day (LCS12) for up to 12 months.	
Reporting group title	Levonorgestrel (BAY86-5028)
Reporting group description:	
Subjects received LCS12 for 12 months with an optional extension phase for further 24 months.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS included all subjects who had the LCS12 inserted or had at least an insertion attempt (successful or unsuccessful).	

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events During Treatment Phase

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events During Treatment Phase[1]
End point description:	
An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An /serious adverse events (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent adverse events were defined as AEs/SAEs that started or worsened after the study drug treatment.	
End point type	Primary
End point timeframe:	
From the start of study treatment up to 12 months	

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	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	304[2]			
Units: Percentage of subjects				
number (not applicable)				
TEAE	82.6			
TESAE	7.6			

Notes:

[2] - FAS

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events During Overall Study

End point title	Percentage of Subjects With Treatment-Emergent Adverse

	Events During Overall Study[3]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An /serious adverse events (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent adverse events were defined as AEs/SAEs that started or worsened after the study drug treatment.

End point type	Primary

End point timeframe:

From start of study treatment until 36 months (end of extension phase)

Notes:

[3] - 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	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	304[4]			
Units: Percentage of subjects				
number (not applicable)				
TEAE	87.8			
TESAE	11.2			

Notes:

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Satisfaction Rating by the 5-Point Likert Item at Month 12

End point title	Overall Satisfaction Rating by the 5-Point Likert Item at Month 12

End point description:

Satisfaction was 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? and the answers were any of the following: 1. Very satisfied 2. Satisfied 3. Neither satisfied nor dissatisfied 4. Dissatisfied 5. Very dissatisfied. The overall satisfaction rate was the percentage of subjects selecting "1. Very satisfied" or "2. Satisfied" for the above question.

End point type	Secondary

End point timeframe:

At Month 12

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	304[5]			
Units: Subjects				
Missing	10			
Very Satisfied	163			
Satisfied	92			

Neither satisfied nor dissatisfied	17			
Dissatisfied	19			
Very Dissatisfied	3			

Notes:

[5] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Contraceptive Efficacy - Pearl Index

End point title	Contraceptive Efficacy - Pearl Index

End point description:

The pearl index was defined as the number of pregnancies per 100 woman years. The following PIs were calculated: First year PI, Second year PI, Third year PI, 2-year PI, 3-year PI and Overall PI. Given the assumption that the number of pregnancies follows a Poisson distribution, the Pearl Index thus is the mean of this distribution. In the table below, "n" signifies the number of subjects evaluable at the corresponding time points.

End point type	Secondary

End point timeframe:

From start of study treatment up to 3 years

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	304[6]			
Units: pregnancies per 100 woman years				
number (confidence interval 95%)				
Year 1 (n = 304)	0 (0 to 1.88)			
Year 2 (n = 234)	0.47 (0.01 to 2.62)			
Year 3 (n = 205)	0.56 (0.01 to 3.1)			
2 year (n = 304)	0.24 (0.01 to 1.36)			
3 year (n = 304)	0.34 (0.04 to 1.23)			
Overall (n = 304)	0.34 (0.04 to 1.23)			

Notes:

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Patterns in Days by 28-day Reference Periods - Reference Period 1

End point title	Bleeding Patterns in Days by 28-day Reference Periods - Reference Period 1

End point description:

The occurrence of vaginal bleeding was recorded by study subjects every day in an e-diary. Bleeding intensity was categorized as: no vaginal bleeding, spotting (less than associated with normal menstruation relative to the subject's experience with no need for sanitary protection except for panty liners), light (less than associated with normal menstruation relative to the subject's experience with need for sanitary protection), normal (similar to normal menstruation relative to the subject's experience) and heavy (more than normal menstruation relative to the subject's experience). Spotting episode (SE) means day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days. Spotting only episodes (SOE) means day(s) with spotting preceded and followed by at least 2 bleeding-free days and Bleeding/spotting-free interval means at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day.

End point type	Secondary

End point timeframe:

At reference period 1 (1 reference period=28-days) during 1-year treatment phase

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	141[7]			
Units: subjects				
at least 1 bleeding/spotting day	141			
at least 1 bleeding day (excluding spotting)	137			
at least 1 bleeding/spotting or SOE	113			
at least 1 bleeding/SE (excluding SOE)	113			

Notes:

[7] - FAS with evaluable subjects for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Patterns in Days by 28-day Reference Periods - Reference Period 5

End point title	Bleeding Patterns in Days by 28-day Reference Periods - Reference Period 5

End point description:

The occurrence of vaginal bleeding was to be recorded by study subjects every day in an e-diary. Bleeding intensity was categorized as: no vaginal bleeding, spotting (less than associated with normal menstruation relative to the subject's experience with no need for sanitary protection except for panty liners), light (less than associated with normal menstruation relative to the subject's experience with need for sanitary protection), normal (similar to normal menstruation relative to the subject's experience) and heavy (more than normal menstruation relative to the subject's experience).
For Bleeding/spotting-free interval at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day. For Spotting-only episode day(s) with spotting preceded and followed by at least 2 bleeding-free days and for Bleeding/spotting episode Day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days.

End point type	Secondary

End point timeframe:

At reference period 5 (1 reference period=28-days) during 1-year treatment phase

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	74[8]			
Units: subjects				
at least 1 bleeding/spotting day	64			
at least 1 bleeding day (excluding spotting)	49			
at least 1 bleeding/spotting or SOE	59			
at least 1 bleeding/SE (excluding SOE)	59			

Notes:

[8] - FAS with evaluable subjects for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Patterns in Days by 28-day Reference Periods - Reference Period 9

End point title	Bleeding Patterns in Days by 28-day Reference Periods - Reference Period 9

End point description:

The occurrence of vaginal bleeding was to be recorded by study subjects every day in an e-diary. Bleeding intensity was categorized as: no vaginal bleeding, spotting (less than associated with normal menstruation relative to the subject's experience with no need for sanitary protection except for panty liners), light (less than associated with normal menstruation relative to the subject's experience with need for sanitary protection), normal (similar to normal menstruation relative to the subject's experience) and heavy (more than normal menstruation relative to the subject's experience). For Bleeding/spotting-free interval at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day. For Spotting-only episode day(s) with spotting preceded and followed by at least 2 bleeding-free days and for Bleeding/spotting episode Day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days.

End point type	Secondary

End point timeframe:

At reference period 9 (1 reference period=28-days) during 1-year treatment phase

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	56[9]			
Units: subjects				
at least 1 bleeding/spotting day	49			
at least 1 bleeding day (excluding spotting)	35			
at least 1 bleeding/spotting or SOE	49			
at least 1 bleeding/SE (excluding SOE)	49			

Notes:

[9] - FAS with evaluable subjects for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Patterns in Days by 28-day Reference Periods - Reference Period 13

End point title	Bleeding Patterns in Days by 28-day Reference Periods - Reference Period 13

End point description:

The occurrence of vaginal bleeding was to be recorded by study subjects every day in an e-diary. Bleeding intensity was categorized as: no vaginal bleeding, spotting (less than associated with normal menstruation relative to the subject's experience with no need for sanitary protection except for panty liners), light (less than associated with normal menstruation relative to the subject's experience with need for sanitary protection), normal (similar to normal menstruation relative to the subject's experience) and heavy (more than normal menstruation relative to the subject's experience). For Bleeding/spotting-free interval at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day. For Spotting-only episode day(s) with spotting preceded and followed by at least 2 bleeding-free days and for Bleeding/spotting episode Day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days.

End point type	Secondary

End point timeframe:

At reference period 13 (1 reference period=28-days) during 1-year treatment phase

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	36[10]			
Units: subjects				
at least 1 bleeding/spotting day	29			
at least 1 bleeding day (excluding spotting)	23			
at least 1 bleeding/spotting or SOE	28			
at least 1 bleeding/SE (excluding SOE)	28			

Notes:

[10] - FAS with evaluable subjects for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Patterns in Days by 90-day Reference Periods - Reference Period 1

End point title	Bleeding Patterns in Days by 90-day Reference Periods - Reference Period 1

End point description:

The occurrence of vaginal bleeding was to be recorded by study subjects every day in an e-diary. Bleeding intensity was categorized as: no vaginal bleeding, spotting (less than associated with normal menstruation relative to the subject's experience with no need for sanitary protection except for panty liners), light (less than associated with normal menstruation relative to the subject's experience with need for sanitary protection), normal (similar to normal menstruation relative to the subject's experience) and heavy (more than normal menstruation relative to the subject's experience). For Bleeding/spotting-free interval at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day. For Spotting-only episode day(s) with spotting preceded and followed by at least 2 bleeding-free days and for Bleeding/spotting episode Day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days.

End point type	Secondary

End point timeframe:

At reference period 1 (1 reference period=90-days) during 1-year treatment phase

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	76[11]			
Units: subjects				
at least 1 bleeding/spotting day	76			
at least 1 bleeding day (excluding spotting)	74			
at least 1 bleeding/spotting or SOE	73			
at least 1 bleeding/SE (excluding SOE)	73			

Notes:

[11] - FAS with evaluable subjects for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Patterns in Days by 90-day Reference Periods - Reference Period 2

End point title	Bleeding Patterns in Days by 90-day Reference Periods - Reference Period 2

End point description:

The occurrence of vaginal bleeding was to be recorded by study subjects every day in an e-diary. Bleeding intensity was categorized as: no vaginal bleeding, spotting (less than associated with normal menstruation relative to the subject's experience with no need for sanitary protection except for panty liners), light (less than associated with normal menstruation relative to the subject's experience with need for sanitary protection), normal (similar to normal menstruation relative to the subject's experience) and heavy (more than normal menstruation relative to the subject's experience). For Bleeding/spotting-free interval at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day. For Spotting-only episode day(s) with spotting preceded and followed by at least 2 bleeding-free days and for Bleeding/spotting episode Day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days.

End point type	Secondary

End point timeframe:

At reference period 2 (1 reference period=90-days) during 1-year treatment phase

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	45[12]			
Units: subjects				
at least 1 bleeding/spotting day	44			
at least 1 bleeding day (excluding spotting)	36			
at least 1 bleeding/spotting or SOE	44			

at least 1 bleeding/SE (excluding SOE)	44			

Notes:

[12] - FAS with evaluable subjects for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Patterns in Days by 90-day Reference Periods - Reference Period 3

End point title	Bleeding Patterns in Days by 90-day Reference Periods - Reference Period 3

End point description:

The occurrence of vaginal bleeding was to be recorded by study subjects every day in an e-diary. Bleeding intensity was categorized as: no vaginal bleeding, spotting (less than associated with normal menstruation relative to the subject's experience with no need for sanitary protection except for panty liners), light (less than associated with normal menstruation relative to the subject's experience with need for sanitary protection), normal (similar to normal menstruation relative to the subject's experience) and heavy (more than normal menstruation relative to the subject's experience). For Bleeding/spotting-free interval at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day. For Spotting-only episode day(s) with spotting preceded and followed by at least 2 bleeding-free days and for Bleeding/spotting episode Day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days.

End point type	Secondary

End point timeframe:

At reference period 3 (1 reference period=90-days) during 1-year treatment phase

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	33[13]			
Units: subjects				
at least 1 bleeding/spotting day	32			
at least 1 bleeding day (excluding spotting)	28			
at least 1 bleeding/spotting or SOE	32			
at least 1 bleeding/SE (excluding SOE)	32			

Notes:

[13] - FAS with evaluable subjects for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Patterns in Days by 90-day Reference Periods - Reference Period 4

End point title	Bleeding Patterns in Days by 90-day Reference Periods - Reference Period 4

End point description:

The occurrence of vaginal bleeding was to be recorded by study subjects every day in an e-diary. Bleeding intensity was categorized as: no vaginal bleeding, spotting (less than associated with normal menstruation relative to the subject's experience with no need for sanitary protection except for panty liners), light (less than associated with normal menstruation relative to the subject's experience with need for sanitary protection), normal (similar to normal menstruation relative to the subject's experience) and heavy (more than normal menstruation relative to the subject's experience). For Bleeding/spotting-free interval at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day. For Spotting-only episode day(s) with spotting preceded and followed by at least 2 bleeding-free days and for Bleeding/spotting episode Day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days.

End point type	Secondary

End point timeframe:

At reference period 4 (1 reference period=90-days) during 1-year treatment phase

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	19[14]			
Units: subjects				
at least 1 bleeding/spotting day	18			
at least 1 bleeding day (excluding spotting)	16			
at least 1 bleeding/spotting or SOE	18			
at least 1 bleeding/SE (excluding SOE)	18			

Notes:

[14] - FAS with evaluable subjects for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Total Levonorgestrel

End point title	Serum Concentration of Total Levonorgestrel

End point description:

Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In the table below, "n" signifies the number of subjects evaluable at the corresponding time points.

End point type	Secondary

End point timeframe:

1, 3, 6, 9, 12 months after insertion

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	304[15]			
Units: nanogram/liter (ng/L)				
geometric mean (geometric coefficient of variation)				
1 month (n=268)	145 (± 24.7)			

3 months (n=263)	110 (± 25.2)			
6 months (n=258)	90.9 (± 25.3)			
9 months (n=246)	82.9 (± 25.2)			
12 months (n=220)	77.8 (± 24.3)			

Notes:

[15] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Unbound Levonorgestrel

End point title	Serum Concentration of Unbound Levonorgestrel

End point description:

Geometric mean and (%CV) were reported. In the table below, "n" signifies the number of subjects evaluable at the corresponding time points.

End point type	Secondary

End point timeframe:

1, 3, 6, 9, 12 months after insertion

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	304[16]			
Units: nanogram/Liter (ng/L)				
geometric mean (geometric coefficient of variation)				
1 month (n=268)	2.21 (± 20.3)			
3 months (n=263)	1.66 (± 20.2)			
6 months (n=258)	1.36 (± 20.1)			
9 months (n=246)	1.24 (± 20.1)			
12 months (n=220)	1.16 (± 19.5)			

Notes:

[16] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Sex Hormone Binding Globulin (SHBG)

End point title	Serum Concentration of Sex Hormone Binding Globulin (SHBG)

End point description:

The PK of LNG is dependent on SHBG levels as LNG binds specifically to SHBG with high affinity and SHBG synthesis, in turn, is inhibited by LNG.

End point type	Secondary

End point timeframe:

1, 3, 6, 9, 12 months after insertion

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	0[17]			
Units: nanomole per liter (nmol/L)				
geometric mean (geometric coefficient of variation)	()			

Notes:

[17] - SHBG needed for calculation of unbound LNG concentration, so data were not summarized and evaluated.

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Evaluation of Intrauterine System (IUS) Insertion Procedure

End point title	Investigator's Evaluation of Intrauterine System (IUS) Insertion Procedure

End point description:

The ease of IUS insertion was evaluated by the investigator as easy, slightly difficult, or very difficult.

End point type	Secondary

End point timeframe:

Month 0

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	303[18]			
Units: subjects				
easy	286			
slightly difficult	14			
very difficult	3			

Notes:

[18] - FAS with evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects' Evaluation of Pain During Intrauterine System (IUS) Insertion Procedure

End point title	Subjects' Evaluation of Pain During Intrauterine System (IUS) Insertion Procedure

End point description:

The subject assessed the pain experienced during the insertion as none, mild, moderate or severe and this was recorded by the investigator.

End point type	Secondary

End point timeframe:

Month 0

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	303[19]			
Units: subjects				
none	62			
mild	104			
moderate	104			
severe	33			

Notes:

[19] - FAS with evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Evaluation of Intrauterine System (IUS) Removal Procedure During Treatment Phase

End point title	Investigator's Evaluation of Intrauterine System (IUS) Removal Procedure During Treatment Phase

End point description:

The ease of IUS removal was assessed by investigator as easy, slightly difficult or very difficult.

End point type	Secondary

End point timeframe:

From start of study treatment until 12 months

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	69[20]			
Units: subjects				
Missing	4			
Easy	64			
Slightly difficult	1			
Very difficult	0			

Notes:

[20] - FAS with evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Subject's Evaluation of Pain During Intrauterine System (IUS) Removal Procedure During Treatment Phase

End point title	Subject's Evaluation of Pain During Intrauterine System (IUS) Removal Procedure During Treatment Phase

End point description:

The subject assessed the pain experienced during the removal as none, mild, moderate or severe and this was recorded by the investigator.

End point type	Secondary

End point timeframe:

From start of treatment up to 12 months

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	69[21]			
Units: subjects				
Missing	2			
None	34			
Mild	25			
Moderate	8			

Notes:

[21] - FAS with evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Evaluation of Intrauterine System (IUS) Removal Procedure During Overall Study

End point title	Investigator's Evaluation of Intrauterine System (IUS) Removal Procedure During Overall Study

End point description:

The ease of IUS removal was assessed by investigator as easy, slightly difficult or very difficult.

End point type	Secondary

End point timeframe:

From start of study treatment up to 36 months (end of optional extension phase)

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	285[22]			
Units: Subjects				
Easy	277			
Slightly difficult	8			
Very difficult	0			

Notes:

[22] - FAS with evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Subject's Evaluation of Pain During Intrauterine System (IUS) Removal Procedure During Overall Study

End point title	Subject's Evaluation of Pain During Intrauterine System (IUS) Removal Procedure During Overall Study

End point description:

The subject assessed the pain experienced during the removal as none, mild, moderate or severe and this was recorded by the investigator.

End point type	Secondary

End point timeframe:

From start of study treatment up to 36 months (end of extension phase)

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	287[23]			
Units: subjects				
None	134			
Mild	116			
Moderate	34			
Severe	3			

Notes:

[23] - FAS with evaluable subjects for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation Rates by Reason and Year

End point title	Discontinuation Rates by Reason and Year

End point description:

The discontinuation rate was calculated from the number of subjects with an expulsion, plus those who had LCS12 removed due to partial expulsion or perforation, plus those who discontinued study treatment for other reasons. The discontinuation rate was classified yearly (Year [Y] 1, Y2 and Y3) for below reasons - Any reason, any adverse event, LCS expulsion, bleeding pattern alterations, increased female genital bleeding, decreased female genital bleeding, and unspecified (unspe) or irregular (irr.) female genital bleeding. In the table below, "n" signifies the number of subjects evaluable at the corresponding time points.

End point type	Secondary

End point timeframe:

From the start of study treatment until the end of extension phase up to 3 years

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	304[24]			
Units: Percentage of subjects				
number (not applicable)				
Y1, Any reason (n=304)	15.8			
Y1, Any adverse event (n=304)	13.2			
Y1, LCS expulsion (n=304)	3.3			
Y1, Bleeding pattern alterations (n=304)	3			
Y1, Increased female genital bleeing (n=304)	2.3			
Y1, Decreased female genital bleeding (n=304)	0			
Y1, Unspe./irr. female genital bleeding (n=304)	2			
Y2, Any reason (n=234)	7.7			
Y2, Any adverse event (n=234)	3.8			
Y2, LCS expulsion (n=234)	1.3			
Y2, Bleeding pattern alterations (n=234)	0.4			
Y2, Increased female genital bleeding (n=234)	0.4			
Y2, Decreased female genital bleeding (n=234)	0			
Y2, Unspe./irr. female genital bleeding (n=234)	0			
Y3, Any reason (n=205)	16.1			
Y3, Any adverse event (n=205)	7.8			
Y3, LCS expulsion (n=205)	1			
Y3, Bleeding pattern alterations (n=205)	4.4			
Y3, Increased female genital bleeding (n=205)	4.4			
Y3, Decreased female genital bleeding (n=205)	0			
Y3, Unspe./irr. femal genital bleeding (n=205)	0			

Notes:

[24] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation Rates by Reason

End point title	Discontinuation Rates by Reason

End point description:

Discontinuation rate was the number and percentage of subjects who discontinued the study drug during the overall period (includes both treatment phase and extension period).

End point type	Secondary

End point timeframe:

Up to 36 months

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	304[25]			
Units: Percentage of subjects				
number (not applicable)				
Any reason	32.6			
Any adverse event	21.4			
LCS expulsion	4.9			
Bleeding pattern alterations	6.3			
Increased female genital bleeding	5.6			
Decreased female genital bleeding	0			
Unspecified or irregular female genital bleeding	0.7			

Notes:

[25] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation Rates by Reason and Parity During 1 Year Treatment Phase

End point title	Discontinuation Rates by Reason and Parity During 1 Year Treatment Phase

End point description:

Discontinuation rate by reason and parity was the number and percentage of subjects who discontinued the study drug during the 1 year treatment phase.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Levonorgestrel (BAY86-5028)			
Subject group type	Reporting group			
Number of subjects analysed	297[26]			
Units: Percentage of subjects				
number (not applicable)				
Nulliparous (NP): Any reason	16.8			
NP: LCS12 expulsion	3.4			
NP: Bleeding pattern alterations	3			
NP: Any adverse event	13.5			
Parous (P): Any reason	14.3			
P: LCS12 expulsion	0			

P: Bleeding pattern alterations	0			
P: Any adverse event	0			

Notes:
[26] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the start of study treatment until the extension phase for up to 3 years	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Levonorgestrel (BAY86-5028)

Reporting group description:

Subjects received levonorgestrel (LNG) intrauterine contraceptive system with an initial in vitro release rate of 12 microgram LNG/day (LCS12) for up to 3 years (the extension phase after 12 months was optional).

Serious adverse events	Levonorgestrel (BAY86-5028)		
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 304 (11.18%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hand fracture			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			

subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cervical vertebral fracture			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Wisdom teeth removal			
subjects affected / exposed	2 / 304 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Allergy prophylaxis			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mammoplasty			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Benign intracranial hypertension			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal			

conditions			
Abortion early			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 304 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Breast enlargement			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic pain			
subjects affected / exposed	2 / 304 (0.66%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Adnexal torsion			

subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Drug dependence			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute psychosis			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 304 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chronic tonsillitis			
subjects affected / exposed	2 / 304 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Endometritis			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal infection			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scarlet fever			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	5 / 304 (1.64%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess jaw			
subjects affected / exposed	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Levonorgestrel (BAY86-5028)		
Total subjects affected by non-serious adverse events subjects affected / exposed	257 / 304 (84.54%)		
Investigations Chlamydia test positive subjects affected / exposed occurrences (all)	10 / 304 (3.29%) 11		
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	41 / 304 (13.49%) 42		
Surgical and medical procedures Wisdom teeth removal subjects affected / exposed occurrences (all)	9 / 304 (2.96%) 11		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all)	40 / 304 (13.16%) 59 7 / 304 (2.30%) 8		
General disorders and administration site conditions Device expulsion subjects affected / exposed occurrences (all)	15 / 304 (4.93%) 15		
Gastrointestinal disorders Abdominal pain lower subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain upper	7 / 304 (2.30%) 9 30 / 304 (9.87%) 36 8 / 304 (2.63%) 8		

subjects affected / exposed	8 / 304 (2.63%)		
occurrences (all)	15		
Nausea			
subjects affected / exposed	15 / 304 (4.93%)		
occurrences (all)	16		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	9 / 304 (2.96%)		
occurrences (all)	9		
Cervical dysplasia			
subjects affected / exposed	7 / 304 (2.30%)		
occurrences (all)	9		
Dysmenorrhoea			
subjects affected / exposed	85 / 304 (27.96%)		
occurrences (all)	111		
Menorrhagia			
subjects affected / exposed	8 / 304 (2.63%)		
occurrences (all)	8		
Ovarian cyst			
subjects affected / exposed	26 / 304 (8.55%)		
occurrences (all)	32		
Pelvic pain			
subjects affected / exposed	63 / 304 (20.72%)		
occurrences (all)	83		
Vaginal discharge			
subjects affected / exposed	7 / 304 (2.30%)		
occurrences (all)	7		
Vaginal haemorrhage			
subjects affected / exposed	19 / 304 (6.25%)		
occurrences (all)	24		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 304 (2.30%)		
occurrences (all)	7		
Oropharyngeal pain			

subjects affected / exposed	13 / 304 (4.28%)		
occurrences (all)	13		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	32 / 304 (10.53%)		
occurrences (all)	35		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 304 (3.95%)		
occurrences (all)	12		
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	9 / 304 (2.96%)		
occurrences (all)	12		
Bacterial vaginosis			
subjects affected / exposed	7 / 304 (2.30%)		
occurrences (all)	9		
Bronchitis			
subjects affected / exposed	13 / 304 (4.28%)		
occurrences (all)	14		
Gastroenteritis			
subjects affected / exposed	14 / 304 (4.61%)		
occurrences (all)	17		
Cystitis			
subjects affected / exposed	30 / 304 (9.87%)		
occurrences (all)	39		
Gastroenteritis viral			
subjects affected / exposed	8 / 304 (2.63%)		
occurrences (all)	8		
Influenza			
subjects affected / exposed	24 / 304 (7.89%)		
occurrences (all)	31		
Sinusitis			
subjects affected / exposed	12 / 304 (3.95%)		
occurrences (all)	20		
Urinary tract infection			

subjects affected / exposed	20 / 304 (6.58%)		
occurrences (all)	31		
Nasopharyngitis			
subjects affected / exposed	46 / 304 (15.13%)		
occurrences (all)	64		
Vaginal infection			
subjects affected / exposed	19 / 304 (6.25%)		
occurrences (all)	25		
Vulvovaginal candidiasis			
subjects affected / exposed	18 / 304 (5.92%)		
occurrences (all)	21		
Vulvovaginal mycotic infection			
subjects affected / exposed	8 / 304 (2.63%)		
occurrences (all)	12		
Chlamydial infection			
subjects affected / exposed	12 / 304 (3.95%)		
occurrences (all)	13		
Vaginitis chlamydial			
subjects affected / exposed	10 / 304 (3.29%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Occurrence of "±" in relation with geometric CV is autogenerated. Decimal places were automatically truncated if last decimal equals zero. SHBG needed for calculation of unbound LNG concentration, so data were not summarized and evaluated.

Notes: