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Multi-center, open-label, uncontrolled study to assess contraceptive efficacy and safety of Mirena during extended use beyond 5 years in women 18 to 35 years of age including a subgroup evaluation of treatment effect on heavy menstrual bleeding

Mirena Extended Trial (MET)

Bayer study drug	Levonorgestrel BAY86-5028 / levonorgestrel-releasing intrauterine system, Mirena		
Study purpose:	Efficacy		
Clinical study phase:	3	**Date:**	10 June 2021
Study No.:	18649	**Version:**	5.0 (supplement, after Year 7 database lock, prior to Year 8 database lock)
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

AE	Adverse event
BPD	Best Practice Document
CI	Confidence interval
eCRF	Electronic Case Report Form
FAS	Full analysis set
HMB	Heavy menstrual bleeding
LLOQ	Lower limit of quantification
LNG	Levonorgestrel
LNG IUS	Levonorgestrel-releasing intrauterine system
MBL	Menstrual blood loss
MedDRA	Medical Dictionary for Regulatory Activities
M&S	Modeling & Simulation
PAS	Primary analysis set
PD	Protocol deviation
PI	Pearl index
PID	Pelvic inflammatory disease
PK	Pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SHBG	Sex hormone binding globulin
SOC	System organ class
TVUS	Transvaginal ultrasound
WHO	World Health Organization

1. Introduction

Mirena, a levonorgestrel-releasing intrauterine system (LNG IUS; initial in vitro release rate 20 µg LNG / day), has been proven a safe and reliable method of contraception over the 5 years of labeled use. It has been on the market since the mid-1990s in most European countries and since 2001 in the US.

This study will evaluate the contraceptive efficacy of Mirena during extended use for up to 8 years. The stability of the effect on heavy menstrual bleeding (HMB) during extended use will be studied in a subgroup of women for whom Mirena was prescribed for HMB (as a secondary indication to contraception).

The Statistical Analysis Plan (SAP) is based on the Integrated Protocol v2.0 (dated 20 SEP 2017), and describes the analysis planned after Year 6, the analysis planned after Year 7 and the final analysis after 8 years of extended use of Mirena. Further details about the analysis planned after Year 6 and Year 7, respectively, are given in Section 4.6.

The SAP v3.0 (supplement) describes post-hoc analyses planned after the Year 6 database lock. The SAP v4.0 (supplement) describes clarifications/corrections and additions, introduced prior to Year 7 database lock. All changes/additions are summarized in the document history in Section 7.

2. Study Objectives

Primary objective of the study is to assess the contraceptive efficacy of Mirena beyond 5 years and up to 8 years of use.

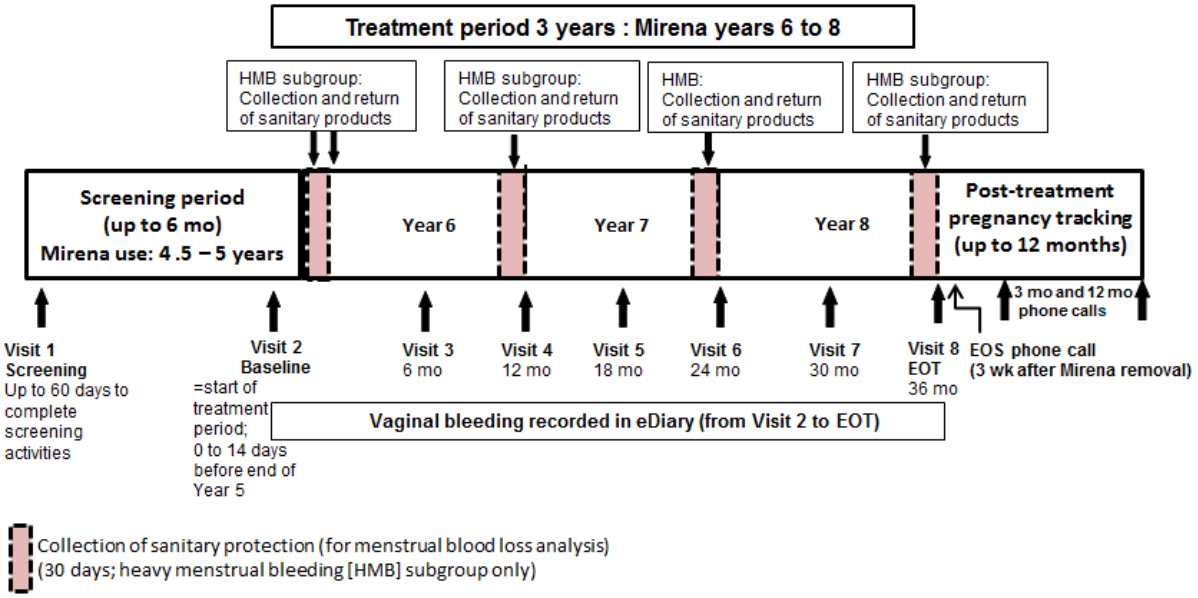
Secondary objectives for the study are the assessment of menstrual blood loss (in women that had Mirena inserted for the indication HMB) and safety.

Further objectives are the population pharmacokinetic evaluation of LNG plasma concentration data and evaluation of user satisfaction.

3. Study Design

This is a multi-center, open-label, uncontrolled, single group study to be conducted in the US only. Study design is presented below in Figure 3–1.

Figure 3–1 Overview of the Study Design



The target for the total number of women to be included in the extended treatment period is 360 women (200 women to complete study treatment). To evaluate the effect of extended Mirena use on HMB, it is targeted that 10% of the women to be treated (i.e. 36 women out of 360) should have Mirena prescribed for the treatment of HMB in addition to contraception. Please note subjects who have Mirena prescribed for contraception and HMB will have to consent to the HMB subgroup procedures.

The study will consist of a screening, treatment, and a follow-up period. Screening can be started when the subject has had the Mirena in place for 4 years and 6 months. Screening activities should be completed within 60 days after signed informed consent to allow enough time for the evaluation of the subjects' eligibility to the study. Baseline visit (Visit 2) will be scheduled to take place 0 to 14 days before the end of Year 5 of Mirena use; and this is the start of the 'treatment period'. The 'treatment period' is defined as the 3-year period following the baseline visit, whereas the 'extension treatment period' is defined as the 3-year period following Day 1 of Year 6 of Mirena use, i.e. Years 6, 7 and 8 of extended use of Mirena (refer to Section 4.1.1 for further details).

Analyses of the efficacy and safety data will be conducted after all subjects have either completed 6 and 7 years of treatment, respectively, or prematurely terminated their study participation before this time point.

Final analysis will be done after all subjects have either completed 8 years of treatment or prematurely terminated their study participation.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Mean, standard deviation, quartiles and median will be presented with one more decimal place than raw data; minimum and maximum will be presented with the same number of decimal places like raw data. Frequency tables will be generated for categorical data.

Summary tables on disposition and demographics will be displayed with three columns:

- Subjects in HMB subgroup, i.e. indication “Contraception and HMB”
- Subjects not in HMB subgroup, i.e. indication “Contraception”
- Total subjects

Summary tables on study drug administration, efficacy, safety and pharmacokinetics will be displayed with one column:

- Total subjects

4.1.1 ‘Treatment Period’ versus ‘Extension Treatment Period”

In order to allow some flexibility, the baseline visit is planned to take place 0 to 14 days before the end of Year 5 of Mirena use (see Integrated Protocol Table 9–1); and this is the start of the ‘treatment period’. The ‘extension treatment period’ will start at Day 1 of Year 6 of Mirena use. As a consequence of the visit window, it is expected there will be various subjects with this baseline visit taking place prior to the start of the ‘extension treatment period’. Please also refer to Section 4.7.

The following variables, collected on an ongoing basis, will primarily be analyzed for the ‘extension treatment period’ starting at Day 1 of Year 6 of Mirena use, i.e., data collected between the baseline visit and Day 1 of Year 6 of Mirena use will be excluded:

- Primary efficacy variable, i.e. occurrence of pregnancies (Section 6.2.1)
- Main safety variable, i.e. adverse events (Section 6.4.2)
- Uterine bleeding / bleeding pattern (Section 6.4.3)

The following variables, collected at pre-specified visits/timeframes only, will be analyzed per visit (unless otherwise stated):

- Secondary efficacy variable, i.e. menstrual blood loss (Section 6.2.2)
- Other safety variables, not listed above (Sections 6.4.4, 6.4.5, 6.4.6)
- Other variables (Section 6.4.6.6)

4.2 Handling of Dropouts

Depending on the time point of withdrawal, a withdrawn subject is referred to as either a "screening failure" or "dropout". A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been deemed eligible to participate and has completed the baseline visit. A subject who terminates the study before completion of the baseline visit is regarded a "screening failure".

Dropouts are not to be replaced.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form (CRF) and the Bleeding Diary, respectively.

Date Mirena last known in situ (as defined in Section 4.7)

- If the day of the month of the date when Mirena threads were visible is missing, it will be imputed as the 15th of that month.
- If the date when Mirena threads were visible is missing (after possible imputation of a missing day), the date of Day 1 Year 6 will be used instead.
- If the day of the month of the date when Mirena location was found to be "In situ" or "Displaced, intrauterine" is missing, it will be imputed as the 15th of that month.
- If the date when Mirena location was found to be "In situ" or "Displaced, intrauterine" is missing (after possible imputation of a missing day), the date of Day 1 Year 6 will be used instead.

Stop date of study drug administration (as defined in Section 4.7)

- If the day of the month of the Mirena expulsion/removal date is missing and the subject was ***not*** pregnant during the extension treatment period, it will be imputed as the 15th of that month of Mirena expulsion/removal.
- If the day of the month of the Mirena expulsion/removal date is missing and the subject ***was*** pregnant during the extension treatment period, it will be imputed as follows:
    - If the subject was confirmed to be pregnant during that month (i.e. estimated date of conception during that month), the day of Mirena expulsion/removal will be imputed by the estimated day of conception.
    - If the subject was confirmed to be pregnant prior to that month (i.e. estimated date of conception prior to that month), the day of the Mirena expulsion/removal will be imputed by the first of that month of Mirena expulsion/removal.

- If the subject was confirmed to be pregnant after that month (i.e. estimated date of conception after that month), the day of the Mirena expulsion/removal will be imputed by the last of that month of Mirena expulsion/removal.

- If the Mirena expulsion/removal date is missing (after possible imputation of a missing day), the 'date Mirena last known in situ' will be used instead.

eDiary data

Missing bleeding diary data will be imputed following the sponsor's Best Practice Document (BPD) on "Recording and Evaluation of Bleeding Data" (RD-SOP-1107) (1) and as described in Section 4.4, respectively.

Adverse event (AE) data

The onset date of AEs is needed to distinguish treatment-emergent and pretreatment AEs. If the day of the month is missing, the last day of that month will be used for the derivations of the treatment emergent flag. If both day and month are missing December 31st will be used. Using this approach, AEs will always considered to be treatment emergent unless this can be ruled out.

Furthermore, the onset date of AEs is needed to distinguish between AEs in 6th / 7th / 8th year. If the day of the month is missing, the 15th of that month will be used for calculation of the year of onset. If both day and month are missing, July 1st will be used. If an upper or lower bound for the date is available (e.g. Day 1 Year 6), this date will be taken into account.

Pregnancy data: Pearl index (PI) calculation and cumulative failure rate

- Partially missing conception dates will be imputed by the minimum approach, i.e. the first possible on-treatment date (Day 1 Year 6) will be used.
- If the day of the month of the Mirena expulsion/ removal date is missing, it will be imputed as the 15th of that month.
- If the Mirena expulsion/ removal date is missing (after possible imputation of a missing day), the 'date Mirena last known in situ' will be used instead.

Time to expulsion/ perforation/ non-compliance

- If the day of the month of the date of expulsion/ perforation/ non-compliance is missing, it will be imputed as the 15th of that month.
- If the date of expulsion/ perforation/ non-compliance is missing (after possible imputation of a missing day), the 'date Mirena last known in situ' will be used instead.

Time to premature discontinuation

- If the day of the month of the date of premature discontinuation of study treatment is missing, it will be imputed as the 15th of that month.
- If the date of premature discontinuation of study treatment is missing (after possible imputation of a missing day), the date of the subject's last scheduled or unscheduled visit prior to the end of treatment visit will be used.

4.4 Handling of Missing Bleeding Intensities and Censored eDiaries

Uterine bleeding data will be handled according to the sponsor's BPD "Recording and evaluation of bleeding data" (RD-SOP-1107) (1).

Up to two consecutive days of missing bleeding intensities will be replaced using a worst case approach during the evaluations. That is, the missing bleeding intensity will be replaced by the maximum of the bleeding intensities of the day before and the day after the missing day(s). If three or more consecutive days are missing bleeding intensities, the entire reference period is to be considered invalid/missing for the analyses.

Up to five days of missing bleeding intensities per 90-days reference period will be replaced. If more than five days are missing bleeding intensities, the entire 90-days reference period is to be considered invalid/missing for the analyses.

Up to two days of missing bleeding intensities per 28-days reference period will be replaced. If more than two days are missing bleeding intensities, the entire 28-days reference period is to be considered invalid/missing for the analyses.

A diary that ends before the end of the reference period will still be evaluated if it is at least two thirds of the length of the reference period. The bleeding pattern indices incorporating the length of an event, such as mean length of the bleeding episodes, will be calculated as for a complete diary. However, the bleeding pattern indices incorporating the number of days or the number of events will be corrected in order to account for the shorter length of the diary. The correction factor is the length of the reference period divided by the length of the diary. For example, 15 days of bleeding recorded in the diary that was kept 75 days instead of the 90 days of the entire reference period will be adjusted to $15 \times (90 / 75) = 18$ days. This rule assumes that the observed average number of bleeding days (15 / 75) stays constant in the reference period ($15 / 75 = 18 / 90$).

4.5 Handling of Censored and Missing Menstrual Blood Loss (MBL) Data

Subjects in the HMB subgroup will collect their used sanitary products during 4 periods of 30 days as described in Integrated Protocol Section 9.1 and Integrated Protocol Table 9–2, i.e. for the following study days:

- beginning of Year 6, i.e. 30 days after baseline visit = study days 2-31
- end of Year 6, i.e. 30 days prior to Visit 4 (-14 days) = study days 322-351
- end of Year 7, i.e. 30 days prior to Visit 6 (-14 days) = study days 687-716
- end of Year 8, i.e. 30 days prior to Visit 8 (-14 days) = study days 1052-1081

MBL data will be available per HMB subject per collection period per day per sanitary product.

The cumulative volume of MBL will be calculated per HMB subject per analysis period (as described in Section 6.2.2) which is the basis for the secondary efficacy variables.

Since MBL is related to the bleeding intensity (which is recorded by the subject on a daily basis in the eDiary):

- missing bleeding intensity data will be imputed using the same approach described in Section 4.4, but imputations will be based on the 30-day collection period for MBL data (i.e. bleeding diary data prior to the 'extension treatment period' will be included, for subjects who had their baseline visit prior to the start of the 'extension treatment period')
- missing MBL data will be imputed depending on the subject's daily (imputed) bleeding intensity, as described in the following paragraphs.

Different types of (complete/ incomplete/ missing) MBL data are expected in a 30-day collection period, [redacted]

Statistical Analysis Plan (Supplement)

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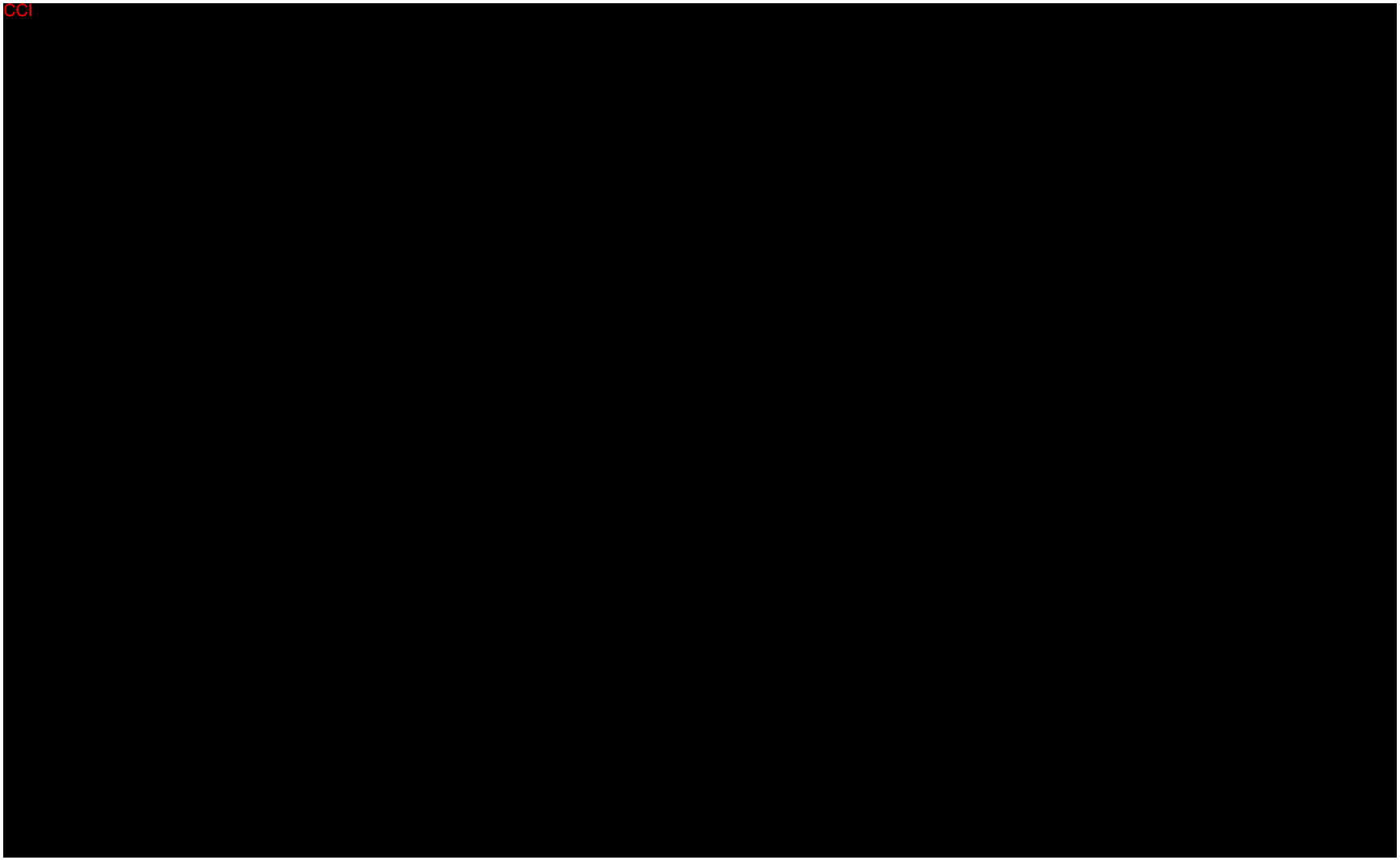


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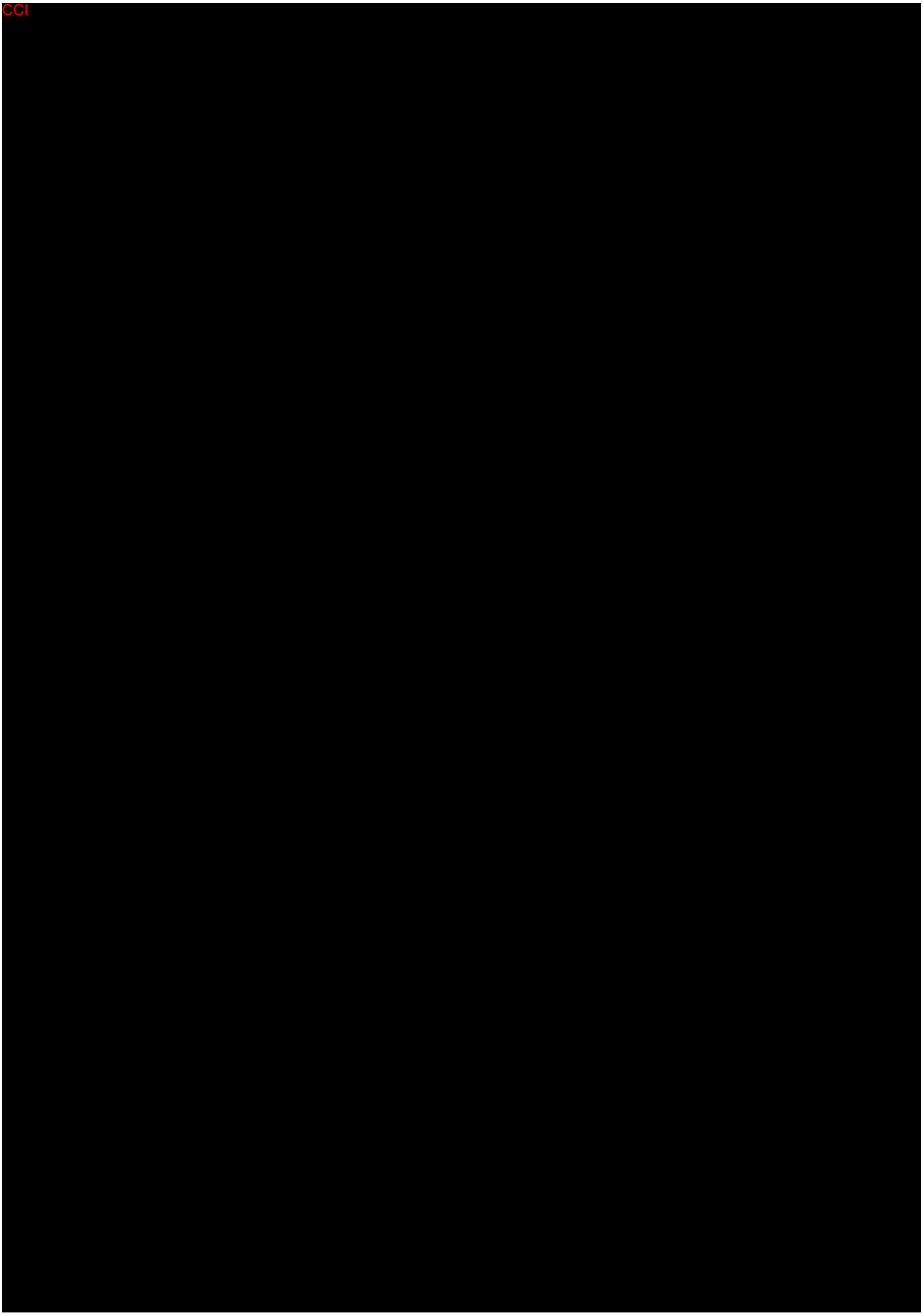
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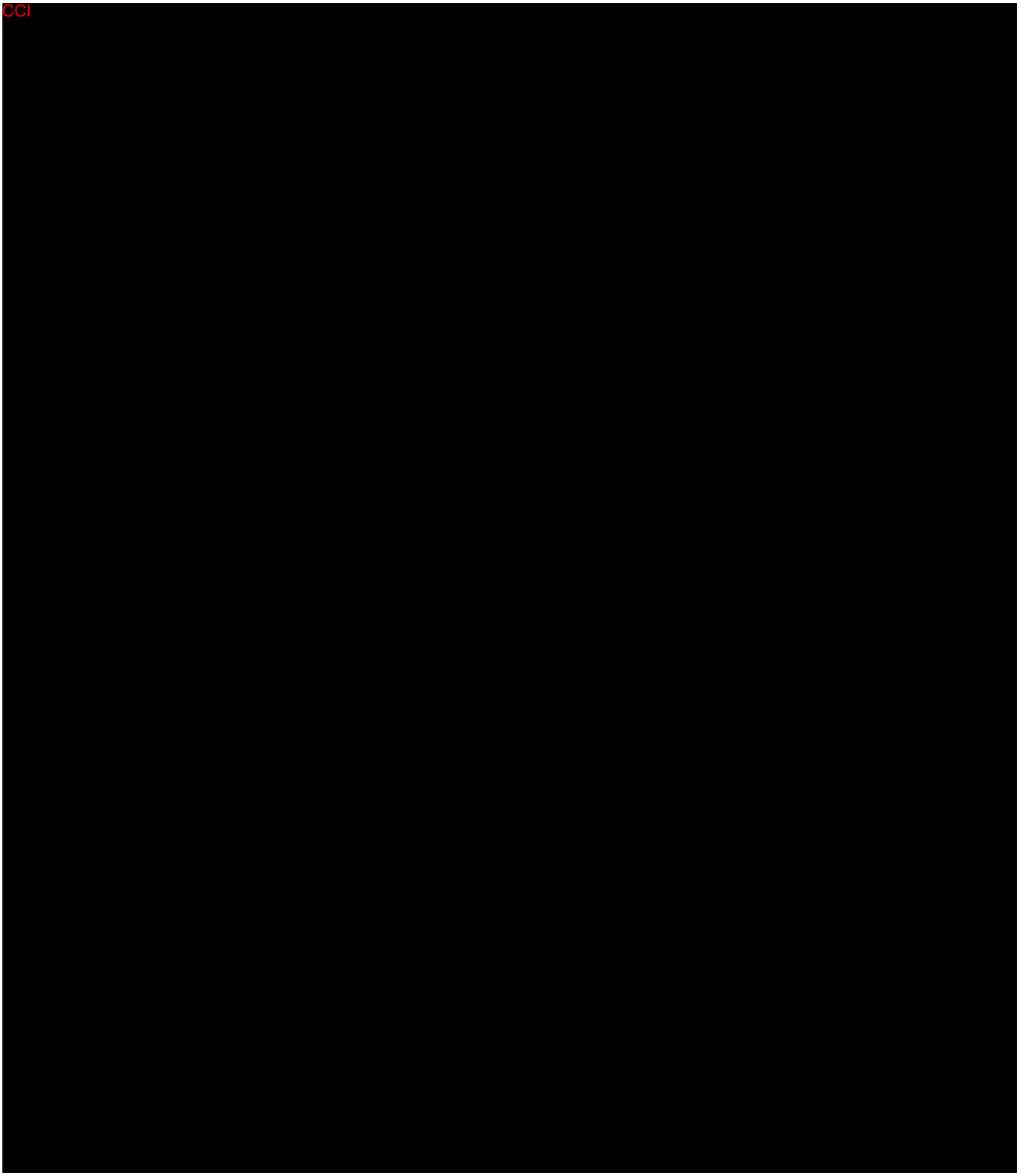


4.6 Interim Analyses and Data Monitoring

No formal interim analysis in the sense of a group sequential or adaptive design is planned. However, an analysis of the data is planned after Year 6, i.e. after all subjects have prematurely discontinued or completed Visit 4, i.e. treated with Mirena for up to 6 years (1 year in the study). Another analysis of the data is planned after Year 7, i.e. after all subjects have prematurely discontinued or completed Visit 6, i.e. treated with Mirena for up to 7 years (2 years in the study). These will cover the full set of analyses as described in the SAP on hand, unless otherwise stated.

For the analysis after Year 6, cumulative data will be used up to the end of Year 6; each subject's data will be cut-off after she has completed Visit 4 or prematurely discontinued (whichever occurs first). For the analysis after Year 7, cumulative data will be used up to the end of Year 7; each subject's data will be cut-off after she has completed Visit 6 or prematurely discontinued (whichever occurs first). Subjects who have completed Visit 4 and Visit 6, respectively, still wearing the Mirena will be considered ongoing subjects.

4.7 Data Rules

Start date of 'treatment period'

The date of baseline visit will be considered the start date of the 'treatment period', i.e. study day 1.

Start date of study drug administration, i.e. start date of 'extension treatment period'

Day 1 of Year 6 of Mirena use will be considered the start date of study drug administration.

Date Mirena last known in situ

The 'date Mirena last known in situ' is referred to in Integrated Protocol Section 10.3.2.1 and Integrated Protocol Table 10–1 and is needed to calculate the crude exposure time for PI calculation for subjects who were lost to follow-up (e.g. because the woman withdrew consent, was lost to follow-up, or died) and for ongoing subjects (during the analyses after Year 6 and Year 7).

The 'date Mirena last known in situ' will be the latest date when the subject was found to be compliant with Mirena, before the first occurrence of non-compliance (if any). Compliance/non-compliance is described in Section 6.1.3.5 and Integrated Protocol Section 9.6.3.8.

Therefore, the 'date Mirena last known in situ' will be the latest of the following:

- Last date (before the first occurrence of non-compliance, if any) when Mirena threads were visible
- Last date (before the first occurrence of non-compliance, if any) when Mirena location was found to be "In situ" or "Displaced, intrauterine"

If any of these dates is missing or partial, it will be imputed individually as described in Section 4.3.

Stop date of study drug administration

If the Mirena was totally expelled or removed during the study, the stop date of study drug administration will be the date of Mirena expulsion or removal.

If the Mirena was not totally expelled or removed during the study (e.g. because the woman withdrew consent, was lost to follow-up, or died), the stop date of study drug administration will be the 'date Mirena last known in situ'.

For ongoing subjects (during the analyses after Year 6 and Year 7), the stop date of study drug administration will be the 'date Mirena last known in situ'.

Woman-years

One woman-year will comprise 365 days of study treatment exposure, unless otherwise stated.

Treatment-emergent AEs

The onset date of AEs will be used to distinguish between treatment-emergent and pre-treatment AEs. If an event occurred on Day 1 of Year 6 of Mirena use or later, it will be considered as treatment-emergent AE. Otherwise, it will be considered as pre-treatment AE.

AEs in 6th / 7th / 8th year

The onset date of treatment-emergent AEs will be used to distinguish between AEs in 6th, 7th and 8th year:

- If [Day 1 Year 6 ≤ onset date ≤ Day 1 Year 6 + 364 days], it will be considered an AE in 6th year
- If [Day 1 Year 6 + 365 days ≤ onset date ≤ Day 1 Year 6 + 729 days], it will be considered an AE in 7th year
- If [Day 1 Year 6 + 730 days ≤ onset date], it will be considered an AE in 8th year (including any AE which may fall into the beginning of Year 9)

Mapping of selected assessments to regular study visits

For subjects who discontinued study treatment prematurely at the timing of one of their regular study treatment visits (i.e. Visits 3, 4, 5, 6 or 7), data will be recorded on the electronic case report form (eCRF) in the End of Treatment (EOT) folder (i.e. EOT / Visit 8).

For the statistical analysis selected assessments will be mapped to regular study treatment visits as described in the following paragraphs, in order to ensure meaningful presentation of information on a visit level, e.g. in summary tables by visit.

The following assessments will be mapped:

- Vital signs
- Checking of Mirena threads
- Pregnancy test
- Urine Sample Collection for Central Lab
- Blood Sample Collection for Central Lab
- Assessment of laboratory results
- Pharmacokinetic (PK) Sample Collection (single sample – blood)
- Continuing Need for Contraception
- Subject satisfaction with Mirena

If study treatment was discontinued prematurely and the EOT visit was performed at the timing of a regular study visit and data were recorded on the eCRF in the EOT folder (i.e. EOT / Visit 8) but not in the regular study visits folder, then assessments will be mapped as follows:

- If EOT visit performed at the timing of Visit 3 / Month 6 (i.e. EOT visit date = study day 183±14 days), then mapping to regular study treatment Visit 3
- If EOT visit performed at the timing of Visit 4 / Month 12 (i.e. EOT visit date = study day 365±14 days), then mapping to regular study treatment Visit 4
- If EOT visit performed at the timing of Visit 5 / Month 18 (i.e. EOT visit date = study day 548±14 days), then mapping to regular study treatment Visit 5
- If EOT visit performed at the timing of Visit 6 / Month 24 (i.e. EOT visit date = study day 730±14 days), then mapping to regular study treatment Visit 6
- If EOT visit performed at the timing of Visit 7 / Month 30 (i.e. EOT visit date = study day 913±14 days), then mapping to regular study treatment Visit 7
- If EOT visit performed at the timing of Visit 8 / Month 36 (i.e. EOT visit date = study day 1095±14 days), then mapping to regular study treatment Visit 8

If study treatment was discontinued prematurely and the EOT visit was performed ***not*** at the timing of a regular study visit and data were recorded on the eCRF in the EOT folder (i.e. EOT / Visit 8), then assessments will be mapped to Visit "End of Treatment".

For subjects who completed study treatment, data will be recorded on the eCRF in the EOT folder (i.e. EOT / Visit 8) and mapped to regular study treatment Visit 8.

Presentation of assessments/results in by-visit summary tables

In subject data listings, assessments/results from both scheduled and unscheduled visits will be presented. In summary tables, only assessments/results from scheduled visits will be presented.

Safety laboratory parameters

If the measured value is below the lower limit of quantification (LLOQ), half the value of LLOQ will be used in summary tables. A difference between two values below LLOQ will be assigned a value of zero.

4.8 Data Review

Protocol deviations (PDs) will be assessed following the CRO's processes. PDs will be reviewed, classified and documented as important or non-important PDs periodically, after Year 6 (prior to first interim database lock), after Year 7 (prior to second interim database lock) and at the end of the study (prior to final database lock). Assignment of subjects to analysis sets will be documented. Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an SAP amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of study data and documented (see Section 4.8).

The following statistical analysis sets will be defined:

Full analysis set (FAS):

All women who completed the baseline visit of the study

Primary analysis set Year 6 (PAS Year 6):

All women in the FAS with an age of 35 years or younger at baseline visit (i.e., an age of 36 or younger at end of Year 6)

Primary analysis set Year 7 (PAS Year 7):

All women in the FAS with an age of 34 years or younger at baseline visit (i.e., an age of 36 or younger at end of Year 7)

Primary analysis set Year 8 (PAS Year 8):

All women in the FAS with an age of 33 years or younger at baseline visit (i.e., an age of 36 or younger at end of Year 8)

The age at baseline (required for PAS Year 6, PAS Year 7 and PAS Year 8) will be used as recorded at baseline (Visit 2). If the age at baseline was not recorded, it will be calculated as the difference between year of baseline visit and year of birth recorded at screening visit.

Safety analysis set (SAF):

The SAF is identical with the FAS, i.e. all women who completed the baseline visit of the study.

6. Statistical Methodology

6.1 Population characteristics

6.1.1 Disposition

Subject disposition will be summarized by descriptive statistics:

- End of screening period (including primary/underlying reason for premature discontinuation)
- Subjects included in PAS Year 6, PAS Year 7 and PAS Year 8, respectively, and in the FAS and SAF
- Inclusion and exclusion criteria

- Important PDs
- End of treatment period (including primary/underlying reason for premature discontinuation)

6.1.2 Demographics

Analyses of demographics will be performed based on the PAS Year 6 (for the analysis after Year 6), PAS Year 7 (for the analysis after Year 7) and the PAS Year 8 (for the final analysis after 8 years), respectively. Furthermore, these analyses will be repeated for the FAS.

6.1.2.1 Baseline characteristics

Baseline characteristics will be summarized by descriptive statistics:

- Demographics
    - Age at baseline
    - Ethnicity
    - Race
    - Height
    - Weight
    - BMI
- Baseline characteristics
    - Educational level
    - Tobacco consumption
    - Alcohol consumption

6.1.2.2 Medical, reproductive and menstrual history

Medical, reproductive and menstrual history will be summarized by descriptive statistics:

- Medical history (displayed by Medical Dictionary for Regulatory Activities [MedDRA] system organ class [SOC], high level term and preferred term [PT])
- Reproductive and menstrual history
    - Age at menarche
    - Number of pregnancies
    - Number of ectopic pregnancies
    - Number of births

- Number of vaginal births
- Number of caesarean births
- Duration from last birth or induced/spontaneous abortion to insertion
- Absence of menstrual/withdrawal bleeding (during last 3 months)
- Intracyclic bleeding (during last 3 months)
- Average length of cycle

6.1.2.3 Previous and concomitant medications

All concomitant medications taken during the study (i.e. starting with the date of informed consent) as well as the extended use of Mirena (i.e. the study drug) with its date of insertion and indication at the time of insertion (contraception, or contraception plus HMB), will be recorded on the eCRF.

The extended use of Mirena (i.e. the study drug) will be summarized as described in Section 6.1.3, whereas all concomitant medications taken during the study (excluding the extended use of Mirena) will be summarized by World Health Organization (WHO) Drug Dictionary substance name.

6.1.3 Study drug administration and compliance

As described in Integrated Protocol Section 7.1, no study drug (Mirena) will be provided by the sponsor. Subjects will enter the 'treatment period' (starting at baseline visit) and the 'extension treatment period' (starting at Day 1 Year 6), respectively, wearing a Mirena that was inserted 5 years earlier and will continue its use for an additional 3 years, i.e. up to a total of 8 years.

6.1.3.1 Insertion procedure

The original indication for Mirena insertion (contraception, or contraception plus HMB) will be summarized descriptively.

The duration since Mirena insertion (at baseline visit) will be calculated as the difference between the Mirena insertion date and the baseline visit date.

For subjects with Mirena insertion on Feb 29th, 2012 or earlier, two leap years of 366 days will be considered between 2012 and 2017, i.e. duration since Mirena insertion will be calculated as:
(date of baseline visit – date of Mirena insertion) / [(366×2+365×3) / 5].

For subjects with Mirena insertion after Feb 29th, 2012, one leap year of 366 days will be considered between 2012 and 2017, i.e. duration since Mirena insertion will be calculated as:
(date of baseline visit – date of Mirena insertion) / [(366×1+365×4) / 5].

The duration of Mirena use since its insertion (at baseline visit) will be summarized descriptively as a continuous variable as well as a categorical variable:

- < 5 years minus 2 weeks
- 5 years minus 2 weeks, to 5 years
- > 5 years

6.1.3.2 Removal procedure

The ease of and pain during Mirena removal will be analyzed as described in Section 6.5.2.

6.1.3.3 Expulsion rates

As described in Integrated Protocol Section 9.6.3.9, total or partial expulsion of the Mirena must be reported as an AE. Furthermore, expulsions must be recorded on the eCRF page "Intrauterine System Removal" as "Totally expelled" and "Partially expelled and removed", respectively.

The number of subjects with expulsion (at least partial, or total) of the Mirena during the 'extension treatment period' (starting at Day 1 Year 6) will be summarized in a frequency table, overall and byparity, BMI, race and ethnicity.

The time from Day 1 Year 6 to expulsion will be analyzed using the Kaplan-Meier estimator. If no expulsion occurred in a subject, this will be considered a censored observation and the stop date of study drug administration (as defined in Section 4.7) will be used as censoring date.

The estimated proportion of subjects with expulsion of the Mirena will be reported for the time points 6 months (5.5 years of Mirena use), 12 months (6 years of Mirena use), 18 months (6.5 years of Mirena use), 24 months (7 years of Mirena use), 30 months (7.5 years of Mirena use), and 36 months (8 years of Mirena use). The cumulative proportion will be estimated.

All subjects with partial or total expulsion of the Mirena will be listed. The listing will contain the parity status and the time in days after Day 1 Year 6 when the expulsion was discovered.

6.1.3.4 Discontinuation rates

The number of subjects who discontinued study treatment prematurely during the 'extension treatment period' (starting at Day 1 Year 6) as well as the primary/ underlying reason for premature discontinuation will be summarized in a frequency table, overall and by parity.

The time from Day 1 Year 6 to premature discontinuation will be analyzed using the Kaplan-Meier estimator. If the subject completed the study treatment period, this will be considered a censored observation and the date of Visit 8 / Month 36 will be used as censoring date. If no premature discontinuation of study treatment occurred because the subject is still continuing

in the study, this will be considered a censored observation and the date of the last visit during the treatment period will be used as censoring date.

The estimated proportion of subjects who discontinued study treatment prematurely will be reported for the time points 6 months (5.5 years of Mirena use), 12 months (6 years of Mirena use), 18 months (6.5 years of Mirena use), 24 months (7 years of Mirena use), 30 months (7.5 years of Mirena use), and 36 months (8 years of Mirena use). The cumulative proportion will be estimated.

6.1.3.5 Compliance

The definition of compliance with Mirena is given in Integrated Protocol Section 9.6.3.8.

The number of subjects compliant and non-compliant, respectively, during the 'extension treatment period' (starting at Day 1 Year 6) will be summarized over time in frequency tables, overall and by parity status (no birth vs. at least one birth).

The time from Day 1 Year 6 to (first) non-compliance will be analyzed using the Kaplan-Meier estimator. If no non-compliance occurred in a subject, this will be considered a censored observation and the stop date of study drug administration (as defined in Section 4.7) will be used as censoring date.

The estimated proportion of subjects who are compliant will be reported for the time points 6 months (5.5 years of Mirena use), 12 months (6 years of Mirena use), 18 months (6.5 years of Mirena use), 24 months (7 years of Mirena use), 30 months (7.5 years of Mirena use), and 36 months (8 years of Mirena use). The cumulative proportion will be estimated as well.

The number of subjects in each sub-category will be summarized over time in frequency tables, overall and by parity, as follows:

- Compliant with Mirena
    - Threads visible
    - Threads not visible and transvaginal ultrasound (TVUS) performed => location of Mirena:
        - In situ
        - Displaced, intrauterine
- Non-compliant with Mirena
    - Threads not visible and TVUS performed => location of Mirena:
        - Partially or totally expelled into vagina or cervical canal
        - Cervical perforation
        - Myometrial perforation
        - Migration to the peritoneal cavity

- Absent
- Other

- Threads visible and TVUS performed => location of Mirena:
  - Partially or totally expelled into vagina or cervical canal
  - Cervical perforation
  - Myometrial perforation
  - Migration to the peritoneal cavity
  - Other

6.1.3.6 Extent of exposure

Data rules for derivation of the start and stop dates of study drug administration are described in Section 4.7. Periods of backup contraception use will not be subtracted from the exposure time, unless stated otherwise (refer to Section 6.2.1).

The exposure with extension treatment (i.e. number of woman-years) will be analyzed descriptively, overall, by parity and by age, BMI, race, ethnicity and indication for Mirena use.

Completion status (introduced post-hoc after Year 6 database lock, prior to Year 7 database lock):

In order to show the number of "completers", the completion status of the Month 12 visit (after Year 6 database lock) will be summarized.

Similar analyses will be performed after Year 7 and Year 8 database lock, showing the completion status of the Month 24 and Month 36 visit (after Year 7 and 8 database lock), respectively.

6.2 Efficacy

The primary analysis set will be the PAS Year 6 (for the analysis after Year 6), the PAS Year 7 (for the analysis after Year 7) and the PAS Year 8 (for the final analysis after 8 years), respectively, unless stated otherwise. Analyses will be repeated for the FAS.

6.2.1 Primary efficacy variable

The primary efficacy variable is the occurrence of pregnancy within years 6 through 8 of Mirena use (i.e. '3-year PI', as defined below). However, for the analysis after 6 years of Mirena use, the primary efficacy variable is the occurrence of pregnancy within year 6 of Mirena use (i.e. '1-year PI', as defined below), and for the analysis after Year 7, the primary efficacy variable is the occurrence of pregnancy within years 6 through 7 of Mirena use (i.e. '2-year PI', as defined below).

The PI is defined as the number of pregnancies per 100 woman-years. The Pearl Index will be analyzed for the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use. That means, for subjects who had her baseline visit prior to Day 1 Year 6, exposure and pregnancies between the baseline visit and Day 1 Year 6 will be excluded; for subjects who had their baseline visit after Day 1 Year 6, exposure and pregnancies between Day 1 Year 6 and baseline visit will be included. The following PIs will be calculated:

- '1-year PI (sixth year)', PI obtained in the sixth year of treatment, i.e., number of pregnancies that occurred during the sixth year of treatment divided by time the women were at risk of getting pregnant in the sixth year of treatment.
- '2-year PI (sixth & seventh year)', PI obtained in the sixth and seventh year of treatment, i.e., number of pregnancies that occurred during the sixth and seventh year of treatment divided by time the women were at risk of getting pregnant in the sixth and seventh year of treatment.
- '3-year PI (sixth, seventh & eighth year)', PI obtained in the sixth, seventh and eighth year of treatment, i.e., number of pregnancies that occurred during the sixth, seventh and eighth year of treatment divided by time the women were at risk of getting pregnant in the sixth, seventh and eighth year of treatment.

Furthermore, the following PI will be analyzed for the entire study period starting at baseline visit, i.e., exposure and pregnancies between the baseline visit and Day 1 of Year 6 of Mirena use will be included:

- 'Overall PI', PI obtained during the whole study, i.e., number of pregnancies that occurred during the entire study period starting at baseline visit divided by the time the women were under a risk of getting pregnant.

The exact rules regarding how the crude exposure time will be calculated are given in Integrated Protocol Section 10.3.2.1 and Integrated Protocol Table 10–1 as well as in Table 6–1 below.

Table 6–1: Definition of crude exposure times

PI	Reason for end of study/ continuation status	Crude exposure time
1-year PI (6th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow-up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)
	Continues into 7th year of treatment	365 days
2-year PI (6th and 7th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow-up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)
	Continues into 8th year of treatment	730 days
3-year PI (6th, 7th and 8th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow-up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)
	Continues into 9th year of treatment	Minimum of (1095 days; Date of EOT visit – Date of Day 1 Year 6 +1)
Overall PI	Total expulsion	Date, when expulsion was discovered – Baseline visit date +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Baseline visit date +1
	Pregnancy	Date of conception – Baseline visit date +1
	Lost to Follow-up	Maximum of (Date Mirena last known in situ – Baseline visit date +1; 1 day)
	Continued until EOT	Date of EOT visit – Baseline visit date +1

PI=Pearl Index; EOT=End of treatment

A pregnancy will be allocated to the time period(s) that are relevant for the calculation of the PIs described above, e.g., a pregnancy that occurs on day 400 will be relevant for the 7th year PI, the 2-year PI (6th & 7th year), the 3-year PI (6th, 7th & 8th year), and the overall PI. Pregnancies that occur before Day 1 Year 6 of Mirena use will not count for the 1-year PI, 2-year PI and 3-year PI. Pregnancies that occur after the Mirena was removed or an expulsion was discovered will not count for any PI calculation.

It should be noted that pregnancies that occur within 7 days after the end of exposure will count for the PI calculations.

Furthermore, it should be noted that pregnancies that occur after partial expulsion or first occurrence of non-compliance but before Mirena removal will count for the PI calculations.

Exposure times to be subtracted for Pearl index analyses:

Subjects who apply backup contraception are not at risk or are at lower risk of getting pregnant than subjects who do not apply backup contraception. In case a subject uses backup contraception (e.g., condoms to prevent sexually transmitted disease), the respective 28-day reference period(s) of backup contraception use will be excluded from the exposure time, unless a pregnancy occurred in that 28-day reference period. In the Pearl index analyses, the first 28-day reference period will start at Day 1 Year 6. Missing data will be considered as no use of backup contraception.

Primary analysis:

The primary method for the evaluation of the occurrence of pregnancy is the PI defined as the number of pregnancies per 100 woman-years.

The PIs and the corresponding 2-sided 95% confidence interval (CI) will be calculated using the model specified below.

Mathematical model for the calculation of the PI:

By assuming that the number of pregnancies follows a Poisson-distribution, the point estimate and the 95% CI for the PI can be calculated as follows:

$PI = x/E,$

lower 95% confidence limit of $PI = 0.5 \times \chi^2_{(0.025,\, 2x)} / E$

upper 95% confidence limit of $PI = 0.5 \times \chi^2_{(0.975,\, 2(x+1))} / E$

where x = number of pregnancies,

E = exposure in 100 woman-years,

$\chi^2_{(alpha,df)}$ is the alpha-quantile from χ^2-distribution with df degrees of freedom.

All PIs described above will also be presented by parity (no births vs. at least one birth), BMI (<30 kg/m² vs. ≥30 kg/m²) and age at insertion (<18 years vs. 18-25 years vs. 26-35 years, and <18 years vs. 18-35 years), age at baseline (18-25 years vs. 26-35 years vs. >35 years, and 18-35 years vs. >35 years), race and ethnicity. The age at insertion will be calculated as: age at baseline (recorded on the eCRF at baseline, Visit 2) minus 5 years.

To assess pregnancies with regard to subgroup combinations, e.g. by age and parity, a listing on all pregnancies providing detailed information regarding subject number, age, parity, date of Mirena insertion, date of baseline visit, date of Day 1 Year 6 of Mirena use, date of Mirena removal, (estimated) date of (partial/total) expulsion, estimated date of conception, location of pregnancy implantation at time of diagnosis, and estimated date of conception relative to Mirena insertion/ relative to Day 1 Year 6 of Mirena use/ relative to stop date of study drug administration will be provided.

Secondary analysis:

In order to fulfill the European guideline EMEA-'Guideline on clinical investigation of steroid contraceptives in women' (EMEA/CPMP/EWP/519/ Rev1, July 2005.) (2), the cumulative failure rate, i.e. the probability of getting pregnant will be calculated using the Kaplan-Meier method in addition to calculation of the different PIs.

Periods of backup contraception use will not be subtracted from the exposure time.

Sensitivity analysis:

The usual assumption for the calculation of the PI is a constant hazard for the event of becoming pregnant over time. As this cannot necessarily be assumed for the study treatment of this study, PIs will be calculated *per year*, as sensitivity analyses.

Similar analyses (PIs and cumulative failure rates) will be provided for ectopic pregnancies.

Sensitivity analysis (introduced post-hoc after Year 6 database lock, prior to Year 7 database lock):

The primary analysis ('1 year PI (sixth year)' after Year 6 database lock based on the PAS Year 6) was conducted using the following rules:

- 1 WY = 365 days
- Complete and incomplete 28-day cycles are used for the exposure calculation (i.e., the days of the last 28-day cycle are used even if incomplete)

A sensitivity analysis will be conducted using the following rules

- 1 WY = 13 28-day cycles (i.e., 364 days)
- Only complete 28-day cycles are used

Similar analyses will be performed after Year 7 and Year 8 database lock, i.e. '2 year PI (sixth and seventh year)' after Year 7 database lock based on the PAS Year 7 and '3 year PI (sixth, seventh and eighth year)' after Year 8 database lock based on the PAS Year 8, respectively. PIs will be also be calculated *per year*, i.e. 'Year 6 PI' and 'Year 7 PI' after Year 7 database lock based on the PAS Year 7 and 'Year 6 PI', 'Year 7 PI' and 'Year 8 PI' after Year 8 database lock based on the PAS Year 8.

As for the primary analysis, pregnancies that occur within 7 days after the end of exposure as well as pregnancies that occur after partial expulsion or first occurrence of non-compliance

but before Mirena removal will count for the PI calculations; 28-day reference period(s) of backup contraception use will be excluded from the exposure time.

Repeated analysis of the primary efficacy variable (introduced prior to Year 8 database lock) for the PAS Year 6 and PAS Year 7 based on the final database after Year 8:

For the analysis after 6 years of Mirena use, the primary efficacy variable was the occurrence of pregnancy within year 6 of Mirena use (i.e. '1-year PI') based on the PAS Year 6, which was analysed based on the interim database after Year 6 and reported in the Year 6 CSR.

For the analysis after 7 years of Mirena use, the primary efficacy variable was the occurrence of pregnancy within years 6 through 7 of Mirena use (i.e. '2-year PI') based on the PAS Year 7, which was analysed based on the interim database after Year 7 and reported in the Year 7 CSR.

These analyses (and the corresponding sensitivity analyses) will be repeated after the final database lock, to provide these results based on the most accurate and complete datasource, i.e. the final database after Year 8:

- For the PAS Year 6, based on the final database after Year 8:
    - '1-year PI' (Year 6)
    - '1-year PI' (Year 6) – based on only complete 28-day cycles
    - '1-year PI' (Year 6) – for ectopic pregnancies
    - '1-year probability of getting pregnant' (Year 6)
    - '1-year probability of getting pregnant' (Year 6) – for ectopic pregnancies
- For the PAS Year 7, based on the final database after Year 8:
    - '2-year PI' (Years 6 and 7) and PIs calculated *per year*, i.e. 'Year 6 PI' and 'Year 7 PI'
    - '2-year PI' (Years 6 and 7) and PIs calculated *per year*, i.e. 'Year 6 PI' and 'Year 7 PI' – based on only complete 28-day cycles
    - '2-year PI' (Years 6 and 7) and PIs calculated *per year*, i.e. 'Year 6 PI' and 'Year 7 PI' – for ectopic pregnancies
    - '2-year probability of getting pregnant' (Years 6 and 7) and probabilities calculated *per year*, i.e. 'Year 6 probability of getting pregnant' and 'Year 7 probability of getting pregnant'
    - '2-year probability of getting pregnant' (Years 6 and 7) and probabilities calculated *per year*, i.e. 'Year 6 probability of getting pregnant' and 'Year 7 probability of getting pregnant' – for ectopic pregnancies

Please note that due to a more accurate and complete exposure in the final database after Year 8 caused by the fact that the study is no longer ongoing but all subjects have completed the study (or discontinued prematurely), minor changes in these PIs and probabilities of getting pregnant (compared to the Year 6 CSR and Year 7 CSR, respectively) are expected.

6.2.2 Secondary efficacy variables

6.2.2.1 Menstrual blood loss

Subjects in the HMB subgroup are requested to collect their used sanitary products during four periods of 30 days each, as described in Integrated Protocol Section 9.1 and Integrated Protocol Table 9–2, i.e. for the following study days:

- beginning of Year 6, i.e. 30 days after baseline visit = study days 2-31
- end of Year 6, i.e. 30 days prior to Visit 4 (-14 days) = study days 322-351
- end of Year 7, i.e. 30 days prior to Visit 6 (-14 days) = study days 687-716
- end of Year 8, i.e. 30 days prior to Visit 8 (-14 days) = study days 1052-1081

MBL data will be available per HMB subject per collection period per day per sanitary product. MBL data from sanitary products collected during these planned 30-day collection periods will be included in the statistical analysis; potential additional MBL data from sanitary products collected outside these planned 30-day collection periods will be excluded from the statistical analysis.

Since MBL is related to the bleeding intensity, missing MBL data during the planned 30-day collection periods will be imputed depending on the subject's daily bleeding intensity recorded in the eDiary, as described in Section 4.5.

The cumulative volume of MBL will be calculated only if a day-wise cumulative MBL (original or imputed value, as described in Section 4.5 and Table 4–1) is available for each day in the planned 30-day collection period (or until the day of premature discontinuation). Otherwise, the collection period will be considered invalid and the cumulative volume of MBL will not be calculated.

If there are less than 20 solid observations in a planned 30-day collection period ("solid" as defined in Section 4.5 and Table 4–1), the collection period will be considered invalid and the cumulative volume of MBL will not be calculated. This rule also applies to HMB subjects who discontinued prematurely during a 30-day collection period, i.e. if there are less than 20 solid observations before the subject discontinued prematurely during a 30-day collection period, the collection period will be considered invalid and the cumulative volume of MBL will not be calculated.

The cumulative volume of MBL will be calculated per HMB subject per analysis period as the sum of MBL values, adjusted for the length of the analysis period (in case of early and/or late collection without gap, and/or in case of premature discontinuation). That means the sum of MBL values will be multiplied by {length of analysis period in units of days divided by 30 days}.

The cumulative volume of MBL at beginning of Year 6, end of Year 6, end of Year 7, and end of Year 8 of Mirena treatment will be presented by descriptive statistics. Furthermore, change from baseline (=beginning of Year 6) will be presented.

The basis for this analysis is the data on MBL assessed by the alkaline hematin method (see Integrated Protocol Section 9.4.2). If a women has sent in no sanitary products and has documented in the eDiary (see Integrated Protocol Section 9.7.1) that no bleeding occurred during one of the considered 30-day time periods for collection of sanitary protection, the MBL will be assumed to be zero in that time period.

This analysis will be conducted in the FAS in the HMB subgroup, i.e. women who had Mirena inserted for both contraception and HMB.

Sensitivity analysis approach #1 of MBL:

As described in Section 4.5, there might be cases when the MBL value remains missing. If such cases occur, a sensitivity analysis will be performed using (imputed) MBL values based on the extended imputation rules given in Section 4.5.

The cumulative volume of MBL will be calculated and summarized similarly as in the above primary analysis approach for MBL.

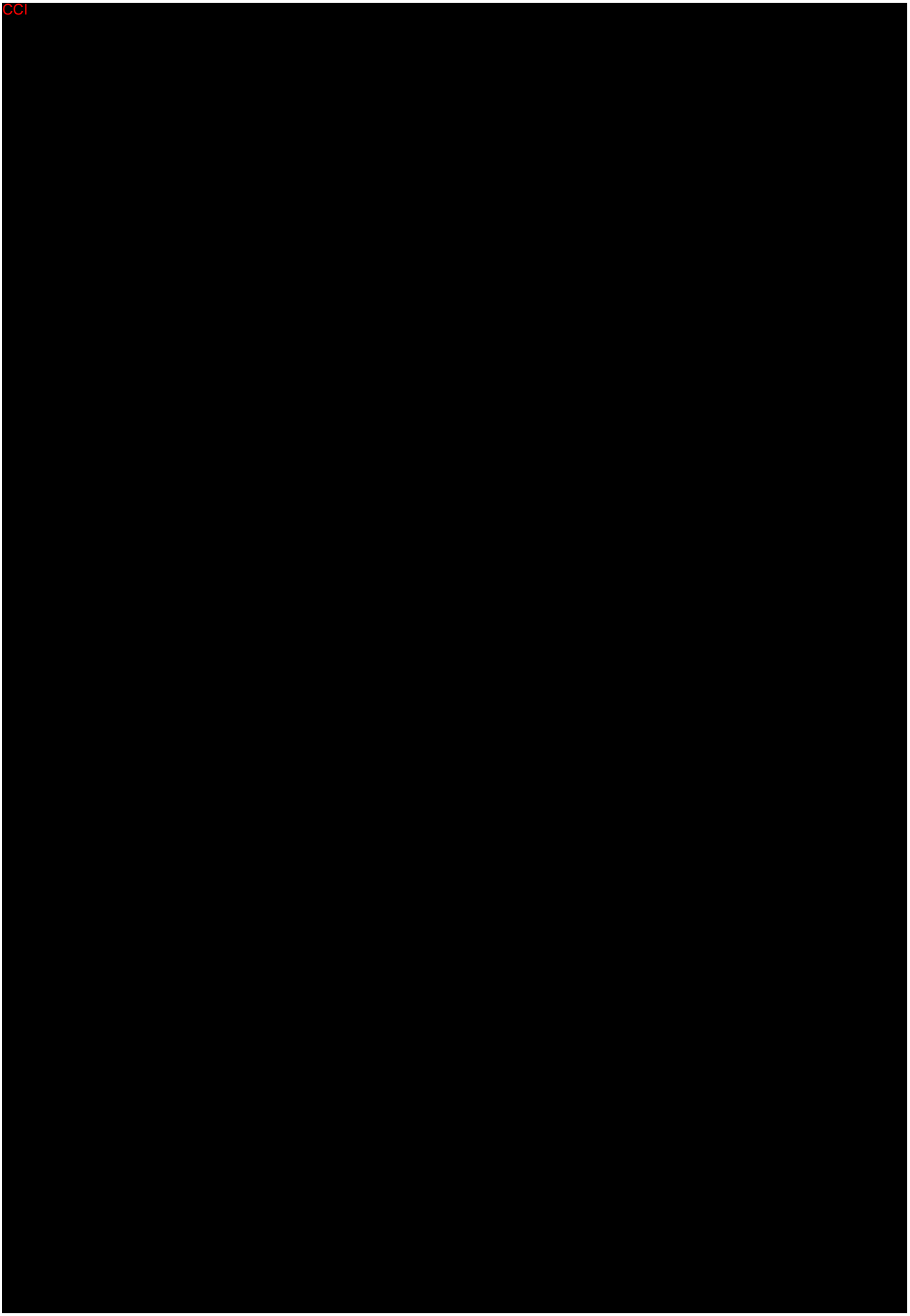
6.2.2.2 Categorized menstrual blood loss (<80 mL / 30 days)

No clinical change in bleeding profile regarding HMB after Year 5 until the end of Year 6, until the end of Year 7 and until the end of Year 8, respectively, will be concluded if the cumulative volume of MBL was < 80mL at the beginning of Year 6 and remained remains <80mL during the end of years 6, 7 and 8, respectively. Vice versa, clinical change in bleeding profile regarding HMB after Year 5 until the end of Year 6, end of Year 7 and end of Year 8, respectively, will be concluded if the volume of blood loss was ≥ 80mL at the beginning of Year 6 or at end of Years 6, 7 or 8, respectively.

Therefore, the proportion of women with clinical change in bleeding profile regarding HMB will be analyzed. Descriptive statistics as well as 95% Clopper-Pearson confidence intervals will be provided.

For the analysis after Year 6, the proportion of women with clinical change in bleeding profile regarding HMB **after Year 5 until the end of Year 6** will be analyzed.

CCI [redacted]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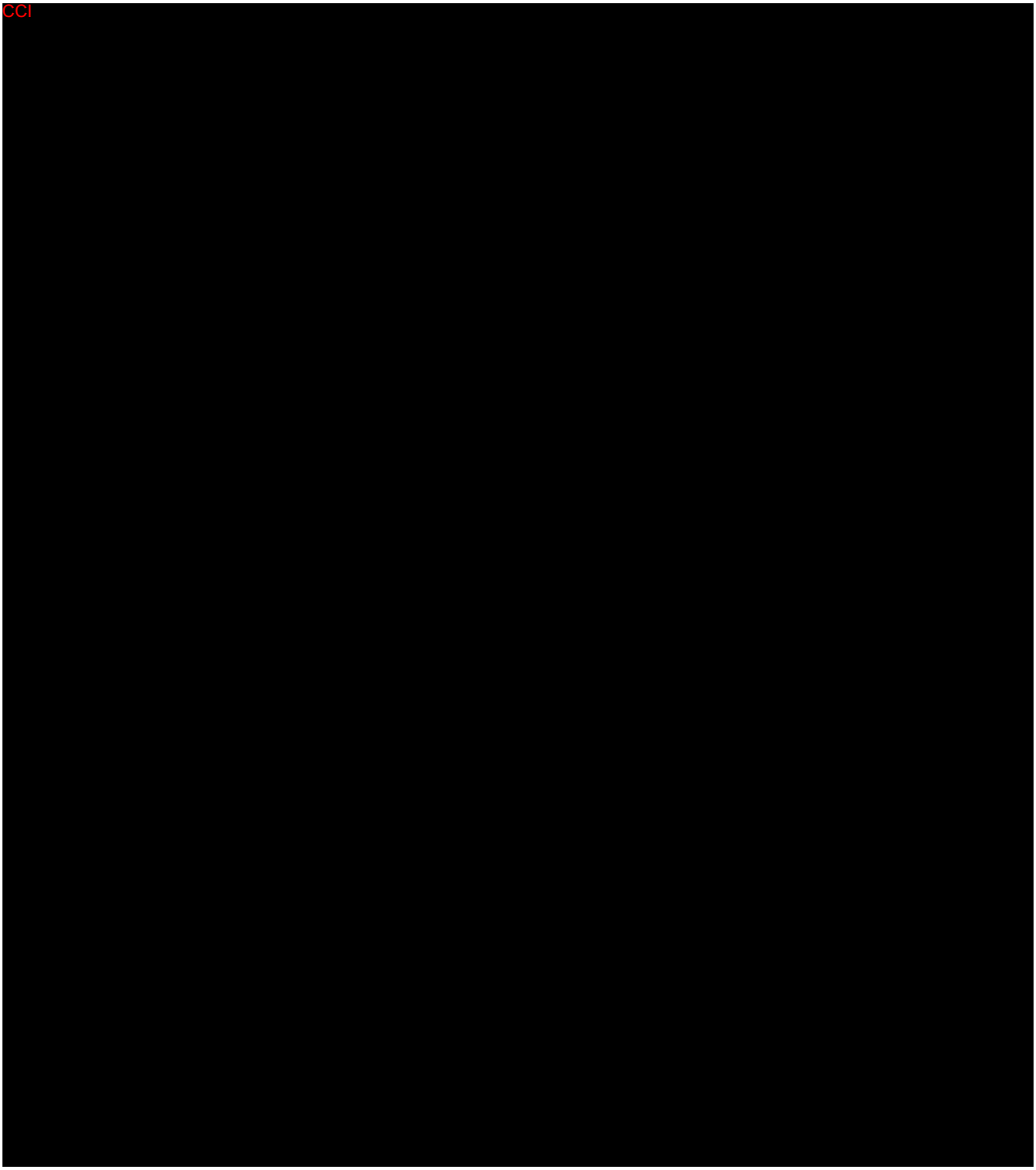

6.3 Pharmacokinetics/pharmacodynamics

6.3.1 Pharmacokinetics

Analyses will be performed based on the FAS.

The following will be determined at several timepoints according to Integrated Protocol Table 9–1:

- LNG concentrations in plasma
- Sex hormone binding globulin (SHBG) concentrations in serum

Data will be analyzed descriptively (including number of measurements, geometric mean with geometric standard deviation and coefficient of variation, arithmetic mean with arithmetic standard deviation and coefficient of variation, minimum, maximum and median) by time point (i.e. Visit 2 to Visit 8). Means at any time point will be calculated only if at least two-thirds of the individual data were measured and were above the LLOQ. For the calculation of the mean value a data point below LLOQ will be imputed by one-half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

The individual PK concentrations will be presented in the subject data listing.

Geometric mean concentration (±geometric standard deviation) curves of LNG and SHBG will be plotted versus time point using a linear and semi-logarithmic scale.

PK concentrations determined after Mirena expulsion/removal will not be included in the descriptive analyses and plots, but only be listed.

Furthermore, the residual content of LNG in used Mirena devices will be determined from all subjects at the end of treatment (i.e. from those who complete the 3 years in the study and from those who discontinue the study treatment prematurely). Data will be listed per subject and time point and individual data will be plotted versus time post baseline using a linear scale.

Residual contents with a partially missing or completely missing date of Mirena expulsion/removal will not be included in the plot, but only be listed.

Population PK analysis will be performed after Year 6, after Year 7 and at the end of study by the Modeling & Simulation (M&S) expert. A separate M&S Analysis Plan will be provided prior to the beginning of the population PK analysis by the M&S expert, including details of the planned model development and analysis. The results will be reported in a separate M&S Report by the M&S expert. A summary of the results will be provided in the Clinical Study Report.

6.3.2 Pharmacodynamics

Not applicable.

6.4 Safety

All safety variables will be analyzed based on the SAF, unless otherwise stated.

The main safety variable is the incidence of treatment-emergent AEs (both serious and non-serious). Treatment-emergent AEs are defined as any AEs occurring during the ‘extension treatment period’ starting at Day 1 of Year 6 of Mirena use. Further data rules are described in Section 4.7.

All AEs will be classified using MedDRA. The latest available version at the time of coding will be used. The results will be summarized on the level of SOC and PT, unless stated otherwise.

6.4.1 Pretreatment adverse events

Pretreatment AEs will be summarized by SOC and PT.

Pretreatment serious AEs (SAEs) will only be listed.

6.4.2 Treatment-emergent adverse events

The following treatment-emergent AEs will be summarized by SOC and PT:

- AEs, by year of occurrence (6th / 7th / 8th year) and overall
- Study-drug related AEs (with causality as assessed by investigator)
- AEs causing discontinuation of study drug
- Study-drug related AEs (with causality as assessed by investigator) causing discontinuation of study drug
- AEs by outcome
- AEs by intensity

The overall summary tables will be displayed by year of occurrence (6th / 7th / 8th year) and overall, whereas AEs will be allocated to the year of occurrence as described in Section 4.7. For the calculation of the percentages by year of occurrence, only the number of subjects that were still under treatment at the beginning of the respective time interval (treatment year) will be used as the denominator.

The following treatment-emergent SAEs will be summarized by SOC and PT:

- SAEs
- Study-drug related SAEs (with causality as assessed by investigator)

6.4.2.1 Perforation rates

As described in Integrated Protocol Section 9.6.3.9, perforation by the Mirena must be reported as an SAE. If a perforation is diagnosed, Mirena must be removed and the subject must discontinue study treatment and the study.

Perforations will be identified from the AEs recorded on the eCRF coded by MedDRA as one of the following:

- Preferred Term “Uterine perforation”
- Preferred Term “Embedded Device”,
- Preferred Term “Fallopian tube perforation”,
- Lowest Level Term “Extrauterine intra-abdominal localisation of IUD”,
- Lowest Level Term “Extrauterine intra-abdominal localization of IUD”,

- Lowest Level Term “IUD migration”,
- Lowest Level Term “Device migration”,
- Lowest Level Term “Device dislocation into abdominal cavity”.

The number of subjects with perforation by the Mirena during the ‘extension treatment period’ (starting at Day 1 Year 6) will be summarized in a frequency table, overall and by parity.

In addition, the time from Day 1 Year 6 to perforation will be analyzed using the Kaplan-Meier estimator. If no perforation occurred in a subject, this is considered a censored observation and the stop date of study drug administration (as defined in Section 4.7) will be used as censoring date.

The estimated proportion of subjects with perforation of the Mirena will be reported for the time points 6 months (5.5 years of Mirena use), 12 months (6 years of Mirena use), 18 months (6.5 years of Mirena use), 24 months (7 years of Mirena use), 30 months (7.5 years of Mirena use), and 36 months (8 years of Mirena use). The cumulative proportion will be estimated as well.

All subjects with perforation by the Mirena will be listed. The listing will contain the parity status as well as the duration from last birth or induced/spontaneous abortion to insertion and the time in days after Day 1 Year 6 when the perforation was discovered.

6.4.2.2 Pelvic inflammatory disease

As described in Integrated Protocol Section 9.6.3.11, any case of pelvic inflammatory disease (PID) will be reported as an AE or SAE on the AE eCRF as well as on the pelvic inflammatory disease eCRF.

PID will be presented as part of the AE summary tables described in Section 6.4.2.

Details recorded on the pelvic inflammatory disease eCRF will be listed only. A diagnosis of PID is made if response to the following questions in the eCRF is a “yes”: “Were the criteria for PID diagnosis met?” and/or “Laparoscopy confirmed PID?”.

6.4.3 Uterine bleeding / bleeding pattern

Recording and evaluation of bleeding data:

The occurrence of uterine bleeding will be recorded every day during the study treatment phase using eDiaries provided by the sponsor. The recording will start at the baseline visit and will be continued daily until Mirena is removed. Subjects are asked to rate their uterine bleeding in the past 24 hours on a daily basis according to the bleeding intensity definitions presented in Integrated Protocol Section 9.6.3.12 and Integrated Protocol Table 9–3.

Uterine bleeding data during the ‘extension treatment period’ starting at Day 1 of Year 6 of Mirena use will be analyzed according to the sponsor’s BPD “Recording and evaluation of bleeding data” (RD-SOP-1107) (1). Bleeding diary data prior to the ‘extension treatment

period' will not be included in the analyses described in this section. That means, for subjects who had her baseline visit prior to Day 1 Year 6, bleeding diary data between the baseline visit and Day 1 Year 6 will be excluded; for subjects who had their baseline visit after Day 1 Year 6, bleeding diary data between Day 1 Year 6 and baseline visit will not be recorded and will be considered as missing data entries. Bleeding diary data after Mirena expulsion/removal will not be included in the statistical analysis. Bleeding diary data after the date of premature discontinuation of study treatment period will not be included in the statistical analysis.

Besides the registration of absolute number of bleeding days, bleeding/spotting episodes will also be assessed according to the sponsor's bleeding intensity codes and the WHO definitions as provided in Integrated Protocol Section 10.3.2.3.2 and Integrated Protocol Table 10–2. This is possible because of the direct eDiary entry.

In addition to the WHO definitions, a "bleeding episode" is defined as day(s) with bleeding / spotting of which at least one day is of intensity 3 or higher, preceded and followed by at least 2 bleed-free days. There are examples given in the sponsor's BPD Section 1.4.1 which illustrate the advantage of this procedure. Another example is given in Integrated Protocol Section 10.3.2.3.2.

The bleeding patterns will be described using the reference period method recommended by the WHO, as given in the sponsor's BPD Section 1.4.3.

Based on daily uterine bleeding data obtained from the eDiary, the bleeding pattern will be reported using reference periods of 28 and 90 days. The first 28-day and 90-day reference period, respectively, will start at Day 1 of Year 6 of Mirena use. For each subject and for each period, the number of bleeding/spotting days and bleeding/spotting episodes will be calculated. If the bleeding intensity is recorded as light, normal or heavy, this will be considered as "bleeding".

Handling of missing bleeding intensities and censored eDiaries:

Details on how to handle missing bleeding intensities and censored eDiaries are given in Section 4.4.

Summary of bleeding pattern indices:

For each subject and for each 28-day reference period and each 90-day reference period, the following bleeding pattern indices will be calculated (compare to sponsor's BPD Section 1.4.3):

- number of subjects with at least one bleeding/spotting day
- number of subjects with at least one bleeding (excluding spotting) day
- number of bleeding / spotting days
- number of bleeding days (excluding spotting-only days)
- number of spotting-only days
- number (mean length, maximal length) of bleeding / spotting episodes
  (will only be calculated for those subjects who have at least 1 bleeding/spotting episode)

- number (mean length, maximal length) of spotting-only episodes
  (will only be calculated for those subjects who have at least 1 spotting-only episode)

Furthermore, for each 90-day reference period the following bleeding indices will be provided according to the WHO criteria:

- number of subjects with amenorrhea, defined as no bleeding/spotting throughout the reference period
- number of subjects with prolonged bleeding, defined as subjects with bleeding/spotting episodes lasting more than 14 days
- number of subjects with frequent bleeding, defined as subjects with more than 5 bleeding/spotting episodes
- number of subjects with infrequent bleeding, defined as subjects with 1 or 2 bleeding/spotting episodes
- number of subjects with irregular bleeding, defined as subjects with 3 to 5 bleeding/spotting episodes and less than 3 bleeding/spotting-free intervals of 14 days or more
- number of subjects with normal bleeding / none of the above

6.4.4 Safety laboratory parameters

Safety laboratory parameters will be summarized by visit using descriptive statistics. If there are multiple observations per subject per scheduled visit, the last observation will be used in summary tables.

6.4.5 Vital signs and body weight

Vital signs and body weight will be summarized by visit using descriptive statistics.

6.4.6 Further safety variables

6.4.6.1 Cervical smear

The results of cervical smear assessment and interpretation will be summarized in frequency tables.

6.4.6.2 Chlamydia test

The results of chlamydia test assessment (chlamydia trachomatis and gonorrhea, if applicable) will be summarized in frequency tables.

6.4.6.3 Gynecological ultrasound

Gynecological ultrasound data will be listed.

6.4.6.4 Pregnancy test

The performance of pregnancy tests as well as the outcome will be presented in frequency tables.

6.4.6.5 Death

Death data will be listed.

6.4.6.6 Post-treatment pregnancy and return-to-fertility tracking

Data on post-treatment pregnancies and return to fertility will be presented in frequency tables and a detailed listing.

6.5 Patient / investigator reported outcomes

Analyses will be performed based on the PAS Year 6 (for the analysis after Year 6), the PAS Year 7 (for the analysis after Year 7) and the PAS Year 8 (for the final analysis after 8 years), respectively. Furthermore, analyses will be repeated for the FAS.

6.5.1 Subject satisfaction with Mirena

The subject's satisfaction with the Mirena on a 5-point scale (very satisfied, somewhat satisfied, neither satisfied or dissatisfied, dissatisfied, very dissatisfied) will be summarized in frequency tables, overall and by parity.

6.5.2 Ease of and pain during Mirena removal

The investigator's assessment of the ease of Mirena removal (easy, slightly difficult, very difficult) will be summarized in frequency tables, overall and by parity.

The subject's assessment of the pain during Mirena removal (none, mild, moderate, severe) will be summarized in frequency tables, overall and by parity.

6.5.3 Continuing need of contraception

The subject's continuing need for contraception since the last contact/visit will be listed.

6.6 Covid-19 pandemic

Additional analyses (introduced prior to Year 7 database lock):

After the Year 7 and Year 8 database lock, subjects affected by the Covid-19 pandemic (due to COVID-19 related adverse event, COVID-19 related protocol deviations or premature discontinuation due to COVID-19 related reason) will be listed with corresponding details.

Furthermore, COVID-19 related protocol deviations will be summarized and listed, as well as premature discontinuation due to COVID-19 related reason.

In addition, scheduled visits (physical or phone) and missed visits will be summarized and listed by timepoint.

7. Document history and changes in the planned statistical analysis

- 05 Oct 2017 Final SAP v1.0
- 14 June 2019 Final SAP v2.0, with the following changes:
  - Section 4.1: Due to low number of subjects in HMB subgroup, only summary tables on disposition and demographics will be displayed with three columns (Contraception, Contraception and HMB, Total), but summary tables on study drug administration, efficacy, safety and pharmacokinetics will be displayed with one column (Total).
  - Section 4.3 / Section 4.7 / Section 6.4: Terminology harmonized ("non-treatment-emergent" changed to "pretreatment").
  - Section 4.3 / Section 4.4 / Section 6.4.3 / Section 8: Reference to BPD updated as RD-SOP-1107.
  - Section 5.1: Derivation rule added how to calculate age at baseline, if not recorded on CRF.
  - Section 6.1.1: Post treatment pregnancy and return to fertility moved to new Section 6.4.6.6.
  - Section 6.1.3.3: Subgroups BMI, race and ethnicity added. Patient data listing to display time in days after Day 1 Year 6, rather than time in days after baseline visit.
  - Section 6.1.3.6: Reference to Section 6.2.1 added. Subgroups BMI, race, ethnicity and indication for Mirena use added.
  - Section 6.2.1, Table 4–1: For Overall PI, formulas to calculate the crude exposure time corrected (use baseline visit date, but not date of Day 1 of Year 6).
  - Section 6.2.1, Primary analysis: Subgroup categories for age at insertion corrected, and subgroups age at baseline, race and ethnicity added.

- Section 6.2.1, Primary efficacy variable: Analysis of ectopic pregnancies added.
- Section 6.2.2.2: Terminology corrected ("nominator" changes to "numerator").
- Section 6.3.1: PK concentrations determined after Mirena expulsion/removal not to be included in the descriptive analyses and plots, but only to be listed. Residual contents with partially/completely missing date of Mirena expulsion/removal not to be included in the plot, but only to be listed.
- Section 6.3.2: Empty section (not applicable) added for sake of completeness.
- Section 6.4.2.1: Updated list of MedDRA codes to identify perforations. Patient data listing to display time in days after Day 1 Year 6, rather than time in days after baseline visit.
- Section 6.4.2.2: Data not to be summarized in a frequency table, but listed only.
- Section 6.4.3: Bleeding diary data after Mirena expulsion/removal not to be included in the statistical analysis. Bleeding diary data after the date of premature discontinuation of study treatment period not to be included in the statistical analysis.

- 21 August 2019 Final SAP v3.0 (supplement), with the following additions (post-hoc analyses after Year 6 database lock):
  - Section 6.2.1: Sensitivity analysis added, to calculate the PI using only complete 28-day reference periods.
  - Section 6.1.3.6: Summary of the completion status of the Month 12 visit and the number of "completers" added.
- 08 June 2020 Final SAP v4.0 (supplement), with the following clarifications/corrections and additions (prior to Year 7 database lock):
  - Section 6.1.3.4: Clarification/correction included about censoring of subject who completed the study treatment period (i.e. at the date of Visit 8 / Month 36 but not at the stop date of study drug administration). Clarification added about censoring of subjects who are continuing in the study (i.e. at the last visit during the treatment period).
  - Section 6.1.3.6: Clarification added about the timepoint when the post-hoc analysis of completion status was introduced (i.e. after Year 6 database lock but prior to Year 7 database lock). Clarification added that similar analysis (completion status of the Month 24 and Month 36 visit, respectively) will be done after Year 7 and Year 8 database lock.
  - Section 6.2.1: Clarification added about the timepoint when the post-hoc analysis to calculate the PI using only complete 28-day reference periods was introduced (i.e. after Year 6 database lock but prior to Year 7 database lock).

Clarification added that similar analysis will be performed after Year 7 and Year 8 database lock, respectively, and the analysis sets to be used for these.

- Section 6.4.2.2: Clarification added about the disgnosis of PID, i.e. a diagnosis of PID is made if response to the following questions in the eCRF is a "yes": "Were the criteria for PID diagnosis met?" and/or "Laparoscopy confirmed PID?".
- Section 6.6: New section added, introducing additional tables and listings to present data on Covid-19 pandemic.

- 10 June 2021 Final SAP v5.0 (supplement), with the following additions (introduced prior to Year 8 database lock):
  - Section 4.7: Definition of AEs in 8th year updated from [Day 1 Year 6 + 730 days ≤ onset date ≤ Day 1 Year 6 + 1094 days] to [Day 1 Year 6 + 730 days ≤ onset date], to include any AE which may fall into the beginning of Year 9.
  - Section 6.1.2.2: Duration from last birth or induced/spontaneous abortion to insertion added to the summary tables of reproductive and menstrual history.
  - Section 6.2.1: Repeated analysis of the primary efficacy variable for the PAS Year 6 and PAS Year 7 based on the final database after Year 8 added.
  - Section 6.4.2.1: Duration from last birth or induced/spontaneous abortion to insertion added in the listing of perforations.

8. References

1. Sponsor's Best Practice Document 'Recording and Evaluation of Bleeding Data' (RD-SOP-1107)
2. European guideline EMEA-'Guideline on clinical investigation of steroid contraceptives in women' (EMEA/CPMP/EWP/519/ Rev1, July 2005.)