POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

PASS INFORMATION

TITLE	Active post-marketing surveillance of Levonorgestrel IUS insertion related difficulties: a non-interventional post-authorisation safety study
PROTOCOL NUMBER	010-100
PROTOCOL VERSION IDENTIFIER	Amendment 5.2
DATE OF LAST VERSION OF PROTOCOL	16. Jan. 2018
EU PASS REGISTER NUMBER	EUPAS7857
ACTIVE SUBSTANCE	Levonorgestrel
MEDICINAL PRODUCT(S)	Levonorgestrel 20 micrograms/24 hours Intrauterine System (IUS) (Levosert® and other associated brand names)
PROCEDURE NUMBER	UK/H/5593/001/DC UK/H/3030/001/DC (As appropriate depending on the approved product on the market)
MARKETING AUTHORISATION HOLDER(S) (MAH)	Gedeon Richter Plc.
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES	The primary objective of this PASS is to characterize the ease of insertion and the safety profile of Levonorgestrel IUS during insertion, under routine clinical practice. The secondary objective of the study is to characterize the utilization pattern for Levonorgestrel IUS in a real-world setting.
COUNTRY(-IES) OF STUDY	Planned in 8 countries (Bulgaria, Czech Republic, Denmark, Hungary, Lithuania, Norway, Poland and UK)

MARKETING AUTHORISATION HOLDER(S)

MARKETING AUTHORISATION HOLDER(S)	Gedeon Richter Plc. Gyömrői út 19-21. Budapest H-1103 Hungary
MAH CONTACT PERSON	Borbala Mércz-Engel MD Medical Safety Physician

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1. LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
CRF	Case report form
CRO	Contract research organisation
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
HCP	Health Care Practitioner
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
INN	International Nonproprietary Name
ISPE	International Society for Pharmacoepidemiology
IUS	Intrauterine system
MAH	Marketing authorisation holder
OTC	Over-the-counter
PASS	Post-authorisation safety study
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SIF	Site Information Form
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology

2. RESPONSIBLE PARTIES

Sponsor

The Marketing Authorisation Holder (MAH) will serve as the Sponsor of this study. It is the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

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INVESTIGATOR SIGNATURE PAGE

Study Title: Active post-marketing surveillance of Levonorgestrel IUS insertion related difficulties: a non-interventional post-authorisation safety study.
Protocol version 5.2, 16. Jan. 2018.

I have read and understand the protocol and agree that it contains the ethical, legal and scientific information necessary to participate in this study. My signature confirms the agreement of both parties that the study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to Good Pharmacoepidemiology Practices (GPP), Good Pharmacovigilance Practices (GVP), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the Study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the study. I am aware that this protocol will need to be approved by an appropriate Ethics Committee prior to any patients being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Investigator:

_____
Print Name

_____ _____
Signature Date

_____
Print Name or stamp of Institution or Practice and Location

RETURN ORIGINAL TO CRO
RETAIN A COPY

SPONSOR SIGNATURE PAGE

Reviewed and Approved by:

György Németh MD, PhD

signature

24-MAY-2018
date

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3. ABSTRACT

Full Study Title: Active post-marketing surveillance of Levonorgestrel IUS insertion related difficulties: a non-interventional post-authorisation safety study

Protocol version 5.2; 16. Jan. 2018

Rationale and background: Levonorgestrel IUS (Levosert® and other associated brand names) a hybrid (art. 10(3) Dir 2001/83/EC) generic of Mirena® (Mirena), is a Levonorgestrel intrauterine delivery system (IUS) indicated for heavy menstrual bleeding and contraception. To complement safety information collected in the Phase 3 clinical trials LVS-20 and M360-L102, and as part of the Risk Management Plan (RMP), the post-authorisation safety study (PASS) will be initiated during the early post-marketing phase of Levonorgestrel IUS to assess the risks linked to insertion-related difficulties in a study population that is representative for the actual users of the Levonorgestrel IUS and thus confirm the safety profile of this IUS under normal conditions of use.

Research question and objectives: The primary objective of this PASS is to characterize the ease of insertion and the safety profile of Levonorgestrel IUS during insertion, under routine clinical practice. The secondary objective of the study is to characterize the utilization pattern for Levonorgestrel IUS in a real-world setting.

Study design: This study is a non-interventional, multinational, multi-centre, PASS of Levonorgestrel IUS. Information regarding utilization, ease of use, patient characteristics, and safety events will be collected during routine insertion of Levonorgestrel IUS.

Population: The study will include women in whom Levonorgestrel IUS is inserted for any indication as part of routine care.

Inclusion criteria:

Willing and able to provide written informed consent

- Prescribed Levonorgestrel IUS as part of routine clinical care prior to enrolment

Exclusion criteria:

There are no exclusion criteria for this study.

Variables:

- Site/Prescriber characteristics (geographic location, specialty of prescriber, practice type, patient volume- only if available)
- Patient demographics and other characteristics: year of birth, height and weight, parity, gravidity, and lactation status.
- Ease of insertion of Levonorgestrel IUS: assessed by a 3-point scale: easy/neutral/difficult.
- Safety profile of Levonorgestrel IUS: insertion-related adverse events (AEs), AE seriousness rating, treatment of related AE.
- Utilization patterns of Levonorgestrel IUS: includes indication/s for use, insertion/attempt date and time, menses status at time of placement visit, placement attempt-related information (including number of previous failed attempts), successful completion of insertion at placement visit, nature of insertion (if local anaesthesia, rigid dilation, and/or ultrasound used), placement performed per instructions, and other concomitant medications.
- Health Care Practitioner (HCP) opinion about readability of the "Instructions for use and handling".

Data Sources: Data will be collected by solicited reporting from HCPs, and sites will enter data into an electronic data capture (EDC) system.
Study size: In order to ensure enough eligible women with valid and complete information are included in the study, a sample size of 1000 women is desirable for this study.
Data analysis: The Enrolled Population consists of all women who are the actual users of the IUS (either new users or patients switching from Mirena or other IUS) and for whom a prescriber filled out the EDC form. All data will be summarized based on the Enrolled Population by overall and two subgroups: those women for whom the Levonorgestrel IUS was successfully inserted and those women for whom the Levonorgestrel IUS was unsuccessfully inserted. Analysis of participating and non-participating sites based on Site Information Form (SIF) data, patient demographics, Levonorgestrel IUS ease of insertion and utilization patterns, and insertion-related AEs, will be summarized descriptively. The reported insertion problems will be provided in a listing which will also be part of the Final Clinical Study Report. Further details on analysis and reporting will be included in the statistical analysis plan (SAP).
Milestones Registration in the EU PASS register: Q4 2016 Start of data collection: Q1 2017 End of data collection: Q1 2020 Final report of study results: Q4 2020

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
5.2	16 Jan 2018	Abstract 8.2 Setting 8.3 Variables Annex 1 Site Information Form Annex 2 Blank Case Report Form	Site selection and non-participating sites defined Variables amended SIF and EDC amended	Updated in line with Assessor's request

5.1	15. Nov. 2017	4. Abstract 5. Amendments and Updates 5. Milestones 8.1 Study design 8.2 Setting 8.3 Variables 8.4 Data Sources 8.6.1 Data Entry/Electronic Data Capture 8.6.2 Source Documents 8.6.3 File Retention and Archiving 8.7.1 General Considerations 8.7.2 Planned Analyses 11. Management and reporting of adverse events/adverse reactions Annex 2	Milestones are updated, Other sections are amended	Delay in milestones due to: o sponsor change and o amendment in study setting Adjustment to study setting
4	12 Apr 2017	PASS information Marketing Authorization Holde(s) 3. Responsible Parties 11.3 Reporting Adverse Events after Study Completion	Sponsor and contact details amended	Sponsor change
3	11 Jan 2016	5 Amendments and updates 6 Milestones 9.4 Data sources 9.6 Data management 9.8 Quality control 9.9 Limitations of research methods 10 Protection of human subjects 11 Management and reporting of adverse events/adverse reactions 12 Plans for disseminating and communicating study results	Sections added	To comply with European Medicines Agency (EMA) Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies
3	11 Jan 2016	9.2 Setting	Method of site/prescriber selection	To target all sites/prescribers of Levonorgestrel IUS in European Union/European Economic Area (EU/EEA) countries where marketing authorisation is granted

5. MILESTONES

The planned dates for key study milestones are:

Milestone	Planned date
Registration in the EU PASS Register	Q2 2016
Start of data collection	Q1 2017
End of data collection	Q1 2020
Final report of study results	Q4 2020

6. RATIONALE AND BACKGROUND

Levonorgestrel IUS (Levosert® and other associated brand names) a hybrid (art. 10(3) Dir 2001/83/EC) generic of Mirena® (Mirena) (1), is a Levonorgestrel intrauterine delivery system (IUS) indicated for heavy menstrual bleeding and contraception.

To complement safety information collected in the Phase 3 clinical trials LVS-20 and M360-L102, and as part of the Risk Management Plan (RMP), the post-authorisation safety study (PASS) will be initiated during the early post-marketing phase of Levonorgestrel IUS to assess the risks linked to insertion-related difficulties in a study population that is representative for the actual users of the Levonorgestrel IUS and thus confirm the safety profile of this IUS under normal conditions of use.

7. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this PASS is to characterize the ease of insertion and the safety profile of Levonorgestrel IUS during insertion, under routine clinical practice.

The secondary objective of the study is to characterize the utilization pattern for Levonorgestrel IUS in a real-world setting.

8. RESEARCH METHODS

8.1. Study Design

This study is a non-interventional, multinational, multi-centre, PASS of Levonorgestrel IUS planned in 8 countries (Bulgaria, Czech Republic, Denmark, Hungary, Lithuania, Norway, Poland and UK) to recruit 1000 study participants.
Information regarding utilization, ease of use, patient characteristics, and safety events will be collected during routine insertion of Levonorgestrel IUS among a sample representative of actual users in the planned countries. See Figure 1. for the Study Flow Chart.

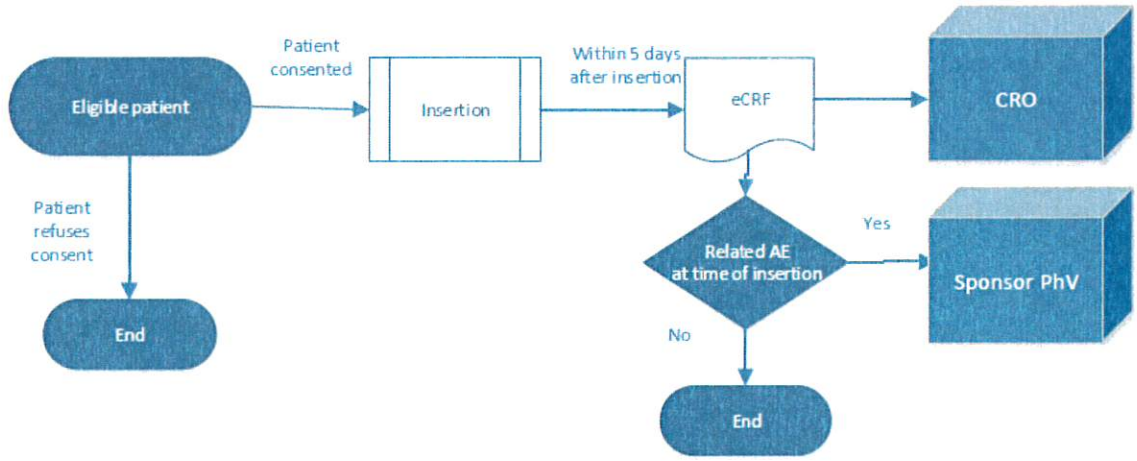

Figure 1. Study Flow Chart

8.2. Setting

It is planned to enroll approximately 1000 patients over approximately 3 years.

The study will include women in whom Levonorgestrel IUS is inserted for any indication as part of routine care.

Data collection will not interfere with the prescribing behaviour of physicians or other Health Care Practitioners (HCPs), or with the individual needs of the patient. This is an active surveillance study which is conducted internationally, in a naturalistic setting, during routine clinical practice, with open patient eligibility criteria (i.e., omitting specific medical inclusion or exclusion criteria). These conditions ensure the external validity of the study.

Prescribers (i.e. HCPs performing the Levonorgestrel IUS insertion procedure) from 8 countries (planned: Bulgaria, Czech Republic, Denmark, Hungary, Lithuania, Norway, Poland and UK) will be invited to participate in this study. The study will include prescribers from Scandinavia, Southern, Eastern and Western Europe, in order to assure that the study results are representative of prescribing across Europe.
Approximately 200 sites (25 sites/country) will be invited to participate in the study based on the databases of former and present sponsors (i.e. Allergan Plc and Gedeon Richter Plc., respectively) which will be provided to the CRO to contact sites considering the representation of the diversity of study sites. To ensure the diversity of the study sites, university and community hospitals, community-based, family planning, and private clinics, from city/town and rural locations, will be invited to join the study. The site selection criteria will be a minimum of 5

eligible patients per site and ability to complete the EDC form in English. The patient/site targets will be reviewed regularly and an increase in the number of the study sites will be considered depending on the enrolment rate. By applying this approach, in addition to the lack of specific medical eligibility criteria, the representativeness and comprehensiveness of the sample in terms of types of prescribers and study population will be enhanced and may allow the generalizability of study results to the broad population of patients that utilise Levonorgestrel IUS. Non-participating sites are defined as those sites which are invited to participate but do not participate for any reason (including non-responders). The characteristics of the participating and non-participating sites will be assessed based on SIF data (see Annex 1). In case patient volume information is not available in the SIF, proxies such as number of HCPs and number of patients per HCP could be used only in those countries with available public information. Finally, screening logs of potential patients will be maintained at each of the sites, to record reasons why the patient failed eligibility screening, or reasons why the patient declined participation. If available, basic demographic information will be recorded in the screening log to allow comparisons between patients who decline to participate and patients who are enrolled.

8.2.1. Inclusion Criteria

The following criteria must be met in order for patients to be enrolled in the study:

- Willing and able to provide written informed consent
- Prescribed Levonorgestrel IUS as part of routine clinical care prior to enrolment

8.2.2. Exclusion Criteria

There are no exclusion criteria for this study

8.2.3. Patient Withdrawal

Patients may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

8.3. Variables

Site/Prescriber characteristics (only if available):
The following information will be collected for each site using data from SIF:

- Geographic location of site (country)
- Specialty of participating HCP (e.g. General Practitioner (GP), nurse, midwife, gynecologist)
- Practice type (e.g. university hospital, community hospital, individual practice, community-based clinic, family planning clinic)
- Practice size (number of prescribers/HCPs at site)
- Patient volume (i.e. number of patients using any intrauterine delivery system within a year and estimated number of patients using Levonorgestrel IUS within 3 months and 12 months period)

Patient demographics and other characteristics:
Demographic and other characteristics will be recorded at the time of the Levonorgestrel IUS placement visit:

- Year of birth
- Height and weight
- Parity
- Gravidity
- Lactation status

Ease of insertion of Levonorgestrel IUS:

- Ease of insertion assessed by a 3-point scale: easy/neutral/difficult

Safety profile of Levonorgestrel IUS:

- Insertion-related adverse events (AEs) (solicited) occurring during placement or soon after placement: AE description, onset and stop date/time, AE recovery status, AE abatement after IUS removal and AE reappearance after new IUS placement. Including but not limited to:
  - Vasovagal events
  - Pain related to placement
  - Expulsion
  - Uterine perforation
  - Infection or sepsis related to IUS insertion
  - Other AE considered relevant by the HCP
- Insertion-related AE seriousness rating
- Treatment of insertion-related AE: treatment/procedure (if drug: International Nonproprietary Name (INN), generic or trade name), dosing regimen and frequency of dosing, form/route, start and end dates, indication (AE)

Utilization patterns of Levonorgestrel IUS:

- Indication/s for use
- Insertion attempt date and time
- Date last menstrual period began
- Menses status at the time of placement attempt
- Placement attempt-related information: first attempt of insertion of any IUS, number of previous failed IUS insertions, date of last attempt ($\leq$ 3 months ago, > 3 and $\leq$ 12 months, >12 months ago), trade name of IUS previously inserted
- Successful completion of insertion at placement visit
- Nature of insertion: if local anaesthesia, rigid dilation and/or ultrasound were used
- Placement performed per instructions
- Concomitant medications (including over-the-counter [OTC] and vaccines, taken within three months prior to or since the insertion attempt): generic/trade name, dosing regimen and frequency of dosing, form/route, start and end dates, indication

Readability of the "Instructions for use and handling"

- Prescriber opinion about the readability of the "Instructions for use and handling": assessed by a 5-point scale: very good, good, neutral, bad, very bad

8.4. Data Sources

Data will be collected by solicited reporting from HCPs selected using the procedure outlined in Section 10.2.

A Data Collection Schedule is provided in Table 1. Data elements will be recorded by the investigator as part of routine clinical practice or for the purposes of the study (i.e. information on ease of insertion, placement performed per instructions, prescriber opinion on readability of "Instructions for use and handling"). No visits or examinations, laboratory tests, or procedures are mandated as part of this study. Data will be recorded into the EDC system.

Table 1. Data Collection Schedule

	Data collected at placement visit for Levonorgestrel IUS
Informed consent	X
Patient year of birth	X
Patient height and weight	X
Parity/Gravidity/Lactation status	X
Levonorgestrel IUS insertion information[a]	X
AEs related to insertion	X

[a]Levonorgestrel IUS insertion information includes the following: ease of insertion; indication/s for use; insertion attempt date and time; date last menstrual period began; menses status at time of insertion; placement attempt-related information; successful completion of insertion; nature of insertion (if local anaesthesia, rigid dilation and/or ultrasound were used); insertion performed per instructions; prescriber opinion on readability of "Instructions for use and handling."

8.5. Study size

The sample size has been estimated using SAS 9.2 (Proc Power) for the incidence of insertion-related difficulties to ensure that the 95% exact Clopper-Pearson confidence interval is included within the true incidence rate with a power of 80%.

A prospective post marketing study conducted on Mirena showed that the incidence of insertion- related difficulties with this IUS is close to 4% (2). It can be postulated that a similar incidence of insertion-related difficulties will be experienced with Levonorgestrel IUS. If the true incidence is 4%, a sample size of 918 patients ensures that the 95% exact confidence interval has a probability of at least 80% to be included within [2% to 6%].

In order to ensure enough eligible women with valid and complete information are included in the study, a sample size of 1000 women is desirable for this study.

8.6. Data management

A data management plan will be created and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The electronic case report forms (eCRFs) will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical, or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

8.6.1. Data Entry/Electronic Data Capture

It will be requested that all data be entered into a secure internet-based EDC system within 5 business days after Levosert IUS insertion, except insertion related Serious Adverse Reaction (SAE), for which reporting should occur within 24 hours. All sites will be fully trained on using the on-line data capture system, including eCRF completion guidelines and help files. Investigators and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRF should be reviewed, electronically signed, and dated by the investigator. All changes or corrections to eCRFs should be documented in an audit trail and an adequate explanation is required. All participating sites will have access to the data entered by the individual site on their own enrolled patients through the EDC system.

8.6.2. Source Documents

In most cases, the source documents are contained in the patient's medical record and data collected on eCRF must be traceable to these source documents in the patient's medical records. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the Sponsor before any destruction of medical records of study participants.

8.6.3. File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agrees to keep records, including the identity of all participating patients, all original signed informed consent forms (ICFs), source documents, and adequate documentation of relevant correspondence (e.g. letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will maintain a study site file that contains all documents necessary for the conduct of the study and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 5 years after the final report or first publication of study results, whichever comes later. Documents to be archived include the signed ICF. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the Sponsor.

8.7. Data Analysis

8.7.1. General Considerations

All AE verbatim terms will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or higher.

All computations and generation of tables, listings, and data for figures will be performed using SAS® version 9.3 or higher (SAS Institute, Cary, NC, USA).

8.7.2. Planned Analyses

The Enrolled Population consists of all women who are the actual users of the IUS (either new users or patients switching from Mirena) and for whom a prescriber filled out EDC form.

All data will be summarized based on the Enrolled Population by overall and two subgroups: those women for whom the Levonorgestrel IUS was successfully inserted and those women for whom the Levonorgestrel IUS was unsuccessfully inserted.

Analysis of participating and non-participating sites characteristics based on SIF data, patient demographics, Levonorgestrel IUS ease of insertion and utilization patterns, and insertion-related AEs, will be summarized descriptively. The reported insertion problems will be provided in a listing which will also be part of the Final Clinical Study Report. Further details on analysis and reporting will be included in the statistical analysis plan (SAP).

General comments about the readability of the "Instructions for use and handling" will be recorded and summarized for future potential improvements of the instruction document.

8.7.3. Handling of Missing Data

Full details on handling of all missing data, which are common in observational studies, will be described separately in the SAP.

8.8. Quality Control

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented.

During the site initiation visit, the clinical monitor (CRO) will provide training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

Each site will be closed out after the last patient has completed the study, all data have been entered, and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in a monitoring plan. Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

8.9. Limitations of research methods

As this is a non-interventional study, potential bias cannot be ruled out. Selection bias may arise from the method by which the study sites/practitioners and patients are selected, and may undermine the external validity (generalizability) of the study data and results. In order to minimize selection bias, the strategy designed for the proposed study will reflect real-life clinical practice since it will capture all possible treatment settings.

It is possible that practitioner awareness of the conduct of this study and in particular collection of data regarding "placement performed per instructions" may influence the behaviour of the participating practitioners. Therefore, the study results may differ somewhat from practices outside of the study.

8.9.1. Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (ie, substantial, significant) amendments will be approved by the relevant regulatory authorities and will usually require submission or notification to the relevant independent ethics committee (IECs) for approval or favourable opinion, if applicable. In such cases, the amendment will be implemented at the site only after approval or favourable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating site and will be submitted to the relevant IEC or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

8.9.2. Study Management

A CRO will be commissioned to provide study management service. The CRO will be responsible for all operational, monitoring and safety aspects of the study including but not limited to training and management of sites, patient recruitment, operation of EDC system and preparation of the study report.

9. PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under regulations and guidance applicable to PASS, including but not limited to the EMA's Guidelines for Good Pharmacovigilance Practices (GVPs) and Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments (3-6), and any applicable national guidelines.

9.1. Patient Information and Informed Consent

An ICF must be signed by the patient (or the patient's legally authorised representative) before participation in the study. The medical file for each patient should document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF must be provided to the patient or the patient's legally authorised representative. All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. Only the most recent ICF should be available for patient's signature. In the event where the ICF is updated, patients who have completed study participation will not be re-consented against the revised ICF.

9.2. Patient Confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon study enrolment. This patient identifier will be used in place of patient name for the purpose of data analysis and reporting. Medical record numbers or other local reference identifiers are not collected as part of the database. All parties will ensure protection of patient personal data and will not include patient names or other identifiable information on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the study countries, patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in collecting, disclosing, processing, transferring, and storing patient data. Participant personal information and confidentiality will be protected according to the requirements of the European Data Protection Directive 95/46/EC on the protection of individuals (7) where applicable, and all applicable laws.

The database will be housed at CRO in a physically and logically secure computer system in accordance with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Conference on Harmonisation (ICH) guideline E6R1 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

9.3. Independent Ethics Committee

Consistent with local regulations and prior to enrolment of patients at a given site, the study protocol will be submitted together with its associated documents (e.g. ICF) to the responsible IEC for its review, as applicable according to country-specific regulations. Patient enrolment will not start at any site before the Sponsor has obtained written confirmation of a favourable opinion/approval from the relevant central or local IEC, as applicable. The IEC will be asked to provide documentation of the date of the meeting at which the favourable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed, as applicable.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with local regulations and requirements. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICFs, and other relevant documents, if applicable, from their local IEC and provide documentation of approval to the study Sponsor. All correspondence with the IEC should be retained in the Investigator Site File.

Should the study be terminated early for any unanticipated reason, the investigator will be responsible for informing the IEC of the early termination.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

AEs (serious and non-serious) that are considered to have a causal relationship with the insertion of Levonorgestrel IUS at the placement visit will be collected and recorded. Insertion-related AEs will be recorded in EDC system as designated by the Sponsor within 5 working days. Any SAE considered related to Levonorgestrel IUS shall be reported into EDC system within 24 hours of becoming aware of it.
Since AEs not having a causal relationship with the insertion of Levonorgestrel IUS and AEs occurring after the placement visit are out of scope of this study, they should be reported directly to the Sponsor's Pharmacovigilance department (drugsafety@richter.hu) or regulatory authorities as per local regulatory requirements..

10.1. Definitions

Adverse events (AEs)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product. Pre-existing conditions that worsen during a study are to be reported as AEs.

If, according to the investigator, there is a worsening of a medical condition that was present prior to the administration of the intervention, this should also be considered a new AE and reported. Any medical condition present prior to the administration of the intervention that remains unchanged or improved should not be recorded as an AE.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to product, action(s) taken, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

Serious adverse events (SAEs)

An SAE is any experience that suggests a significant hazard, contraindication, side effect, or precaution. An SAE must fulfil at least one of the following criteria at any dose level:

- *Results in death*
- *Is life-threatening as it occurred*
  Patient was at risk of death at the time of the event. This does not refer to an event which hypothetically might have caused death if it were more severe.
- *Requires inpatient hospitalization or prolongation of existing hospitalization*
- *Results in persistent or significant disability/incapacity*
  Defined as a substantial disruption of a patient's ability to conduct normal life functions.
- *Results in a congenital anomaly or birth defect*
- *Constitutes an important medical event*
  Based upon appropriate medical judgment, event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Relationship to treatment
Causal relationship must be assessed by answering the following question:
Is there a reasonable possibility the product (Levonorgestrel IUS) caused the event?

Yes: There is evidence to suggest a causal relationship between the product and adverse event; ie:

- There is a reasonable temporal relationship between the product and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease, other products, or other factors, and/or
- Positive dechallenge and/or rechallenge exist

No: There is no evidence to suggest a causal relationship between the product and adverse event, i.e.:

- There is no reasonable temporal relationship between the product and the event, or
- The patient did not have the product inserted, or
- The event is likely to be attributed to underlying/concurrent disease, other investigational products, or other factors, or the event is commonly occurring in the (study) population independent of product exposure

An ADR is defined as a response to a medical product that is noxious and unintended and which arise from the use of a medicinal product within the terms of marketing authorisation; the use outside the terms of marketing authorisation, including overdose, off-label use, misuse, abuse, and medication errors; and occupational exposure.

10.2. Procedures for Reporting Adverse Events

All AEs (serious and non-serious) which are considered related to the placement of the IUS in the opinion of the Investigator, will be recorded into EDC, on a specific AE form including the description, seriousness criteria, duration (onset and resolution date), causal relationship (related) with the study treatment, actions taken with the study treatment, any other required treatment, and outcome.

The outcome of each AE (serious or non-serious) should be entered with a term such as those described below:

- Recovered/Resolved without sequelae
- Ongoing, Not recovered/Not resolved
- Recovered/Resolved with sequelae
- Fatal
- Unknown

The Investigator must report any SAE considered related to Levonorgestrel IUS into EDC system within 24 hours of becoming aware of it.
The investigator must report any AEs considered related to the placement of the IUS into the EDC system within 5 working days.
Sponsor's Pharmacovigilance team will be notified by EDC system automatically and simultaneously when any AE/SAE or special situation (e.g. lactating, other indication recorded, on menses at time of insertion) is recorded by the site. Reports about these events will be available in the EDC system for Sponsor's Pharmacovigilance team.
In case a technical difficulty prevents the study staff to enter the data into the EDC, the AE/SAE pages of the paper CRF form (accessible from the site file) must be used for SAE reporting. SAE must be reported to the Sponsor's Pharmacovigilance team via e-mail (drugsafety@richter.hu) within 24 hours.
In order to maintain compliance with international and national regulatory bodies, Investigators may be further contacted by the Sponsor's Drug Safety department or a third-party in order to collect additional information required to evaluate the potential event. Insertion-related AEs/SAEs will be reported to local and regional health authorities by the Sponsor, when appropriate, in accordance with applicable local and regional regulations. The Investigator is responsible for maintaining compliance with any applicable site-specific requirements related to the reporting of SAEs or other safety information to the local IEC that approved the study.

10.3. Reporting Adverse Events after Study Completion

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report any further AEs involving Levonorgestrel IUS after the visit where Levonorgestrel IUS was inserted and any AEs not having a causal relationship with the insertion of Levonorgestrel IUS please contact the Sponsor's Pharmacovigilance team (drugsafety@richter.hu) and depending on national requirements, please report the AEs via your national reporting system.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Final Analysis and Reporting

A final study report will be generated after all data collection is complete. The final study report will be submitted to the competent authorities within 9 months of the end of data collection. The final report will encompass all planned analyses, as described above and in the SAP.
In accordance with the 2010 EU pharmacovigilance legislation, information about this PASS will be entered into the publicly available EU PAS Register. The study protocol will be entered into the register. Updates to the study protocol in case of substantial amendments, the final study report, and any external publications will also be entered in the register.

11.2. Publications

Any publication of the results from this study must be consistent with the Sponsor's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010 (8). The rights of the investigator and of the Sponsor with regard to publication of the results of this study are described in the investigator contract.

All reporting will be consistent with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Initiative checklist for cohort studies (9).

12. REFERENCES

1. Velev R. A multiple center, randomised, parallel group, single-blind clinical trial, to assess the therapeutic equivalence in terms of efficacy and safety of Test product (Levosert®) and Reference product (Mirena®) in patients with menorrhagia - Phase III (Therapeutic equivalence). 1-134. 17-6-2010.

2. Trinh XB, Tjalma WA, Makar AP, Buytaert G, Weyler J, van Dam PA. Use of the levonorgestrel-releasing intrauterine system in breast cancer patients. Fertil Steril 2008; 90(1):17-22.

3. EMA [Internet]. Guideline on good pharmacovigilance practices (GVP). Module VI – Post- authorisation safety studies. 16 September 2014. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf.

4. EMA [Internet]. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post- authorisation safety studies. 20 February 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC5 00123204.pdf.

5. ISPE [Internet]. Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Safety 2008;17:200-208.

6. Declaration of Helsinki 59th World Medical Association General Assembly, Seoul, October 2008 [Internet]. Available from: http://www.wma.net/en/30publications/10policies/b3/17c.pdf.

7. Directive 95/46EC of the European Parliament and the council on the protection of individuals with regard to the processing of personal data and on the free movement of such data [Internet]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:NOT.

8. International Committee of Medical Journal Editors (ICMJE) [Internet]. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. April 2010. Available from: http://www.icmje.org/urm_full.pdf.

9. STROBE Group [Internet]. STROBE Statement: STrengthening the Reporting of OBservational studies in Epidemiology. March 30, 2008. Available at: http://www.strobe-statement.org/News%20Archive.html.

Annex 1. Site Information Form

Site Information and Physician Information

Question 1 Please provide the following contact information for the person completing this survey.			
Job Title:			
First Name:			
Last Name:			
Hospital / Organization Name:			
Department Name:			
Street			
Postal / ZIP code		City	
State		Office Phone	
Mobile		Fax	
E-mail			

Principal Investigator: Information

Question 2 Please provide the following contact information for the Principal Investigator (PI).			
Are you the PI, who is completing this survey?		❒ Yes	❒ No
If yes, then please continue with Question 3 as there is no need to complete your contact details again. If no, please completed the details for the PI below.			
Country:			
Principal Investigator's Title:			
Principal Investigator's First Name:			
Principal Investigator's Last Name:			
Hospital / Organization Name:			
Department Name:			
Street			
Postal / ZIP code		City	
State		Office Phone	
Mobile		Fax	
E-mail			
Question 3			
Are you the Primary Site Contact in case of questions?		❒ Yes	❒ No
Question 4			

Principal Investigator primary and secondary specialties (please select all that apply):

General Practice / Medicine	❒ Primary	❒ Secondary
Critical Care Medicine	❒ Primary	❒ Secondary
Gynecologic Oncology	❒ Primary	❒ Secondary
Maternal and Fetal Medicine	❒ Primary	❒ Secondary
Obstetrics and Gynecology	❒ Primary	❒ Secondary
Reproductive Endocrinology	❒ Primary	❒ Secondary
Other (e.g. Nurse / Midwife),, please specify:	❒ Primary	❒ Secondary

Question 5	
Do you have experience in conducting non-interventional studies?	❒ Yes ❒ No
Question 7	
Are you currently participating or planning to participate in any study within the next 12 months that would compete for enrollment into LST-MD-01 Levosert PASS? If Yes, how many	❒ Yes ❒ No

SIF and Interest to participate

Question 8
How would you best describe your facility setting?

❒ Clinical Research Unit	❒ Individual Pract., Multi-spec.
❒ Group Practice, Multi-spec.	❒ Individual Pract., Single-spec.
❒ Group Practice, Single-spec.	❒ Nursing Home (For Aged)
❒ HMO-Staff/Group Model	❒ Other Research Facility
❒ Hospital, Active Military	❒ Phase I Research Facility
❒ Hospital, Other	❒ Rehabilitation Center
❒ Hospital, Retired Military VA	❒ Satellite Site
❒ Hospital, Teaching	

❒ Other, (e.g. Family Planning Clinic'), please specify:
.....

Question 9
After reviewing the study synopsis, are you interested in participating in LST-MD-01 Levosert PASS?
❒ Yes ❒ No - *If **No**, please could you kindly indicate the main reasons from the options below*: ❒ Competing Studies ❒ Long Ethics/Regulatory Approval timelines ❒ Patient Inclusion/Exclusion criteria ❒ No longer doing research ❒ Lack of staff/resources ❒ No time/Not taking studies ❒ Lack of subject population ❒ Protocol conflict with standard of care ❒ Not Interested in participating in a non-interventional study ❒ Study design concerns, please specify..... ❒ Other concerns, please specify.....

Potential Study Population

Question 10	
How many patients have been prescribed an intrauterine delivery system at your site in the last 12 months?	
Question 11	
Please read the inclusion/exclusion criteria carefully (c.f. protocol synopsis).	
Are you prescribing Levosert?	❒ Yes ❒ No
Question 12	
How many patients that have been prescribed Levosert do you currently have in your data base?	
Question 13	
How many patients do you estimate you will be able to enroll into LST-MD-01 Levosert PASS Within a 3 months period:	
How many patients do you estimate you will be able to enroll into LST-MD-01 Levosert PASS Within a 12 months period:	
Question 14	
Are there any concerns / barriers with regard to prescribing Levosert at your site?	

Question 15
Please clarify the Levosert status at your site: ❒ Levosert is NOT reimbursed yet ❒ Levosert is reimbursed, but not yet available at your local/ central pharmacy❒ Levosert is reimbursed and available ❒ Other, Please specify:

Study Staff

Question 16 Is there a Co/Sub-Investigator, Study Nurse, Contract Responsible Contact or Research Assistant who will be assigned to support the Principal Investigator to coordinate/conduct the study?			
❒ Yes ❒ No			
If yes, please provide the contact details in the below sections:			
Role/Function:			
Title:			
First Name:			
Last Name:			
Office Phone		Mobile	
E-mail		Fax	
Primary Site Contact in case of questions?			❒ Yes ❒ No
Role/Function:			
Title:			
First Name:			
Last Name:			
Office Phone		Mobile	
E-mail		Fax	
Primary Site Contact in case of questions?			❒ Yes ❒ No

Regulatory and Contracting

Question 17			
Is your site covered by a local or central institutional review board (IRB)/ ethics committee (EC)?			
Local IRB/EC	❒ No	❒ Yes	If yes, complete Question 18.
Central IRB/EC	❒ No	❒ Yes	If yes, complete Question 19.
Both a local and central IRB/EC	❒ No	❒ Yes	If yes, complete Question 20-22.

Question 18	
Please provide the following information about your site's IRB/EC: *If uncertain, please provide your best estimate.	
How often does your IRB/EC meet?	
How many weeks prior to the IRB/EC's meeting date must materials be submitted for review?	
Approximate review/approval response time (in weeks):	
Next IRB/EC meeting date:	

Name and contact details for local IRB/EC			
First Name:			
Last Name:			
Street			
Postal / ZIP code		City	
State		Office Phone	
Mobile		Fax	
E-mail			

Question 19 Please provide the following information about your site's central IRB/EC: *If uncertain, please provide your best estimate.			
Next central IRB/EC meeting date:			
Name of Central IRB/EC:			
First Name:			
Last Name:			
Street			
Postal / ZIP code		City	
State		Office Phone	
Mobile		Fax	
E-mail			
Question 20 Please provide the following information about your site's local and central IRB/EC: *If uncertain, please provide your best estimate.			
Approximate review/approval response time (include both local and central review time) **(in weeks)**:			
Question 21 Is there a specific person at your site responsible for the EC submission?			
❒ Yes ❒ No			
If yes, please provide the contact details in the below sections:			
First Name:			
Last Name:			
Street			
Postal / ZIP code		City	
Mobile		Office Phone	
E-mail		Fax	
Question 22			
In addition to the EC, would your facility require approval from any other party (e.g., scientific committee, hospital board)? If yes, please specify:.....			❒ Yes ❒ No

Question 23	
Approximately, how long does your site need to finalize budget and contract negotiations **(in weeks)**?	
Question 24	
Does your site accept Sponsor Clinical Trial Agreement templates?	❒ Yes ❒ No
If not, do you have a specific template that is used at your site/EC?	❒ Yes ❒ No
Is there any local process that we need to consider?	❒ Yes ❒ No
If yes, please provide more details.	
Question 25	
Can your site do EC/IRB submission and Contract negotiation in parallel?	❒ Yes ❒ No

Question 26			
Is there a specific person at your site empowered to discuss/negotiate contracts on behalf of your facility?	❒ Yes ❒ No		
If yes, please provide the contact details in the below sections:			
First Name:			
Last Name:			
Street			
Postal / ZIP code		City	
Mobile		Office Phone	
E-mail		Fax	

Data Collection and Electronic Data Capture System

Question 27	
Has your site already used electronic case report forms (eCRFs)?	❒ Yes ❒ No
Question 28	
Are you and your study staff comfortable to complete the eCRF in English (including data query handling)?	❒ Yes ❒ No
Do you have a High Speed Internet Connection to support the eCRF?	❒ Yes ❒ No
Do you foresee any Firewall issues at your site when accessing the eCRF?	❒ Yes ❒ No

Referrals

Question 29 If possible, please provide the name (s) and contact details of any other investigators that you would recommend for consideration to participate in the study?			
Country:			
Principal Investigator's Title:			
Principal Investigator's First Name:			
Principal Investigator's Last Name:			
Hospital / Organization Name:			
Department Name:			
Street			
Postal code		City	
Office Phone		Mobile	
E-mail		Fax	

Additional Information

Question 30 Is there anything else that you think would be helpful for us to know about your site?

Thank you for taking the time to complete this form!

Annex 2. Blank Case Report Form in EDC system

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IBM Clinical Development Blank CRFs

Study Name	Levosert PASS
Generated	27-APR-18 10:21:31 GMT

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MSU 3

Schedule

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Unique Identifier	Placement Visit	Visit - Page	Visit ID, Page ID	Notes
visit-10	Placement Visit		10	Added: On Add Subject
		Eligibility	10,10	
		Patient Data	10,20	
		IUS Medication	10,30	Added by visit schedule rule(s) #32
		Placement Visit	10,40	Added by visit schedule rule(s) #33
		Adverse Event	10,50	Repeats, Maximum= Unlimited Added by visit schedule rule(s) #38
		Concomitant Medication Questions	10,60	Added by visit schedule rule(s) #34
		Treatment Related To Adverse Event	10,70	Repeats, Maximum= Unlimited Added by visit schedule rule(s) #41
		Other Concomitant Medications	10,80	Repeats, Maximum= Unlimited Added by visit schedule rule(s) #42
		Medical History Questionnaire	10,90	Added by visit schedule rule(s) #35
		Other Relevant Tests and Indications	10,100	Repeats, Maximum= Unlimited Added by visit schedule rule(s) #43
		Other Relevant Medical History	10,110	Repeats, Maximum= Unlimited Added by visit schedule rule(s) #44
		Study Completion	10,120	
visit-20	Investigator Signature		20	Added: by visit schedule rule(s) #45
		Investigator Signature	20,10	

Placement Visit

Eligibility

[Revision: MSU 3]

(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 10 / Page Display Name = Eligibility / Description = Eligibility)

Inclusion Criteria

The following criteria must be met in order for patients to be enrolled in the study:

* Willing and able to provide written informed consent	○	No
	○	Yes
* Prescribed Levonorgestrel IUS as part of routine clinical care prior to enrolment	○	No
	○	Yes

Informed Consent

* Informed Consent Date		(DD-MMM-YYYY)
* Informed Consent Version number		(format xx.xx)

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Patient Data

[Revision: MSU 3]

(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 20 / Page Display Name = Patient Data / Description = Patient Data)

* Visit Date		(DD-MMM-YYYY)
* Year of Birth		(format xxxx)

Assessments

* Were assessment performed?
- ○ No
- ○ Yes

Test	Result		Unit	Not Assessed
Height		(xxx.x)	○ in ○ cm	☐
Weight		(xxx.xx)	○ lb ○ kg	☐

* Parity		(format xx)
If Parity >=1: Date of Birth of last-born child		
* Date		(DD-MMM-YYYY)
* Gravida		(format xx)

* Lactating
- ○ No
- ○ Yes

If recently lactating, date of stopping: (UNK-UNK-UNK)

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IUS Medication

[Revision: MSU 3]

(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 30 / Page Display Name = IUS Medication / Description = IUS Medication)

* Medication (Trade Name)	○ Levosert ○ Benilexa ○ Donasert ○ Mireffix ○ Tresovelle ○ Levonortis	
* Insertion/Attempt Date		(DD-MMM-YYYY)
* Time		(HH24:MI)
* Time Unknown	☐	
* Indication	○ Contraception ○ Heavy bleeding ○ Other	
* Other, specify		
* Batch Number		

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Placement Visit

[Revision: MSU 3]

(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 40 / Page Display Name = Placement Visit / Description = Placement Visit)

Placement Visit		
* Date Last Menstrual Period Began		(UNK-UNK-UNK)
* On Menses at Time of Levonorgestrel IUS Placement Attempt?	○ No ○ Yes	
* Was this the first attempt of insertion of any IUS for this patient?	○ No ○ Yes	
* Please give the number of previous failed IUS insertion		(format xx)
* When did the last attempt occur?	○ Less than or equal to 3 months ago ○ More than 3 and up to 12 months ○ More than 12 months ago	
* Was the last attempt of insertion performed with Levonorgestrel IUS ?	○ No ○ Yes	
Please provide trade name of IUS previously inserted		
* Was placement completed successfully this time?	○ No ○ Yes	
* If NO, please explain		
* If placement was successfully completed, please rate the ease/difficulty of placing Levonorgestrel IUS	○ Easy ○ Neutral ○ Difficult	

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* Was local anesthesia used?	○ No ○ Yes
If YES, please complete below	
* Cervical lip just for tenaculum placement?	○ No ○ Yes
* Given during procedure for clinical necessity?	○ No ○ Yes
If YES, please complete below	
* Due to discomfort during sounding?	○ No ○ Yes
* Due to discomfort during IUS placement?	○ No ○ Yes
* Used prophylactically to prevent discomfort?	○ No ○ Yes
Other, specify	
* Was rigid dilation performed?	○ No ○ Yes
* If YES	○ OS Finder ○ Pratt Dilator ○ Other
* Other, specify	
* Largest Dilator Size Used	
* Was ultrasound guidance used?	○ No ○ Yes
* Was placement performed per instructions?	○ No ○ Yes
* If NO, please explain	

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* What is your opinion about the readability of the "Instructions for use and handling"?	○ Very Good ○ Good ○ Neutral ○ Bad ○ Very Bad
Additional comments:	
* During or after placement, did any adverse event(s) occur which you believe are considered RELATED to the IUS or the placement of the IUS?	○ No ○ Yes

If YES, please complete AE page(s) for each event(s) as needed.

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Adverse Event

[Revision: MSU 3]

(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 50 (*) / Page Display Name = Adverse Event / Description = Adverse Events)

If response to 'During or after placement, did any adverse event(s) occur which you believe are considered RELATED to the IUS?' is YES, AE_RP page will be available to be completed for each event.

Sequence Number		
* Adverse Event Description		
* Onset Date		(UNK-UNK-UNK)Day and Month required
Onset Time		(HH24:MI)
Onset Time Unknown	☐	
Stop Date		(UNK-UNK-UNK)Day and Month required
Stop Time		(HH24:MI)
Stop Time Unknown	☐	
N/A if Continuing	☐	
What was the severity of the adverse event?	○ Mild ○ Moderate ○ Severe	
Is this event related to study treatment?	○ No ○ Yes	
* Is the related Adverse Event recovering?	○ Recovered / Resolved ○ Not Recovered / Not Resolved ○ Recovered / Resolved with Sequelae ○ Fatal ○ Unknown	

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Was subject withdrawn due to Adverse Event?	○	No
	○	Yes
* Did AE abate after the IUS removal?	○	No
	○	Yes
	○	N/A device not removed
* Did AE reappear after new IUS placement?	○	No
	○	Yes
	○	N/A device not replaced

Seriousness Rating

* Did the adverse event meet any of the definitions below to indicate it was a Serious AE?	○	No
	○	Yes

If YES, check the box that describes the reason for seriousness of the AE

Patient died	☐
Involved or prolonged inpatient hospitalization	☐
Involved persistent or significant disability or incapacity	☐
Life threatening	☐
Congenital anomaly/birth defect	☐
Other medically important reason	☐

* Have you previously reported this related adverse event to a Regulatory Agency?	○	No
	○	Yes

Concomitant Medication Questions

[Revision: MSU 3]

(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 60 / Page Display Name = Concomitant Medication Questions / Description = Concomitant Medication Questions)

* Are there any treatment related to adverse event(s) to report?	○	No
	○	Yes

If YES, please complete Treatment related to AE page(s) as needed.

* Are there any other concomitant medications to report?	○	No
	○	Yes

If YES, please complete Other concomitant medication page(s) as needed. (Please complete all drugs (including OTC)/vaccines taken by the patient within 3 months prior to or since the insertion/attempt)

Treatment Related To Adverse Event

[Revision: MSU 3]
(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 70 (*) / Page Display Name = Treatment Related To Adverse Event / Description = Treatment Related To Adverse Events)

Sequence Number	
* Treatment/Procedure (if drug provide INN, generic or trade name)	
Dose	
Dose Unit	○ mg ○ ug ○ g ○ mL ○ ug/kg ○ mg/kg ○ mL/Kg ○ mL/h ○ IU ○ Tbsp ○ tsp ○ gtt ○ TABLET ○ CAPSULE ○ PUFF ○ OTHER
Other, specify	

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Frequency of Dosing	○ QD ○ BID ○ TID ○ QID ○ QOD ○ ONCE ○ EVERY WEEK ○ QM ○ PRN ○ PA ○ UNKNOWN ○ OTHER	1 One a day (QD) 2 Twice a day (BID) 3 Three times a day (TID) 4 Four times a day (QID) 5 Every other day (QOD) 6 ONCE 7 EVERY WEEK 8 Every morning (QM) 9 When necessary (PRN) 10 PA 11 UNKNOWN 99 OTHER
Other, specify		

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Form/Route	○ Oral (PO) ○ Subcutaneous (SU) ○ Intramuscular (IM) ○ Intravenous (IV) ○ Rectal ○ Topical (TOP) ○ Nasal ○ Respiratory (Inhalation) ○ Opthalmic ○ Sublingual ○ Intra-Arterial ○ Transdermal ○ Intralesional ○ Intraperitoneal ○ Vaginal ○ Other	
Other, specify		
* Start Date		(UNK-UNK-UNK)
* End Date		(UNK-UNK-UNK)
* N/A if Continuing	☐	
* Indication (adverse event)		

Other Concomitant Medications

[Revision: MSU 3]

(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 80 (*) / Page Display Name = Other Concomitant Medications / Description = Other Concomitant Medications)

Sequence Number	
* Reporting Drug/Vaccine/OTC Name (generic or trade name)	
Dose	
Dose Unit	○ mg ○ ug ○ g ○ mL ○ ug/kg ○ mg/kg ○ mL/Kg ○ mL/h ○ IU ○ Tbsp ○ tsp ○ gtt ○ TABLET ○ CAPSULE ○ PUFF ○ OTHER
* Other, specify	

Frequency of Dosing	○ QD ○ BID ○ TID ○ QID ○ QOD ○ ONCE ○ EVERY WEEK ○ QM ○ PRN ○ PA ○ UNKNOWN ○ OTHER	1 One a day (QD) 2 Twice a day (BID) 3 Three times a day (TID) 4 Four times a day (QID) 5 Every other day (QOD) 6 ONCE 7 EVERY WEEK 8 Every morning (QM) 9 When necessary (PRN) 10 PA 11 UNKNOWN 99 OTHER
* Other, specify		

Form/Route	○ Oral (PO) ○ Subcutaneous (SU) ○ Intramuscular (IM) ○ Intravenous (IV) ○ Rectal ○ Topical (TOP) ○ Nasal ○ Respiratory (Inhalation) ○ Opthalmic ○ Sublingual ○ Intra-Arterial ○ Transdermal ○ Intralesional ○ Intraperitoneal ○ Vaginal ○ Other	
* Other, specify		
* Start Date		(UNK-UNK-UNK)
* End Date		(UNK-UNK-UNK)
N/A if Continuing	☐	
* Indication		

Medical History Questionnaire

[Revision: MSU 3]

(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 90 / Page Display Name = Medical History Questionnaire / Description = Medical History Questionnaire)

* Are there any other relevant tests and investigations to report?	○	No
	○	Yes

If YES, please complete other relevant tests and investigations page(s) as needed.

* Are there any other relevant medical history to report?	○	No
	○	Yes

If YES, please complete other relevant medical history page(s) as needed.

Other Relevant Tests and Indications

[Revision: MSU 3]
(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 100 (*) / Page Display Name = Other Relevant Tests and Indications / Description = Other Relevant Tests and Indications)

Sequence Number		
* Test/Investigation		
* Date		(UNK-UNK-UNK)
* Findings/Results (units)		
* Not available	☐	
* Normal Range (Units)		
* Not applicable	☐	

Other Relevant Medical History

[Revision: MSU 3]
(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 110 (*) / Page Display Name = Other Relevant Medical History / Description = Other Relevant Medical History)

Sequence Number		
* Medical History condition/event		
Start Date		(UNK-UNK-UNK)
End Date		(UNK-UNK-UNK)
N/A if Continuing	☐	

Study Completion

[Revision: MSU 3]

(Visit ID = 10 / Visit Display Name = Placement Visit / Visit Abbrev = PV / PageID = 120 / Page Display Name = Study Completion / Description = Study Completion)

* End of study date		(DD-MMM-YYYY)
* Did the patient complete the study?	○ No ○ Yes	
* Primary reason for discontinuation	○ Procedure not done ○ Pregnancy ○ Adverse Event ○ Withdrawal of consent ○ Physician decision ○ Death ○ Other	
* Other, please specify		
* If Died, what was the date of death		(DD-MMM-YYYY)

Investigator Signature

Investigator Signature

[Revision: MSU 3]

(Visit ID = 20 / Visit Display Name = Investigator Signature / Visit Abbrev = PI SIGN / PageID = 10 / Page Display Name = Investigator Signature / Description = Investigator Signature)

I certify that I have reviewed all pertinent source documentation and all corresponding data entered in this eCRF. By applying my electronic signature, I confirm that this information is correct to the best of my knowledge.	☐