NON-INTERVENTIONAL STUDY PROTOCOL

Gedeon Richter

Protocol Title: A Drug Utilization Study on the Real-world Usage of Levonorgestrel 20microgram/24 Hours Intrauterine Delivery System

Syneos Protocol Number: 7037167

Author:

Research Type:	Non-Interventional Drug Utilization Study
Sponsor:	Varga György, MD, PharmD
	Post-Approval Lead
	Gedeon Richter
	Budapest, Hungary
	Tel: +36-1-505-7511
	Email: vargagyorgy@richter.hu
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PROTOCOL APPROVAL SIGNATURES

Protocol Title:	A Drug Utilization Study on the Real-world Usage of Levonorgestrel 20microgram/24 Hours Intrauterine Delivery System
Protocol Number:	7037167

This study will be conducted in compliance with the study protocol and applicable regulatory requirements.

APPROVALS		
Syneos Health Approval		
Erwin De Cock *Electronically signed by: Erwin De Cock* *Reason: I am the approver* *Date: Mar 2, 2023 12:40 GMT+1*		
Erwin De Cock, Executive Director, Real World & Late Phase	Signature	Date (DD-Mmm-YYYY)
Gedeon Richter Approval		
György Varga MD. *Electronically signed by: György Varga MD.* *Reason: I am the approver* *Date: Mar 9, 2023 14:16 GMT+1*		
György Varga, MD, PharmD Post-approval Lead	Signature	Date (DD-Mmm-YYYY)

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Drug Utilization Study on the Real-world Usage of Levonorgestrel 20microgram/24 Hours Intrauterine Delivery System

Protocol Number: 7037167

- I, the undersigned, have read and understand the contents of this Study Protocol noted above dated 13-Feb-2023 and will conduct the study in compliance with the protocol (and any potential amendments), Declaration of Helsinki, relevant International Council for Harmonisation (ICH) guidelines, and all applicable national laws and regulations.
- After the protocol has been approved by the ethics committee (EC), I will not modify this protocol without obtaining prior approval of Gedeon Richter and the Study Coordinating Centre. I will submit any potential protocol amendments and/or informed consent form modifications to the EC, and approval must be obtained before any amendments are implemented except when the change(s) involve(s) only logistical or administrative aspects of the study (e.g., typographical errors, inconsistencies).
- I will ensure that any persons or parties assisting me with the study are adequately qualified, understand the content of this study protocol and understand their delegated study-related duties and functions.
- I will maintain all information supplied to me as part of my study involvement in confidence and, when this information is submitted to an EC, it will be submitted with a designation that the material is confidential. I understand that information resulting from this Non-Interventional Drug Utilization Study may be disclosed by Gedeon Richter to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

<Institution>

_____

Principal Investigator Signature

_____

Date (DD-Mmm YYYY)

1 GENERAL INFORMATION

Sponsor

Gedeon Richter Plc.

Gyömrői út 19-21

Budapest, Hungary

H-1103

Study Coordinating Centre

Syneos Health

1030 Sync Street

Morrisville, North Carolina, USA 27560

USA

Syneos Health will oversee all study logistics including communication with the Sponsor and Principal Investigators, identification of on-line survey participants, on-line survey platform build, survey deployment, data analysis, and reporting. All reports will be submitted to the Sponsor.

2 SYNOPSIS

Title of Study	A Drug Utilization Study on the Real-world Usage of Levonorgestrel 20microgram/24 Hours Intrauterine Delivery System
Protocol Number	7037167
Selected Countries	Czech Republic, Poland, Serbia, Slovakia
Background and Rationale	Levosert®is a levonorgestrel (LNG)-releasing intrauterine system (IUS) containing 52 mg of levonorgestrel. In Europe, Levosert is indicated for use in 1) contraception and 2) menorrhagia or heavy menstrual bleeding. Levosert was first authorised in Europe via Decentralised Procedure (DCP; licence number UK/H/3030/001/DC) on 28 Dec 2012 for the treatment of heavy menstrual bleeding for three years. Countries targeted for the proposed study (Czech Republic, Poland, Serbia, and Slovakia) authorized Levosert for the treatment of heavy menstrual bleeding in a separate DCP (HU/H/0580/001/DC) in 2013. In 2014, the second indication 'contraception' was approved with new supportive data from the ongoing pivotal Phase 3 study M360-L102. Since then and based on the results of the same Phase 3 study, the duration of use of Levosert® for use in contraception was extended to 5 years, then to 6 years in all European countries where the product is marketed. However, the ongoing Study M360-L102 was designed to evaluate contraceptive efficacy only (not heavy menstrual bleeding), and thus, there is need for further evidence regarding usage for the menorrhagia indication to support its use up to the recommended duration determined for the contraception indication. In the context of a lack of data to support extension of recommended duration of use for menorrhagia indication, the Sponsor has committed to the Danish Medicines Agency to conduct a drug utilisation study (DUS) concerning the real-world usability of Levosert 20 microgram/24 hours Intrauterine Delivery System in the menorrhagia indication.
Objectives	The primary objective is to describe the duration of Levosert utilization for the indications of contraception and heavy menstrual bleeding (with and without intended contraception) amongst prescribing OB-GYNs in the selected countries. The secondary objective is to characterize IUS prescribing practices, utilization patterns of Levosert, and level of satisfaction with Levosert for both indications.
Study Design	This is a cross-sectional study collecting data from OB-GYNs who prescribe Levosert in four (4) European countries: Czech Republic, Poland, Serbia, and Slovakia. The questionnaire will collect quantitative data by means of closed-ended questions. Responding to the questionnaire is expected to take not more than twenty (20) minutes. Prescribers will be asked to report about all the patients they have managed with Levosert, including numbers of Levosert prescriptions and removals (with or without replacements). Individual patient date will not be reported. Instead, data will be considered aggregate and will be fully anonymous. The estimated duration of the study (from programming the survey to statistical analysis and report writing) is approximately 1 year.

Selection of Survey Population (Prescribers)	Inclusion criteria: • HCP has its primary practice located in Czech Republic, Poland, Serbia, and Slovakia • HCP's primary state-certified medical specialty is Gynaecology and Obstetrics. • HCP spends at least 25% of their professional time in direct patient care, as opposed to teaching, research, or administrative roles • HCP has prescribed Levosert for HMB to at least two (2) patients • HCP has removed or replaced Levosert from at least one (1) patient who received the product for HMB Exclusion criteria: • HCP is not a physician • HCP never prescribed Levosert • HCP or any member of the HCP's household is affiliated with or employed by any pharmaceutical companies as a consultant and/or researcher (other than participating in clinical studies or clinical investigations)
Data Management and Quality Control	The survey will be fielded through an online survey platform tool and data will be collected on a real-time basis and will be stored in a cloud-based environment. The collection of personal data of participating Prescribers will be limited to the amount necessary to achieve the aims of the research and for respondent compensation. No patient-level data (e.g., from healthcare records) will be collected. De-identified data will be sent to the Study Coordinating Centre for statistical analysis. Data will only be collected in electronic form and no hard copy documents will be retained. The Study Coordinating Centre will be responsible for data quality, ensure that the study is conducted in accordance with the protocol and monitor data accrual on an ongoing basis.
Sample Size and Statistical Analysis	Based on expected availability of OB-GYN respondents in a large physician panel, a convenience sampling approach is applied with a target sample size of 380 physicians who collectively are estimated to have removed approximately 820 Levosert IUS across both indications. **Primary endpoint:** Expected usage duration of Levosert for both indications, defined as the difference in time between removal (with or without replacement) and insertion of the device. **Secondary endpoints:** Number of IUS prescriptions, number of Levosert prescriptions and removals (with or without replacement), distribution of patients by type of contraception, distribution of patients using IUSs who are receiving Levosert, distribution of patients receiving Levosert for heavy menstrual bleeding who show treatment effectiveness by the end of each year, distribution of patients getting Levosert removed by the end of each year, and level of satisfaction with Levosert. All analyses will be descriptive (total, by country, by indication). Categorical variables will be summarized using counts and percentages. Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum, interquartile ranges (IQR), and 95% confidence intervals (CI), as appropriate.

Ethical and Regulatory Obligations	The study will be approved by an appropriately constituted Ethics Committee in Czech Republic, Poland, Serbia, and Slovakia. Approval is required for the study protocol, any potential protocol amendments, recruitment material (i.e., screener) and participant facing material (i.e., questionnaire) before any Prescriber can be enrolled. All applicable laws and regulations will be followed within the countries in which the survey is performed.
Sponsor	Gedeon Richter
Study Coordinating Centre	Syneos Health

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
DCP	Decentralised Procedure
DUS	Drug Utilization Study
HCP	Healthcare Provider
HMB	Heavy Menstrual Bleeding
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IUS	Intrauterine System
LNG	Levonorgestrel
OB-GYN	Obstetrician - Gynaecologist

5 BACKGROUND AND RATIONALE

5.1 Background

Levosert®is a levonorgestrel (LNG)-releasing intrauterine system (IUS) containing 52 mg of levonorgestrel. When inserted into the uterus, it slowly releases this hormone to be absorbed by the user. The initial release of levonorgestrel is approximately 20 micrograms per day. This rate decreases progressively to approximately 8.6 micrograms/day after 6 years. The average in vivo release rate of LNG is approximately 14.3 micrograms/day over a period of 6 years.

In Europe, Levosert is indicated for use in 1) contraception and 2) heavy menstrual bleeding, hereafter referred to as menorrhagia or HMB.

1) Contraception. Levosert prevents pregnancy by thinning the lining of the uterus, by making the normal mucus in the opening of the uterus thicker, so that the sperm cannot get through to fertilise the egg and by preventing ovulation in some women.

2) Treatment of menorrhagia. The hormone in Levosert acts by thinning the lining of the uterus, so that there is less bleeding every month.

Levosert was first authorised in Europe via Decentralised Procedure (DCP; licence number UK/H/3030/001/DC) on 28 Dec 2012 for the treatment of menorrhagia for three years. Countries targeted for the proposed study (Czech Republic, Poland, Serbia, and Slovakia) authorized Levosert for the treatment of menorrhagia in a separate DCP (HU/H/0580/001/DC) in 2013. The applications were based on a therapeutic equivalence study conducted with Levosert and Mirena®. On 16 Oct 2014, the second indication ‘contraception’ was approved with new supportive data from the ongoing pivotal Phase 3 study M360-L102. Since then and based on the results of the same Phase 3 study, the duration of use of Levosert for use in contraception extended to 5 years, then to 6 years in all European countries where the product is marketed. However, the ongoing Study M360-L102 was designed to evaluate contraceptive efficacy only (not menorrhagia), and thus, there is need for further evidence regarding usage for the menorrhagia indication to support its use up to the recommended duration determined for the contraception indication.

5.2 Rationale

In the context of a lack of data to support extension of recommended duration of use for menorrhagia indication, Gedeon Richter has committed to the Danish Medicines Agency to conduct a drug utilisation study (DUS) concerning the real-world usability of Levosert 20 microgram/24 hours Intrauterine Delivery System in the HMB indication.

6 OBJECTIVES

This descriptive study aims to generate insights into the real-world prescribing practices and usability/utilization of Levosert, including duration of use, for the treatment of HMB (with and without intended contraception) within the selected countries.

6.1 Primary Objective

The primary objective is to describe the duration of Levosert utilization for the indications of contraception and HMB (with and without intended contraception) amongst prescribing OB-GYNs in the selected countries.

6.2 Secondary Objectives

The secondary objective is to characterize IUS prescribing practices, utilization patterns of Levosert, and level of satisfaction with Levosert for the indications of contraception and menorrhagia amongst prescribing OB-GYNs in the selected countries.

7 METHODOLOGY

This is a retrospective cross-sectional study collecting secondary data on the experience of OB-GYNs who prescribe Levosert in four (4) European countries: Czech Republic, Poland, Serbia, and Slovakia.

Respondents are healthcare providers (HCPs) who have their primary specialization in obstetrics and gynaecology. Hereinafter, this document shall refer to the respondents, who are prescribers of Levosert, as Prescribers. Refer to Section 8.1 for Prescriber eligibility criteria.

The survey will be fielded through an online survey platform tool and data will be stored in a cloud-based environment. The questionnaire will collect quantitative data by means of closed-ended questions.

Prescribers will be asked to report their real-world experience with Levosert in patients who have used or are still using the drug for contraception and HMB (with and without intended contraception). Prescribers will be asked to report about all the patients they have managed with Levosert (including numbers of Levosert prescriptions and replacements or removals). Individual patient data will not be reported. Instead, data will be considered aggregate and will be fully anonymous.

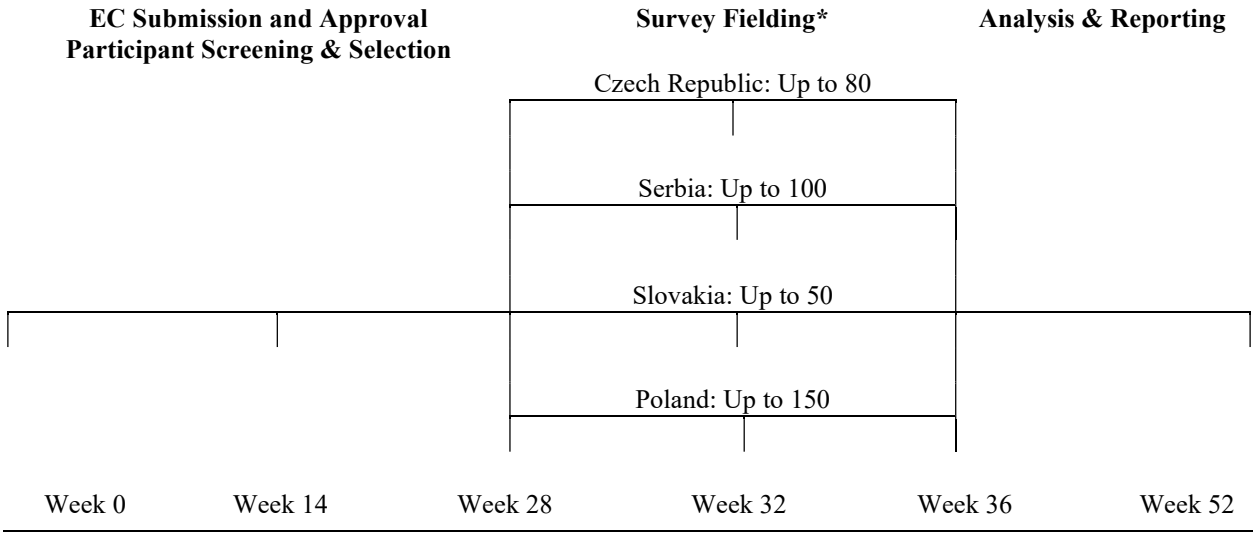
7.1 Discussion of Study Design

This is a cross-sectional study where Prescribers complete the questionnaire only once. Responding to the questionnaire is expected to take not more than twenty (20) minutes.

The sample target is 380 respondents, with the sample distribution guided by expected available OB-GYN respondents in a large physician panel that is active in the study countries.

The estimated duration of the study (from EC submission through reporting) is approximately 1 year (see Figure 1). The duration of survey fielding is up to 4 weeks per country.

Figure 1. Study Design



* Survey fielding will be staggered dependent on the timing of the EC Approval.

7.2 Survey Population

This DUS will be conducted with Prescribers and will be approved by an ethics committee (EC) in each participating country prior to implementation. Prescribers who successfully complete the screener (i.e., who are not terminated based on any of the screening questions) quality to complete the questionnaire. All Prescribers will be asked to respond to the same closed-ended questions, translated into the language predominantly spoken in the country of their practice location (i.e., Czech in Czech Republic, Serbian in Serbia, Slovakian in Slovakia, and Polish in Poland).

The sample of Prescribers will be selected from a pool of potentially eligible OB-GYNs in a large physician panel that is active in the selected four countries.

8 SELECTION OF SURVEY POPULATION

8.1 Prescriber Eligibility Criteria

Prescribers will be selected from a large physician panel that is active in the study countries. This process will be managed by the study coordinating centre.

8.1.1 Inclusion Criteria

- HCP has its primary practice located in Czech Republic, Poland, Serbia, or Slovakia
- HCP's primary state-certified medical specialty is Gynaecology and Obstetrics.
- HCP spends at least 25% of their professional time in direct patient care, as opposed to teaching, research, or administrative roles
- HCP has prescribed Levosert for HMB to at least two (2) patients
- HCP has removed or replaced Levosert from at least one (1) patient who received the product for HMB

8.1.2 Exclusion Criteria

- HCP is not a physician
- HCP never prescribed Levosert
- HCP or any member of the HCP's household is affiliated with or employed by any pharmaceutical companies as a consultant and/or researcher (other than participating in clinical studies or clinical investigations)

8.2 Randomization

Only Prescribers who meet all screening criteria will be admitted to the survey. There is no randomization by any HCP characteristic.

8.3 Risk and Benefit

This DUS will be directed towards Prescribers. Patients will neither be contacted, nor will they be exposed to any additional risk because of this study. Also, this study does not intend to collect any patient-level data, including any personal data. For the Prescribers, there are no foreseeable risks or discomforts associated with participation in this study, however, there is always a possible risk of loss of confidentiality. The research team has safeguards in place to ensure that the confidentiality of the Prescribers is guaranteed. No Prescriber identifiable data will be shared by the panel provider with the Study Coordinating Centre, Sponsor, or any other third party.

8.4 Study Withdrawal, Removal, and Replacement of Prescribers

All Prescribers have the right to withdraw from or terminate the DUS for any reason and at any time during the study (i.e., during the screening process or on-line survey completion). Prescribers who prematurely discontinue the DUS will be replaced. If, for whatever reason, a Prescriber withdraws from the DUS no further action will be initiated other than the recruitment of a replacement.

9 DATA MANAGEMENT AND QUALITY CONTROL

9.1 Data Handling

Data will be collected on a real-time basis using a cloud-based platform for creating and distributing web-based surveys.

The platform is GDPR (General Data Protection Regulation) compliant. The collection of personal data of participating Prescribers will be limited to the amount necessary to achieve the aims of the research and to compensate the respondents, so that no unneeded sensitive information is being collected. No responses will be attributed to individual Prescribers, and all data will be reported in aggregate form. No patient-level data (e.g., from healthcare records) will be collected as part of this DUS. De-identified data will be sent to the Study Coordinating Centre for statistical analysis.

Data will only be collected in electronic form and no hard copy documents will be retained. The electronic data records will be stored in a password-protected, cloud-based environment.

9.2 Quality Control

Quality Control and Quality Assurance will be achieved through data validation provisions applied to the programming of the survey, which is the responsibility of the Study Coordinating Centre. The Study Coordinating Centre will also be responsible to ensure that the DUS is conducted in accordance with the protocol and monitor data accrual on an ongoing basis.

10 STATISTICAL METHODOLOGY

This section provides an overview of the statistical methods that will be applied to answer the research questions. This is a descriptive study without any hypotheses being tested.

10.1 Primary Endpoint Definition

The primary objective of this study is to describe the expected real-world usage duration of Levosert for its different indications.

Duration of Levosert usage is defined as the difference in time between removal (with or without replacement) and insertion of the device. In the absence of detailed patient-level data and in the context of this survey, expected duration of Levosert usage for each indication will be calculated as follows:

$$Expected\ usage\ duration\ of\ Levosert\ (years)$$
$$= \sum_{i=1}^{6} (i\ x\ likelihood\ of\ Levosert\ removal\ in\ Year\ i)$$
$$+ (likelihood\ of\ Levosert\ removal\ beyond\ Year\ 6\ x\ total\ expected\ usage\ duration\ in\ those\ patients)$$

10.2 Determination of Sample Size

A convenience sampling approach was chosen aiming to reach a sufficiently large group of eligible HCPs who have collectively treated a substantial number of patients with Levosert for the HMB indication.

Based on the size and composition of the physician panel in the four study countries, it is estimated that a sample of approximately 380 HCPs would qualify to complete the questionnaire. Assuming an estimated 27,500 Levosert removals (from product launch until 2020) by approximately 11,200 OB-GYNs across the study countries (average 2.46 Levosert removals per OB-GYN), a sample of approximately 380 HCPs would achieve collective experience with the removal of approximately 820 Levosert IUS. Assuming an approximately balanced distribution by both indications – i.e., contraception only vs. HMB with and without intended contraception: 45% and 55%, respectively (Römer et al., 2009) –, this sample would cover approximately 450 Levosert removals in patients with HMB. Coverage of such a level of collective experience is deemed sufficient to generate a robust estimate on the expected duration of Levosert usage.

See Appendix 1 for detailed data supporting this convenience sampling approach.

10.3 Data Analysis

All analyses will be descriptive in nature. Categorical variables will be summarized using counts and percentages. Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum, interquartile ranges (IQR), and 95% confidence intervals (CI), as appropriate. In addition, utilization patterns of Levosert will be visualized using plots or similar techniques.

1. Geographical distribution of Prescribers (by country)

2. Count and percentage of Prescribers by ranges of their professional time spent on direct patient care
3. Count and percentage of Prescribers by duration of their medical practice
4. Count and percentage of Prescribers by practice setting
5. Count and percentage of Prescribers having prescribed each brand of levonorgestrel IUS
6. Count and percentage of Prescribers having experience removing each brand of levonorgestrel (with or without replacement)
7. Descriptive statistics on Prescribers' count of IUS prescriptions in the past 10 years
8. Descriptive statistics on Prescribers' count of Levosert prescriptions and removals (with or without replacement), by indication
9. Descriptive statistics on Prescribers' count of patients they personally manage in a typical month without COVID-19 restrictions
10. Descriptive statistics on percentage of Prescribers' patients by type of contraception, by indication
11. Descriptive statistics on percentage of Prescribers' patients using IUSs who are receiving Levosert, by indication
12. Distribution of Prescriber's patients at the time of Levosert prescription among age categories, by indication
13. Count and percentage of Prescribers among categories of duration-of-effectiveness of Levosert for heavy menstrual bleeding
14. Percentage of Prescribers' patients getting Levosert removed by the end of each year, by indication
15. Descriptive statistics on the total duration of use of Levosert in patients who use Levosert for more than six years, by indication
16. Percentage of Prescribers' patients who use Levosert for heavy menstrual bleeding indication who would continue to show treatment effectiveness by the end of each year
17. Distribution of Prescribers' patients among reason-for-removal categories, by indication
18. Count and percentage of Prescribers by overall level of satisfaction with Levosert in patients who use it for three or more years, by indication
19. Count and percentage of Prescribers by their knowledge of the recommended duration of use of Levosert for heavy menstrual bleeding

10.4 Analysis of Subgroups

The planned subgroup analyses are summarized in Table 1.

Table 1. Key Subgroups for Analysis

Factor	Factor Classification	Subgroups to be Analysed
Prescribing Indication	Binary	HMB with and without intended contraception Contraception only
Prescriber Country	Categorical	Czech Republic Poland Serbia Slovakia

Where relevant, data will be further analysed by duration of Prescriber's medical practice, practice setting, number of Levosert prescriptions (by prespecified ranges), and number of Levosert removals (by prespecified ranges).

To simplify descriptive comparisons, subgroup analyses will be graphically displayed by means of forest plots, where relevant.

11 ETHICAL AND REGULATORY OBLIGATIONS

11.1 Compliance with Laws and Regulations

This DUS will be conducted in compliance with the protocol (and any potential amendments), the Declaration of Helsinki, relevant International Council for Harmonisation (ICH) guidelines, and all applicable laws and regulations of the countries in which the survey will be performed.

11.2 Ethics Committee (EC)

Conduct of the study must be approved by an appropriately constituted EC in each country. Approval is required for the study protocol, any potential protocol amendments, recruitment material (i.e., screener) and participant facing material (i.e., questionnaire) before any Prescriber can be enrolled in the DUS. Any amendment to any of these documents will require review and approval by the applicable EC in each country before the changes are implemented.

11.3 HCP Informed Consent

Prescribers will be approached through their participation in a large physician panel that is active in the study countries. Participants in this panel have already pre-consented to be approached for survey activities and do not need to be consented specifically for this study.

Screening criteria will ensure that eligible Prescribers are selected (see Section 8.1). Eligible Prescribers will be informed that their participation is voluntary, but remunerated, and that they may withdraw at any time. Premature termination of the survey will lead to waiver of the remuneration.

12 ADMINISTRATIVE REQUIREMENTS

The approved protocol shall be conducted as described; any significant protocol deviation must be documented.

12.1 Protocol Deviation/Violation

A protocol deviation/violation is any noncompliance with the DUS design. The noncompliance may be either on the part of a participating Prescriber or the survey administrator (i.e., Study Coordinating Centre). As the result of any deviation/violation, a corrective action will be developed by the survey administrator and implemented promptly. All protocol deviations/violations will be documented using the protocol deviations form and submitted to the competent EC according to their reporting guidelines.

12.2 Protocol Revisions

After the protocol has been approved by the ethics committee (EC), neither the Principal Investigators nor Study Coordinator Centre staff or Sponsor will modify this protocol without obtaining the concurrence of the others. The Principal Investigator will submit any potential protocol amendments and/or informed consent form modifications to the EC, and approval must be obtained before any amendments are implemented, except when the change(s) involves only logistical or administrative aspects of the study (e.g., typographical errors, inconsistencies).

12.3 Record Retention

Data will be maintained for 12 months following the closure of the survey. This DUS will comply with all applicable laws and regulations relating to the privacy of participant's personal information.

12.4 Management and Reporting of Adverse Reactions

Due to the nature of the study, there will be no collection or management of adverse reactions.

12.5 Premature Termination or Suspension of Study

The DUS may be suspended or prematurely terminated if there is sufficient reasonable cause. If the DUS is prematurely terminated or suspended, the Sponsor will promptly inform the appropriate EC and will provide the reason(s) for the termination or suspension. The study may resume once concerns about protocol compliance or data quality are addressed to the satisfaction of the Sponsor and/or the appropriate EC.

12.6 Publication Policy/Disclosure of Data

This study has been requested by a National Competent Authority (i.e., Danish Medicines Agency) during a regulatory procedure. The study report shall be submitted to the requesting National Competent Authority to fulfil the Sponsor's obligation. Scientific publication of the results from this DUS is also foreseen.

13 REFERENCES

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Appendix 1: Supporting Data for HCP Sample Size Determination

A feasibility assessment was conducted to understand the estimated number of Levosert removals since product launch in each country, the total number of practicing OB-GYNs, and the expected number of OB-GYNs that could be recruited from a large physician panel across the study countries (i.e., OB-GYNs who would be eligible and willing to participate).

The number of Levosert removals in the countries of interest has been estimated from:

1. The number of pharmacy-level Levosert sales per country and per year from product launch in 2014 until the last full year of product sales which is 2020 (IMS pharmacy sales database, 2021).
2. LNG-IUS user retention after 1 to 5 years of usage as reported by a post-marketing study: 0.94, 0.87, 0.82, 0.76, 0.65, respectively (Backman et al., 2001). For years outside the reported years, 0% retention is assumed resulting in a conservative estimate.

Table 2. Levosert Removals Since Product Launch, Estimation

Country		2020	2019	2018	2017	2016	2015	2014	Total
Czech Republic	Sold	5,803	5,320	5,206	4,233	4,326	2,768	99	27,755
	Removed since (estimated)	348	692	937	1,016	1,514	2,768	99	**7,374**
Poland	Sold	8,736	11,765	8,971	9,282	8,619	7,931	40	55,344
	Removed since (estimated)	524	1,529	1,615	2,228	3,017	7,931	40	**16,884**
Serbia	Sold	690	907	805	794	907	323	0	4,426
	Removed since (estimated)	41	118	145	191	317	323	0	1,135
Slovakia	Sold	1,771	1,824	1,733	1,469	1,485	549	3	8,834
	Removed since (estimated)	106	237	312	353	520	549	3	2,080
User retention (estimated)		94%[1]	87%[2]	82%[2]	76%[2]	65%[2]	0%	0%	--

The number of practicing OB-GYNs per country has been estimated based on data from multiple sources (WHO 2021, LKCR 2022, NIL 2021)

Distribution by indications has been estimated based on a multinational LNG-IUS patient survey, which showed that 55% of removals were in patients where IUS was prescribed for heavy menstrual bleeding and the remaining 45% for contraception (Römer et al., 2009).

A summary of Levosert sales and removals from product launch until 2020 in the four study countries, the geographical distribution of OB-GYNs, the expected achievable sample of OB-

[1] Based on epidemiological survey of 23,885 LNG-IUS users (Backman et al., 2001).

GYNs in a large physician panel that is active in the study countries, and an estimation of the total number of Levosert removals projected to have been performed by participating Prescribers are shown in Table 3 below:

Table 3. Expected Levosert Removals Performed by Participating Prescribers, Estimation

Item	Czech Republic	Poland	Serbia	Slovakia	Total
Levosert sales since product launch	27,800	55,300	4,400	8,800	96,300
Estimated Levosert removals since product launch	7,400 (27%)	16,900 (31%)	1,100 (25%)	2,100 (24%)	27,500 29%
Total practicing OB-GYNs	2,600	5,900	1,600	1,100	11,200
Estimated Levosert removals per practicing OB-GYN	2.85	2.86	0.69	1.91	2.46
Expected achievable sample of OB-GYNs (from market research panel database)	**80**	**150**	**100**	**50**	**380**
Expected Levosert removals performed by participating Prescribers	**227**	**429**	**69**	**96**	**821**
Expected Levosert removals performed by participating Prescribers: IUS indicated for HMB (with and without intended contraception) [2]	125	236	38	53	452
Expected Levosert removals performed by participating Prescribers: IUS indicated for contraception only (no HMB) [3]	102	193	31	43	369

[2] 55% of users reported the aim to shorten/lighten bleeding in a multinational LNG-IUS utilization study (Römer et al. 2009, n=8680)

Appendix 2: Screener

S1. In which country is your primary practice located?

1	Poland	POLAND QUOTA=150
2	Czech Republic	CZECH REPUBLIC QUOTA=80
3	Serbia	SERBIA QUOTA=100
4	Slovakia	SLOVAKIA QUOTA=50
98	Other (specify)	TERMINATE

S2. What is your role within your practice?

1	Physician	CONTINUE
2	Nurse	TERMINATE
98	Other (specify)	TERMINATE

S3. What is your primary state-certified medical specialty?

1	General Practice/Internal Medicine	TERMINATE
2	Dermatology	TERMINATE
3	Endocrinology	TERMINATE
4	Gynecology and Obstetrics	CONTINUE
98	Other (specify)	TERMINATE

S4. Approximately what percent of your professional time is spent on direct patient care, as opposed to teaching, research, or administrative roles?

1	Less than 25% of the time	TERMINATE
2	25-50% of the time	CONTINUE
3	51-75% of the time	CONTINUE
4	More than 75% of the time	CONTINUE

S5. How many years have you been practicing Gynecology and Obstetrics since gaining this specialization?

1	0 - 3 years	**TERMINATE**
2	4 - 10 years	**CONTINUE**
3	11 - 20 years	**CONTINUE**
4	More than 20 years	**CONTINUE**
97	I am not a certified specialist yet	**TERMINATE**

S6. Which of the following intrauterine systems (IUSs) have you prescribed to your patients?

Please select all that apply.

1	Levosert (levonorgestrel)	**TERMINATE IF NOT SELECTED**
2	Mirena (levonorgestrel)	
3	Skyla (levonorgestrel)	
4	Liletta (levonorgestrel)	
98	Other **[ANCHOR]**	

S7. Which of the following intrauterine systems (IUSs) do you have experience removing (with or without replacement)?

Please select all that apply.

1	Levosert (levonorgestrel)	**TERMINATE IF NOT SELECTED**
2	Mirena (levonorgestrel)	
3	Skyla (levonorgestrel)	
4	Liletta (levonorgestrel)	
98	Other **[ANCHOR]**	
97	None **[ANCHOR, EXCLUSIVE]**	

S8. In the past **10 years**, approximately how many intrauterine systems (IUSs) have you prescribed?

	___#	**TERMINATE IF < 2**

S9. Since **Levosert (levonorgestrel)** has been available in your country, for approximately **how many** patients have you prescribed and removed (with or without replacement) Levosert (levonorgestrel)?

		Contraception only	Heavy menstrual bleeding (with and without intended contraception)
	Total number of Levosert **prescriptions**	___#	___# **TERMINATE IF < 2**
	Total number of Levosert **removals (with or without replacement)**	___#	___# **TERMINATE IF = 0**

S10. Are you, or any member of your household, affiliated with or employed by any pharmaceutical companies as a consultant and/or researcher **other than participating in clinical studies or clinical investigations**?

1	Yes	**TERMINATE**
2	No	

Thank you. You qualify to participate in this research. When you click "Next" you will be taken to a questionnaire which should take about **10 minutes** to complete.

Please answer as completely and as accurately as you can. There are no wrong answers; we are only interested in your experience with and expert opinion on contraceptive products.
The questionnaire is to be completed now and at one sitting. However, if for any reason you are interrupted (e.g., connection failure), you will be able to restart the questionnaire where you left it by clicking back onto your invitation message link.

Let's proceed…

Appendix 3: HCP Questionnaire

Q1. In a typical month without COVID-19 restrictions, approximately how many patients do you personally manage?

Please consider patients seen both in-person or via virtual/online visit.

Please exclude any patients only seeking prescription refills.

	___# of total patients / month	

Q2. Approximately, how many of your patients are **currently using** one of the following types of contraception by indication?

- ✓ Oral/pill
- ✓ Intrauterine device (IUD)
- ✓ Intrauterine system (IUS)
- ✓ Hormonal ring
- ✓ Implant
- ✓ Injection

		Contraception only	Heavy menstrual bleeding (with and without intended contraception)
	# of patients currently using any of the above treatment types	___#	___#

Q3. Considering **all your patients by indication,** approximately what percentage are currently using the different types of contraception listed below?

		Contraception only	Heavy menstrual bleeding (with and without intended contraception)
	Oral/pill	____%	____%
	Intrauterine device (IUD)	____%	____%
	Intrauterine system (IUS)	____%	____%
	Hormonal ring	____%	____%
	Implant	____%	____%
	Injection	____%	____%
	Total	**100%**	**100%**

Q4. Considering **all your patients currently using intrauterine systems (IUSs)** by indication, approximately what percentage are using **Levosert (levonorgestrel)**?

	Contraception only	Heavy menstrual bleeding (with and without intended contraception)
Proportion of patients currently using IUSs who receive Levosert	___%	___%

Q5. Considering **all** your patients ever having used and/or currently using **Levosert (levonorgestrel)**, what is the age distribution at the time of prescription, by indication?

		Contraception only	Heavy menstrual bleeding (with and without intended contraception)
	16-24 years of age	____%	____%
	25-34 years of age	____%	____%
	35-44 years of age	____%	____%
	45-54 years of age	____%	____%
	55+ years of age	____%	____%
	Total	**100%**	**100%**

Q6. When using **Levosert (levonorgestrel)** for **heavy menstrual bleeding (with and without intended contraception)**, what is the average time from insertion to achieving treatment effectiveness (defined as significant reduction in menstrual blood loss)?

1	Less than one month	
2	One to less than two months	
3	Two to less than three months	
4	Three to less than four months	
5	Four months or more	

Q7. In your experience, approximately what percentage of patients using **Levosert (levonorgestrel)** for the following indications need to get it **removed (with or without replacement)** by the end of each year (cumulatively since insertion)?

Please note your responses must be cumulative over time (since insertion).

		Contraception only	Heavy menstrual bleeding (with and without intended contraception)
	By the end of Year 1	____%	____%
	By the end of Year 2	____%	____%
	By the end of Year 3	____%	____%
	By the end of Year 4	____%	____%
	By the end of Year 5	____%	____%
	By the end of Year 6	____%	____%

VALIDATION MESSAGE REQUIRING TRANSLATION:

ERROR: Please note your responses for each column must be cumulative. For example, your response for the end of year 2 must be equal to or greater than your response for the end of year 1, etc.

Q8. For patients who use **Levosert (levonorgestrel)** for **contraception only** for more than six years, for approximately how many years in total do these patients typically use **Levosert (levonorgestrel)**?

Please feel free to provide a fractional number of years.

	___# of years	**RANGE 7-10**

Q9. For patients who use **Levosert (levonorgestrel)** for **heavy menstrual bleeding (with and without intended contraception)** for more than six years, for approximately how many years in total do these patients typically use **Levosert (levonorgestrel)**?

Please feel free to provide a fractional number of years.

	___# of years	**RANGE 7-10**

Q10. Among your patients using **Levosert (levonorgestrel)** for **heavy menstrual bleeding (with and without intended contraception)**, what percentage would continue to **show treatment effectiveness** by the end of each year (cumulatively since insertion), while continuing to use the same Levosert (levonorgestrel) device.

Please note your responses must be cumulative over time since insertion.

Treatment effectiveness is defined as significant reduction in menstrual blood loss.

		Heavy menstrual bleeding (with and without intended contraception)
1	By the end of Year 1	___%
2	By the end of Year 2	___%
3	By the end of Year 3	___%
4	By the end of Year 4	___%
5	By the end of Year 5	___%
6	By the end of Year 6	___%
7	Beyond 6 years	___%

VALIDATION MESSAGE REQUIRING TRANSLATION:

ERROR: Please note your responses for each column must be cumulative. For example, your response for the end of year 2 must be equal to or less than your response for the end of year 1, etc.

Q11. Considering **all** your patients ever having used and/or currently using **Levosert (levonorgestrel)** for the following indications and who had it removed (with or without replacement), approximately what percentage of these patients had **Levosert (levonorgestrel)** removed for each of the following reasons?

		Contraception only	Heavy menstrual bleeding (with and without intended contraception)
	Removed per Schedule (IUS Expiry)	____%	____%
	Planning for family	____%	____%
	Side effects	____%	____%
	Lack of effectiveness	____%	____%
	Menopausal	____%	____%
	Other (specify)	____%	____%
	Total	**100%**	**100%**

Q12. Overall, how satisfied are you with **Levosert (levonorgestrel)** in patients who use it **for three or more years** for the following indications?

		Contraception only	Heavy menstrual bleeding (with and without intended contraception)
	Not at all satisfied	**1**	**1**
	Not very satisfied	**2**	**2**
	Somewhat satisfied	**3**	**3**
	Very satisfied	**4**	**4**
	Do not have enough experience to rate	**99**	**99**

Q13. What is the recommended duration of use of **Levosert (levonorgestrel)** for **heavy menstrual bleeding (with and without intended contraception)** in your country?

1	3 years	
2	4 years	
3	5 years	
4	6 years	
99	Do not know	

In closing, we would like to ask you a few last questions about your practice…

Q14. Please enter the postal code of the practice setting where you spend the majority of your time?

_____

Q15. Which of the following best describe the practice setting where you spend the majority of your time?

1	Hospital-based/inpatient practice	
2	Multi-specialty outpatient practice, including OB/GYN specialty	
3	Single specialty outpatient OB/GYN practice	
98	Other	

Thank you for your time! Please read this and make sure to click the arrow button below to submit your survey.

If you are aware of individual adverse reactions with **Levosert (levonorgestrel)** *that were not reported previously, please kindly report them to the national reporting system of your practice location or the drug safety contact of the Sponsor!*

Contact details of the national reporting system and the Sponsor for your primary practice location:

Poland	**National Reporting System** Departament Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych Al. Jerozolimskie 181C PL-02 222 Warszawa Tel.: + 48 22 49 21 301 Faks: + 48 22 49 21 309 https://smz.ezdrowie.gov.pl **Sponsor Drug Safety Contact** Gedeon Richter Polska Sp. z o.o. E-mail: lekalert@grodzisk.rgnet.org Tel: +48 22 755 96 48 https://www.gedeonrichter.pl/zgloszenie-dzialania-niepozadanego/
Czech Republic	**National Reporting System** Státní ústav pro kontrolu léčiv Šrobárova 48 100 41 Praha 10 http://www.sukl.cz/nahlasit-nezadouci-ucinek **Sponsor Drug Safety Contact** Gedeon Richter Marketing ČR, s.r.o. Na Strži 65 140 00 Prague 4 E-mail: drugsafety.cz@gedeonrichter.eu Tel.: +420 261 141 215 https://www.richtergedeon.cz/hlaseni-nezadoucich-ucinku/
Serbia	**National Reporting System** Medicines and Medical Devices Agency of Serbia

	458 Vojvode Stepe Street Belgrade 11221 E-mail: nezeljene.reakcije@alims.gov.rs https://www.alims.gov.rs/farmakovigilanca/prijavljivanje-nezeljenih-reakcija-na-lek/ **Sponsor Drug Safety Contact** Predstavništvo Richter Gedeon NYRT Direktor predstavništva Dr sci. med. Jelena Ristić, specijalista kliničke farmakologije Vladimira Popovića 6 11070 Beograd E-mail: prijava@richter.rs Tel: +381 11 660 8998 https://www.gedeonrichter.com/rs/sr/kontaktirajte-nas/adverse-event-reporting
Slovakia	National reporting system Štátny ústav kontroly liečiv Kvetná 11 825 08 Bratislava E-mail: neziaduce.ucinky@sukl.sk https://www.sukl.sk/hlavna-stranka/slovenska-verzia/bezpecnost-liekov/hlasenie-podozreni-na-neziaduce-ucinky-liekov/ **Sponsor Drug Safety Contact** Gedeon Richter Slovakia s.r.o. Karadžičova 10 821 08 Bratislava E-mail: drugsafety.sk@gedeonrichter.eu Phone: +421 (2) 33070414 https://richter.sk/kontakt/hlasenie-neziaducich-ucinkov/

7037167_Levosert DUS Protocol Amendment V2.0_13Feb23_final

Final Audit Report 2023-03-09

Created:	2023-03-02
By:	Richard Robert (richard.sandor@syneoshealth.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAAjGBwX9-KRu_UBtwV9jdbKZ2iOshXH0s1

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Document created by Richard Robert (richard.sandor@syneoshealth.com)
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