Centre for Pharmacoepidemiology

PHARMACOEPIDEMIOLOGICAL STUDY (DRUG UTILIZATION STUDY) OF JAYDESS USE IN ROUTINE CLINICAL PRACTICE IN SWEDEN

PASS NUMBER: *8498*

Final Report

Date: August 22, 2022

This report was prepared by the Centre for Pharmacoepidemiology (CPE), Department of Medicine, Solna, Karolinska Institutet for Bayer AG.

The ethical permission for this study was initially granted by the regional ethical board in Stockholm, Sweden on 26 November 2014 (Dnr 2014/1884-31). A new ethical application was submitted for study Parts 1 & 2, and approved by the Swedish Ethical Review Authority on 22 September 2020 (Dnr 2020-03530). For the medical record review (Part 3), an ethical amendment was approved by the Swedish Ethical Review Authority on 10 December 2020 (Dnr 2020-06326).

Post Authorization Safety Study (PASS)

Acronym/Title	Jaydess DUS/ Pharmacoepidemiological study (Drug Utilization Study) of JAYDESS use in routine clinical practice in Sweden.
Report version and date	Final Report v1.0, 22 AUGUST 2022
IMPACT study number	16903
Study type / Study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	8498
Active substance	Levonorgestrel (ATC code G03AC03)
Medicinal product	Jaydess Intrauterine delivery system, 13.5 mg (ATC code G02BA03)
Product reference	Jaydess: 2011-1607 47317
Procedure number	Jaydess: SE/H/1186/01/DC
Study Initiator and Funder	Bayer AG
Research question and objectives	Characterize new users of Jaydess and estimate duration of use. Describe hormonal contraceptive methods used before and after using Jaydess.
Country(-ies) of study	Sweden
Author	PPD MD, PhD, professor PPD of CPE (Centre for Pharmacoepidemiology) Karolinska Institutet PPD Karolinska University Hospital SE 171 76 Stockholm Sweden

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG 13342 Berlin Germany
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Confidentiality statement:

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1. Abstract

Acronym/Title	Jaydess DUS/ Pharmacoepidemiological study (Drug Utilization Study) of JAYDESS use in routine clinical practice in Sweden.
Report version and date **Author**	Final Report v1.0, 20 AUGUST 2022 Centre for Pharmacoepidemiology Karolinska Institutet
Keywords	levonorgestrel, intrauterine device, health registers, secondary data, drug utilization study.
Rationale and background	Jaydess, a levonorgestrel-releasing intrauterine system containing 13.5 mg of levonorgestrel, was approved for contraception by the European Medicines Agency in 2013. The aim of this post-marketing utilization study is to investigate the characteristics of new users of Jaydess in a "Real World" setting.
Research question and objectives	Primary objectives: 1) describe the characteristics (demographic, clinical, social) of first-time users of Jaydess, 2) estimate the average duration of use. Secondary objectives: study the contraceptive use patterns before and after Jaydess use and evidence of off-label use.
Study design	This observational, population-based study was conducted in 3 parts: 1) a national cohort study using data from the Swedish population-based national registers, 2) a regional cohort study including a subset of women with primary care data from Stockholm county, 3) a medical chart review
Setting	The national registers include information on all Swedish inhabitants (approx.10 million). The regional database includes information on individuals receiving primary health care in Stockholm county, Sweden's largest region. Medical records of Jaydess users were requested from gynecology clinics in teaching hospitals throughout Sweden.

Subjects and study size, including dropouts	The National cohort study population included all women in Sweden with a recorded dispensation of Jaydess between 1 January 2014 to 31 December 2016 (n=38,327), and were followed until 31 December 2020. The Stockholm cohort was a subset of the national cohort (n=13,323). The medical charts for 168 women were reviewed.
Variables and data sources	Data from the following national registers were used: the Prescribed Drug Register (PDR), National Patient Register, Medical Birth Register, and population registers from Statistics Sweden. For the Stockholm cohort, data was added from the Regional Databases on Hospital and Primary Care Diagnoses from Stockholm County. The index date was the date of Jaydess dispensing. Duration of use was estimated based on the index date and one of the following events: an IUD removal procedure code, dispensation of another hormonal contraceptive, the start of pregnancy, or insertion of a copper IUD. From the medical records, data on the indication of use and the insertion and removal dates were extracted.
Results	In the National cohort, the mean age of first-time Jaydess users was 26 (SD±7) years and over 80% received their Jaydess prescription from a midwife. The rate of comorbidities was low, with the most common (2-3%) being diagnoses of depression, anxiety, premenstrual syndrome, menorrhagia, or inflammatory diseases of female genital organs. The duration of Jaydess use was estimated in 83% of women and was a median of 31.3 months. More than 50% of women who continue with hormonal contraception after the index Jaydess used a hormonal IUD. Results from the Stockholm cohort were similar to those of the National cohort. Contraception was the main indication for Jaydess (87%).
Discussion	In this post-marketing utilization study of first-time users of Jaydess in Sweden, we conclude that Jaydess users reflect the general population of reproductive-aged women regarding sociodemographic and health factors. The estimated duration of use was 31 months. Off-label use of Jaydess is likely negligible in clinical practice in Sweden.
Marketing Authorization Holder(s)	Bayer AG 13342 Berlin Germany

2. List of abbreviations

ATC	Anatomical Therapeutic Chemical (Classification System)
CDR	Cause of Death Register
CPE	Centre for Pharmacoepidemiology
DDD	Defined daily dose
GDPR	General Data Protection Regulation
ICD	International Classification of Diseases
IUD	Intrauterine device
HRT	Hormone replacement therapy
IQR	Inter quartile range
KI	Karolinska Institutet
LNG-IUS	Levonorgestrel intrauterine system
MBR	Medical Birth Register
NBHW	Swedish National Board of Health and Welfare
NCSP	NOMESCO Classification of Surgical Procedures
NOMESCO	Nordic Medico-Statistical Committee
NPR	National Patient Register
OS	Observational Study
PDR	Prescribed Drug Register
PIN	Personal identification number
SD	Standard deviation
VAL/GVR	Regional databases on hospital and primary care diagnoses from Stockholm County

3. Investigators

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4. Other responsible parties

4.1 Study Team (internal or external)

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Role:	PPD
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Contact details of the responsible parties are available upon request.

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual Date	Comments
Start of data collection	February 2014	February 2014	
End of data collection	September 2021	April 2022	Due to the lag in data availability from the register holder, complete follow-up data was not available until April 2022.
Registration in the EU PAS register	02 February 2015	02 February 2015	

Interim report	March 2018	Finalized October 2018	A delay in the delivery of the interim report from Q1 to Q2 was due to a delay in the delivery of data by the Swedish register holders to the research team.
Final report of study results	December 2021	August 2022	An extension of the due date for the final report from Q4 2021 to Q2 2022 was agreed upon by all parties to ensure that the final report included complete follow-up data to December 31, 2020.

6. Rationale and background

The purpose of this proposed post-marketing pharmacoepidemiology study is to characterize new users of the Jaydess in a "Real World" setting (i.e., a drug utilization study). Jaydess, a levonorgestrel-releasing intrauterine system (LNG-IUS) containing 13.5 mg of levonorgestrel, has a smaller size, provides a shorter duration of action (3 versus 5 years), and lower hormonal content compared to other IUS at the time of release onto the Swedish market.(1) Jaydess was approved for the indication of contraception by the European Medicines Agency in 2013 and by the Swedish Medical Products Agency on 10 September 2013.

Previous studies of LNG-IUSs with higher dosages have found good acceptability and high continuation rates.(2-5) Randomized clinical trials and smaller clinical studies have shown high efficacy and a similar safety profile of JAYDESS, and that it is generally well tolerated in women of all ages and parity.(6-12)

Specific areas of interest to be addressed in this post-marketing utilization study include a description of first-time Jaydess users, the duration of use, and contraceptive use patterns before and after Jaydess. A secondary aim is an investigation into the use of Jaydess beyond the 3-year labeled use and off-label use for indications other than contraception.

The study protocol was developed based on a pilot study finalized in 2016 which explored the feasibility of using national and regional register health care data for identifying hormonal IUD insertion and removal procedures.(13) An interim report of the study was submitted to the Market Authorization Holder (Bayer) in October 2018 with the objective of describing the main study population of first-time users of Jaydess in Sweden between 2014 and 2016, with 0 to 3 years of follow-up. Approximately 38 000 women were included in the study, which was a higher number that estimated prior to the start. In the interim report, it was shown that women using Jaydess reflected the general population of women of reproductive-age in Sweden in terms of socio-demographic and medical characteristics. One-third of the women terminated use of Jaydess within three years, the majority of whom returned to the method of contraception used before Jaydess. Among the 38 000 women approximately 5000 were hormonal contraceptive naïve users (defined as not having a dispensation of hormonal contraception prior to use of Jaydess). Notably, the hormonal contraceptive naïve and non-naïve Jaydess users were similar regarding sociodemographic characteristics.

The objectives of the final report were to continue to describe the study population with a complete follow-up period of 5 to 7 years (to the end of 2020) with regards to duration of Jaydess use and contraceptive use patterns. In Sweden, IUDs are primary inserted and removed in primary care. Therefore, the same objectives were addressed in a subset of the study population with regional primary health care data. Lastly, a medical record review was undertaken to collect information regarding the indication of Jaydess use.

7. Research question and objectives

The aim of the study was to describe first time users of Jaydess in a "Real-World" setting.

1. Primary objectives

a. To describe the characteristics (demographic, clinical, social) of first-time users of Jaydess.

b. To estimate the average duration of use of Jaydess.

2. Secondary objectives

a. To study contraceptive switching patterns among women using Jaydess, e.g., what are the hormonal contraceptive methods used before and what are the methods after discontinuing Jaydess.

b. To study off-label use of Jaydess:

i. Use of Jaydess for a duration of more than 3 years

ii. Use of Jaydess for indications other than contraception

8. Amendments and updates

None.

9. Research methods

9.1 Study design

The overall study was conducted in 3 parts:

- Part 1: A National cohort study (addressed objectives 1a, 1b, 2a, 2b)
- Part 2: A Stockholm cohort region Study (addressed objectives 1a, 1b, 2a, 2b)
- Part 3: A Medical Record Review (addresses objectives 1b, 2bii)

9.2 Setting

Part 1: National Cohort

Part 1 was an observational, population-based cohort study using data from the Swedish national registers to describe first time users of Jaydess in "real world" setting. The national registers include information on all Swedish inhabitants (approximately 10 million). Section 9.5 contains detailed information about the registers.

Upon request, eligible individuals were identified by the Swedish Board of Health and Welfare (NBHW) from the Prescribed Drug Register (PDR). Women who had at least one dispensation of Jaydess in Sweden between 01 January 2014 and 31 December 2016 constituted the study population and were followed until 31 December 2020. Only diagnosis and medical procedure data from specialist health care is available in the national registers.

Part 2: Stockholm Cohort

Part 2 included a subset of the National cohort who received primary health care in the Stockholm Region during 2014 to 2016 (referred to as the Stockholm Cohort). Stockholm County is Sweden's largest region with approximately 2.2 million inhabitants. For this subset, primary care data was available from the Regional Databases on Hospital and Primary Care Diagnoses (VAL/GVR). IUDs are primary inserted and removed in primary care. Therefore, the purpose of the Stockholm cohort was to use the primary care data on IUD insertion and removal for more accurate estimation of duration of Jaydess use and identification of contraceptive use patterns, including the use of copper IUDs which are not dispensed at pharmacies and therefore not identifiable in the PDR.

At the time when the study protocol was written, there was no feasible way to link the data from the national registers to the VAL/GVR. Since then, a mechanism for linkage has been established by the register holders. Hence for this final report, the Stockholm cohort contains data from both the national registers and VAL/GVR. Specifically, the VAL/GVR register holder sent a dataset containing the personal identification number (PIN) for all women receiving primary health care in Stockholm between 2014-2016 between the ages of 15 to 55 to the NBHW, who then identified the women among them had a recorded dispensation of Jaydess in the PDR during the same time period, and only the primary care data for this subset was provided for this study.

Part 3: Medical Record Review

The PDR does not contain information on the indication of use for dispensed drugs. Neither the IUD insertion procedure codes in the National Patient Register (NPR) or primary care data provide information on the reason for IUD use. Hence, to investigate potential off-label use of Jaydess, the indication of use was collected from the medical records. Further, medical record data on the date of insertion and removal of Jaydess was extracted with the intention of validating the accuracy of the estimated duration of Jaydess use in the Stockholm cohort.

With the approval from the Swedish Ethical Review Authority, the NBHW provided the PIN of women who met for the following criteria: 1) had at least one Jaydess dispensation between 01 January 2014 and 31 December 2016 recorded in the PDR, and 2) had at least one healthcare contact for an IUD insertion procedure recorded in the NPR between 1 January 2013 and 31 December 31, 2017 at one of seven pre-selected hospitals in Sweden. The pre-selected hospitals were chosen based on their size and their high response rate to medical record requests in the 2016 Pilot study and other (unrelated) studies conducted by the research team.

In the 2016 Pilot study, approximately 70% of the requested medical records were retrieved. Therefore, to achieve the goal of 150 medical records, the PIN for 204 women, randomly selected after fulfilling the criteria, were requested. The study team then requested permission from the head of the department at each hospital for the medical records and copies were provided to the research team by clinic staff.

Note that the study protocol indicated that medical records from only 3 Stockholm-based hospitals would be requested. However, with only these 3 hospitals the study sample of 150 women was not achieved and therefore medical records were requested from an additional 4 hospitals in other regions of Sweden.

9.3 Subjects

Part 1: National Cohort

In Sweden, Jaydess was approved for use on 9 September 2013 and the first Jaydess was dispensed on 10 January 2014. To capture first time users of Jaydess, all women 10 years of age and older meeting the following criteria were eligible for inclusion in the study population:

- At least one dispensation of Jaydess identified in the PDR between 01 January 2014 and 31 December 2016.

Women were excluded when 1) there was a dispensing of a second hormonal contraceptive on the same day as the index Jaydess recorded in the PDR; 2) immigration or emigration events occurred during 2014 to 2016. These women were excluded to ensure adequate look back and follow-up time.

Jaydess index date: was defined as the date of the first dispensation of Jaydess between 01 January 2014 and 31 December 2016, as recorded in the PDR.

Follow-up: The eligible study individuals were followed from the index date to whichever of the following events occurred first:

- Death;
- Emigration;
- End of available data (31 December 2020)

Accordingly, in the case of no death or immigration, the follow-up time in all data sources for each individual is a minimum of 4 years and a maximum of 7 years.

Naïve vs. Non-naïve users: Women in the study population were categorized as “hormonal contraceptive naïve Jaydess users” (from this point forward referred to as naïve users) or “hormonal contraceptive non-naïve Jaydess users” (from this point forward referred to as non-naïve users) according to previous use of any other prescribed hormonal contraceptive method.

Naïve users were defined as women with no dispensations of a hormonal contraceptive method from the beginning of the PDR (1 July 2005) to the Jaydess index date. Non-naïve users were defined as

women with a dispensation of one or more hormonal contraceptive method(s) recorded from 1 July 2005 to the Jaydess index date.

For each non-naïve user, the stop date for the method of contraceptive prior to the Jaydess index date was estimated using the reported package size and the recommended duration of use for that method. (**Supplementary Table 1**) With this stop date, non-naïve Jaydess users were then subdivided into "recent contraceptive users" (those who dispensed a hormonal contraceptive method with supply overlapping the six months prior to Jaydess index date) and "past contraceptive users" (those who had no recorded dispensation of a hormonal contraceptive method with a supply overlapping the six months prior to Jaydess index date). Hence, past contraceptive use was between the six months and eight years prior to Jaydess index date.

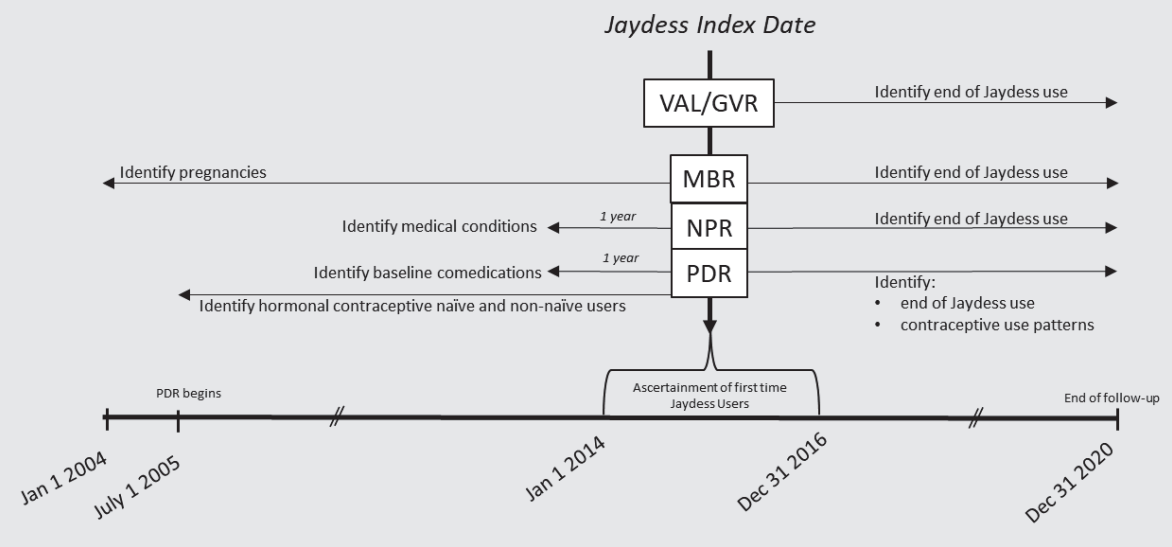

Figure 1: Outline of data sources, study period, and follow-up for the National and Stockholm Cohorts

Abbreviations: MBR, Medical Birth Register; NPR, National Patient Register; PDR, Prescribed Drug Register; VAL/GVR, Regional databases on hospital and primary care diagnoses from Stockholm County.

Part 2: Stockholm Cohort

The Stockholm cohort is a subset of the National cohort including women aged 15 to 55 years at the Jaydess index date with a record of receiving primary care in the county of Stockholm. Women in the Stockholm cohort are linked to their primary care data in the VAL/GVR database and are similarly followed until migration, death, or end of available data (31 December 2020).

Part 3: Medical Record Review

For 204 women, medical records from 1 January 2014 to 31 December 2020 were requested from 7 hospital-based clinics in Sweden (**Supplementary Table 5**). In total, 195 (96%) were retrieved and 9 could not be found in the electronic health records system by the clinic staff. Copies of the 195 medical records were scrutinized by the project team's data abstractor and relevant data extracted

and entered into an excel database. Twenty-four medical records (12%) were not included in the final record review because the medical records had no information regarding contraception use or indicated that an IUD other than Jaydess was used. Of the 171 medical records with information about Jaydess use, two sets were for care received by two women at different hospitals. Therefore, data from the medical records of 168 women were included (**Figure 2**).

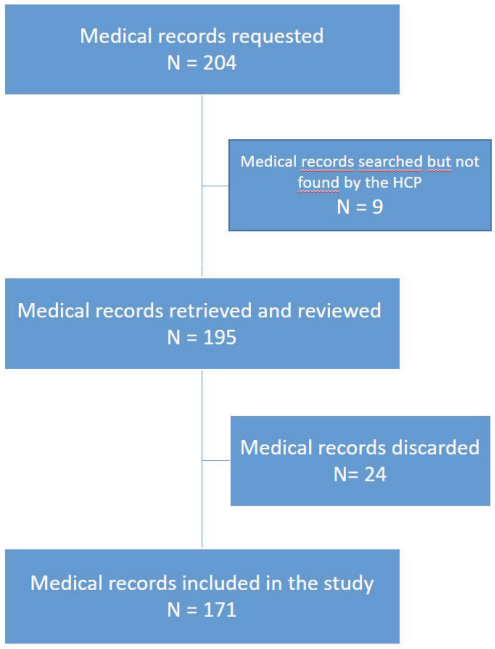

Figure 2: Flowchart illustrative of medical record retrieval and review process
The total number of medical records (n=171) contained data on 168 women using Jaydess
Abbreviations: HCP: Health care provider.

9.4 Variables

Part 1 & 2: National and Stockholm Cohort

Start date of Jaydess Use: In the absence of reliable IUD insertion procedure data, start date of Jaydess use was established by the date of Jaydess dispensing in the PDR identified by Anatomical Therapeutic Chemical Classification System (ATC) code G02BA03 with product name "Jaydess".

Duration of Jaydess Use: Duration of Jaydess use was measured as the period between the Jaydess dispensation date and the date of one of the following events:

- an IUD removal procedure code (Nordic Classification of Surgical and Medical Procedures (NCSP) code TLC10) recorded in the NPR or VAL/GVR
- the estimated first day of the last menstrual period before pregnancy recorded in the Medical Birth Register (MBR)

- a dispensation of another hormonal contraception method recorded in the PDR (ATC codes G02B or G03A)
- insertion of a copper IUD identified by an IUD insertion procedure code (NCSP code TLC00) with no corresponding dispensation of a hormonal IUD within 40 days before or after the date of the procedure

The definition of one month, used to calculate the length of time of Jaydess use, was (365.25/12)= 30.44 days.

Immigration/Emigration: If a migration event occurred during the cohort ascertainment period (2014-2016), the individual was excluded from the study population. Follow-up ended if a migration event was recorded after the index date.

Death: Follow-up of an individual in the study population ended if a date of death was recorded in the Cause of Death Register (CDR) after the index date.

Demographic and social characteristics:

- *age at Jaydess index date*: calculated from birthdate and Jaydess dispensation date (Source: Statistic Sweden and PDR, respectively)

- *highest attained education in year before Jaydess index date* (Source: Statistics Sweden)
    - high school
    - college/university
    - post-graduate
    - missing

- *income in year before Jaydess index date* (Source: Statistics Sweden; see **Supplementary Table 2** for median income for women in Sweden, stratified by age and year)
    - below median income
    - median or above
    - missing

- *civil status in year before Jaydess index date* (Source: Statistics Sweden)
    - registered relationship
    - no registered relationship
    - missing

- *country of birth* (Source: Statistics Sweden)
    - Sweden
    - Nordic countries except Sweden
    - EU except the Nordic countries
    - Europe except EU and Nordic countries

  - Asia
  - Other
  - missing

- *profession of prescriber of Jaydess* (Source: PDR)
  - midwife
  - gynecologist
  - missing

- *parity at index date* (Source: MBR. Note: the MBR only contains data on pregnancies resulting in the delivery of a liveborn or stillborn infant after 22 weeks of gestation. Data from the MBR is from 2004 onwards, therefore for women with a recorded pregnancy in the MBR, the parity recorded in the last pregnancy before the Jaydess index date is reported. For women who had pregnancies prior to 2004, no parity data is available)
  - no pregnancies recorded from 2004 to Jaydess index date
  - parous

- *county of where the index dispensation of Jaydess occurred* (Source: PDR)
  - Stockholm
  - Skåne
  - Västra Götaland
  - Värmland
  - Other
  - missing

Co-medication: Dispensations recorded in the PDR within the 1 year prior to the Jaydess index date were identified by ATC codes. Co-medications included: gonadotropins, fertility medications and procedures, hormone replacement therapy, cardiovascular drugs (e.g., antihypertensive, antiplatelets, anticoagulants, antiarrhythmics), antidiabetic agents, antibiotics, tranexamic acid, NSAIDs, disease-modifying anti-rheumatic drugs, asthma drugs, analgesic drugs, antimigraine drugs, antidepressant drugs, antihypertensive medication and emergency contraception. **Supplementary Table 4** contains the ATC codes used to define these co-medication categories.

Medical diagnoses: Medical conditions recorded in the NPR within the 1 year prior to the Jaydess index date were identified by ICD-10 codes. Comorbidities include: rheumatoid arthritis, osteoarthritis, venous thromboembolism, acute coronary syndrome, cerebrovascular disease, cardiovascular risk factors (e.g., hypertension, diabetes, hyperlipidemia), peripheral arterial disease, gallbladder disease, liver disease, smoking related disease (e.g., chronic obstructive pulmonary disease, emphysema), respiratory failure, gastrointestinal disease (e.g., peptic ulcer disease, gastrointestinal hemorrhage, gastritis and duodenitis, dyspepsia, and inflammatory bowel syndrome, cancer related to sex hormones, alcohol related disorders, inflammatory diseases of female

genitalorgans, endometriosis, pre-malignant disease of the cervix and endometrium (e.g., endometrial polyps, endometrial hyperplasia, cervical polyps, cervical intraepithelial neoplasia, and cervical carcinoma in situ), benign tumors of the female genital tract such as fibroids/myoma, anxiety, depression, acne, premenstrual syndrome, menorrhagia, previous ectopic pregnancy, history of sterilization and interventions for heavy menstrual bleeding (e.g., endometrial ablation). **Supplementary Table 4** contains the ICD codes used to identify these comorbidity categories.

Hormonal contraceptive use before and after Jaydess use: All dispensations of hormonal contraception (ATC codes G02 and G03) before and after the index date were identified using the ATC codes listed in **Supplementary Table 3**.

Copper IUD use before and after Jaydess use: Copper IUD use was identified by an IUD insertion procedure code (NCSP code TLC00) with no corresponding dispensation of a hormonal IUD within 40 days before or after the insertion code date.

Part 3: Medical Record Review
The following data was extracted from the medical records:

- Date of insertion
- Date of removal
- Indication for Jaydess use, categorized into:
    - Contraception
    - Menorrhagia
    - Dysmenorrhea
    - Endometriosis
    - Hormone-replacement therapy (HRT)
    - Missing

Note: some women had more than 1 indication recorded in their medical record. In these circumstances, the woman was included under only 1 indication option with the hierarchy of the indications as listed above.

9.5 Data sources and measurement

A unique personal identity number (PIN) is issued to all citizens of Sweden upon birth, immigration, or to all residents staying at least 1 year in Sweden and is used, unchanged, throughout life. The PIN is used to link patient-level data from the different registers.(14) All residents and citizens, independent of socioeconomic status, have unrestricted access to health services including partial or complete reimbursement of purchased medicines because of a tax-supported public health service with universal coverage. The **Total Population Register** (15) includes data on demographic variables for all Swedish residents including information on country of birth, county of residence,

migration and education, and can be linked to the major national healthcare registers in Sweden, including:

The **Prescribed Drug Register** (PDR) (16-19) includes information on all prescribed drugs dispensed for the entire Swedish population since July 1, 2005. The register contains patient level data on dispensed medicine including information on the dispensed drug (product, quantity, price) as well as the dates of prescription and dispensing. Data on total and reimbursed expenditure and certain characteristics of the prescriber and the workplace of the prescriber are also recorded. All drugs are classified according to the World Health Organization ATC classification and the register is updated monthly. Medications administered during hospitalization are not available in the PDR.

The Swedish **National Patient Register** (NPR) (20, 21) includes more than 99% of all somatic (including surgery) and psychiatric hospital discharges and visits. It is mandatory for all physicians providing private or publicly funded hospital-based care to deliver data to the NPR. Since 1997 ICD-10 codes have been used. A Swedish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures has been used since 1997. Current procedures are listed in the Nordic Classification of Surgical and Medical Procedures (NCSP), has been used since 1997. The NPR was initiated by the NBHW in the 1960's when it started to collect data on individuals receiving inpatient care at public hospitals. Since 1987, the Patient Register has covered all public inpatient care in Sweden and since 2002 there is almost full coverage of all out-patient hospital visits.

The **Swedish Medical Birth Register** (MBR) (22-25) was established in 1973 by an act of the Swedish Parliament, for the purpose of compiling information on ante- and perinatal factors and their importance for infant health. The basic structure of the register has remained unchanged since 1973. Pre-specified data is extracted from the records and forwarded electronically to the NBHW. Specific diagnoses are noted with the currently used version of ICD (International Classification of Diseases) and certain other conditions are captured by means of check boxes.

The **Cause of Death Register** (CDR) (26, 27) comprises all deaths among Swedish residents, whether occurring in Sweden or abroad. The causes of death are coded centrally at Statistics Sweden according to the international (English) version of ICD-10. The NPR can be linked and matched with the cause-of-death register to attain an even better coverage of disease events and, to some extent, to include patients managed outside hospitals.

The **Regional databases on hospital and primary care diagnoses from Stockholm County** (VAL/GVR) includes information on diagnoses and procedures from hospitals and from consultations in primary care in the county of Stockholm since 2002. In addition, the database includes information on dispensed drugs (since 2008) and sociodemographic variables. The county has approximately 2.2 million inhabitants.

Medical Records All hospitals and the absolute majority of private practices in Sweden use one of the electronic medical data systems available on the Swedish market. Among the most used are Take Care, Cosmic and Melior. Each health care provider (i.e. hospital or clinic) is responsible for their

data and the safety of the data storage which is stored electronically. Patients may request a copy of their data from their health care provider and may also request that their medical journal is kept confidential from other health care providers.

9.6 Bias

As this is a utilization study with no exposure-outcome associations estimates, bias according to the traditional epidemiological definition is not relevant and is therefore not discussed.

Jaydess use: Misclassification of Jaydess use may occur in cases where a woman dispenses a Jaydess prescription but does not have the IUD inserted. In order to reduce misclassification, women who dispensed any other contraception on the same date as Jaydess were excluded from the study.

Jaydess start date: Data in the NPR is based only on inpatient care and out-patient specialist care. Insertion of IUDs is mostly performed in primary care, and therefore information on insertion and removal of IUDs (i.e., procedure codes) is not well covered in the NPR. Accordingly, for the National Cohort in Part 1, the dispensation date of Jaydess was used as the start date of use, which may lead to an overestimation of the length of Jaydess use if the woman does not have Jaydess inserted on the date of dispensation. However, even for the Stockholm cohort (Part 2) where primary care data was available, the dispensation date was still used as the start date of Jaydess since the 2016 Pilot study reported incomplete data on IUD insertion codes in the VAL/GVR. The 2016 Pilot study found that using the dispensation date of the hormonal IUD had a sensitivity of 84% (95% confidence interval 78-93%) with a time window of 1 month when compared to primary care data IUD procedure code for insertion.

Jaydess end date: Additionally, the 2016 Pilot study found that a dispensation of another contraception had a low sensitivity for identifying IUD removal within 1 to 3 months. Therefore, in addition to subsequent contraception dispensations, IUD removal procedure codes, data in the MBR regarding pregnancy and removal of an IUD prior to pregnancy, and IUD insertion procedure codes (of a subsequent IUD) were used to identify the end of Jaydess use. However, these methods have not been validated and may have potentially low sensitivity and therefore misclassify the date of the end of Jaydess use.

Duration of Jaydess use: Based on the potential misclassification of the estimated Jaydess start and end date, there further exists the risk that the duration of Jaydess use is also over- or -under-estimated. Data from the medical record review (Part 3) was intended to be used to validate the duration of Jaydess used estimated in the Stockholm cohort (Part 2). However, the PIN for these women were requested separately from the national and regional data order and therefore the register data was not linked to the medical record data. Therefore validation could not be performed. Of note, only 50% of the medical records contain data on the date of IUD insertion or removal. Additionally, the women in the medical record review were not representative of the typical Jaydess users as they were receiving care at a hospital-based gynecology clinic and therefore the duration of use calculated in Part 3 is not generalizable to the larger study population.

9.7 Study size

Power calculations are not required due to the purely descriptive nature of this study.

However, in the study protocol, the following projection was made: "*To estimate how many women would use Jaydess, the use of Mirena, a LNG-IUS on the market prior to the release of Jaydess in Sweden, was investigated. Prior to 2014, approximately 5000 women in Sweden had Mirena inserted for the first time. It was estimated that 10% of the first-time users of Mirena will instead choose Jaydess. Therefore, it was estimated that total of 1500 women will use Jaydess during the three-year study period*."

9.8 Data transformation

Raw data was obtained from Statistics Sweden, the NBHW, the VAL/GVR, and the relevant data extracted from medical records were transformed into analysis datasets or used directly, as appropriate.

9.9 Statistical methods

Only descriptive data of the study population characteristics (numbers, proportions, time) are presented (i.e., no formal hypothesis testing), including data on demographics, concomitant medications/treatments, and diagnoses in the study cohort.

All data summaries were performed using SAS® version 9.4.

9.9.1 Main summary measures

Continuous variables were summarized using mean and standard deviation (SD) or median with inter- quartile range (IQR) where appropriate. Categorical variables were summarized with counts and proportions.

9.9.2 Main statistical methods

No formal statistical methods were applied in this descriptive report. The cohorts were sub-grouped into naïve and non-naïve hormonal contraceptive users prior to Jaydess use, and by recent and past hormonal contraceptive use within the non-naïve users.

9.9.3 Missing values

Given that the Swedish national registers collect comprehensive data on each patient, the amount of missing data on important study variables such as medication and diagnoses are limited. Missing data were not imputed. All variables included a category for missing values, where applicable.

9.9.4 Sensitivity analyses

None.

9.9.5 Amendments to the statistical analysis plan

None.

9.10 Quality control

The data were managed and analyzed in accordance with the Guidelines for Quality Control at the CPE, KI. The statistical analyses, output, and the report were reviewed by the project epidemiologist and statistician.

Register holders (i.e., NBHW, Statistics Sweden, Stockholm Region) perform regular quality controls of their register data. Additionally, validation studies have been conducted and published for some aspects of the national registers. See Section 9.5 for further information and references.

During the medical record data extraction process, when the primary data abstractor wanted a second opinion, the project team's medical advisor who is specialized in obstetrics and gynecology, read the medical record and confirmed that the correct and relevant information had been extracted.

10. Results

10.1 Participants

National Cohort

In total, 38,864 women dispensed Jaydess for the first time in Sweden between 01 January 2014 and 31 December 2016, of which 537 were subsequently excluded due to either having another type of contraceptive dispensed on the same day as Jaydess or a recorded migration event during 2014-2016. The final study population consisted of 38,327 women, including 5,071 contraceptive naïve users (13%), (**Figure 3a**). The final study population for the interim report and the final report differed by 17 women which is the result of regular updates conducted by the national register holders, changes in data cleaning procedures, or a change in the data request extraction methods.

Stockholm Cohort

The derivation of the Stockholm cohort is illustrated in **Figure 3b**. The Stockholm Cohort consisted of 13,323 (35%) women from the National Cohort who resided in Stockholm region. Similarly, 14% (n=1838) were contraceptive naïve Jaydess users.

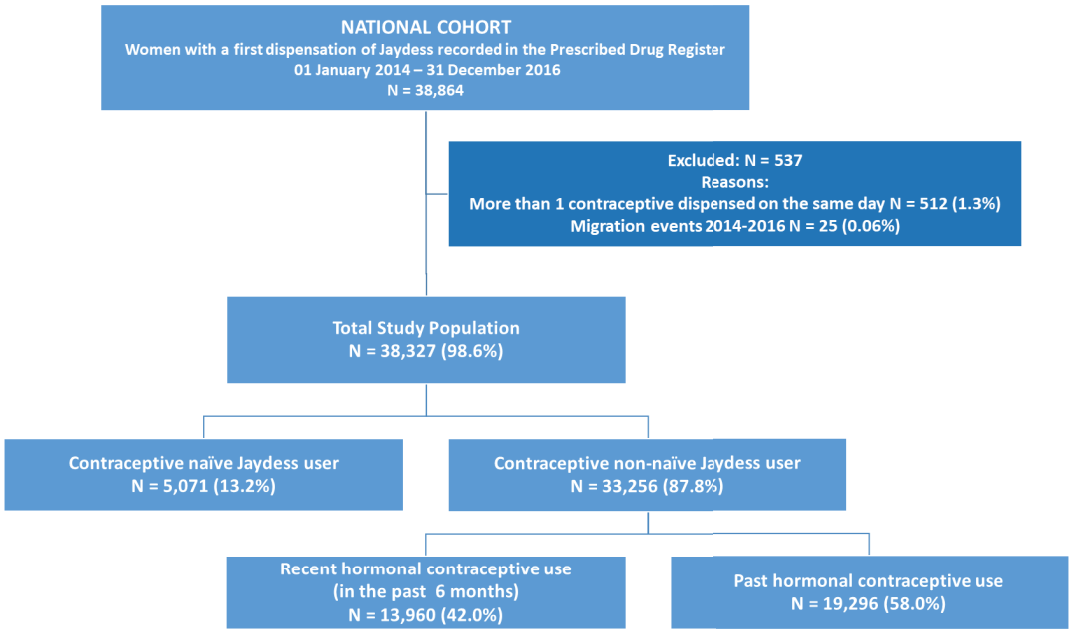

Figure 3a: Illustration of the derivation of the study population in the National Cohort

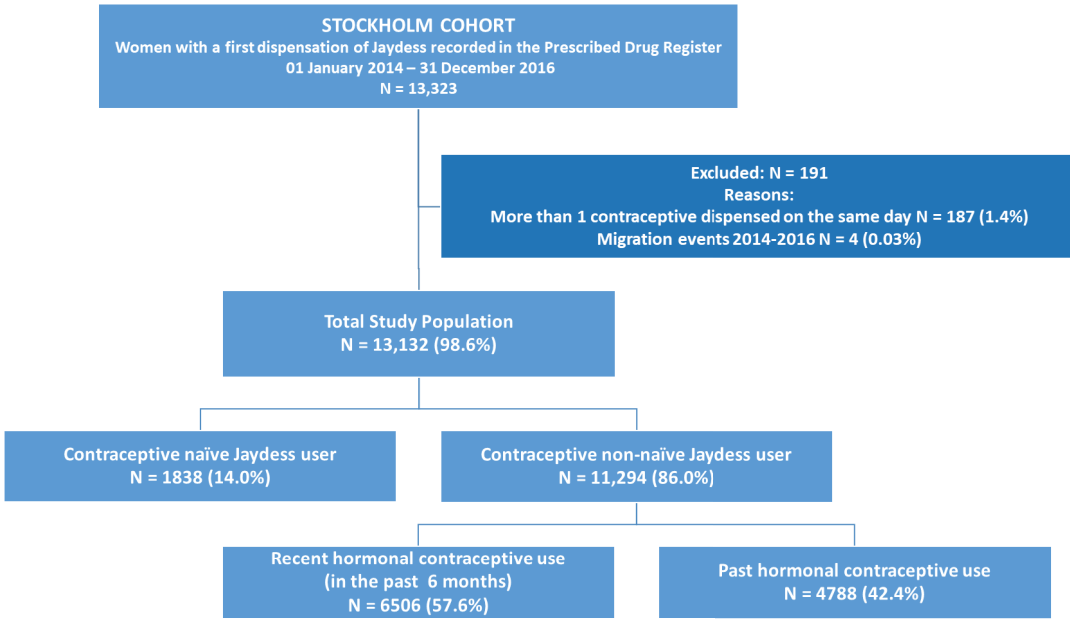

Figure 3b: Illustration of the derivation of the study population in the Stockholm Cohort

Medical Record Review

A total of 171 medical records from 168 women which reported information on the use of 169 Jaydess (hence, 1 woman used more than 1 Jaydess during the study period between 2014-2016) were included in Part 3.

10.2 Descriptive data

Objective 1a: To describe the characteristics (demographic, clinical, social) of first-time users of Jaydess.

National Cohort The first dispensation of Jaydess in Sweden occurred on 11 January 2014. **Table 1a** presents the characteristics of the study population at the Jaydess index date. In total, 38,327 women dispensed Jaydess for the first time during the study period, among these 13% (n=5071) were identified to be naïve contraceptive users, i.e., they had not dispensed any form of hormonal contraception up to 8 years before dispensing Jaydess. Among the 33,256 contraceptive non-naïve Jaydess users, 58% (n= 19,296) were classified as recent users, i.e., they had filled a prescription for any hormonal contraception within six months before the Jaydess index date. The age range of Jaydess users was 12 to 88 years with a mean age at dispensing of 27 and 26 years for naïve and non-naïve users, respectively. The large majority of the study population were born in Sweden (90%), had no recorded pregnancy in the 10 years before the start of the study (66%), and had received their prescription from a midwife (86%).

The frequency of selected comorbidities in the study cohort for the naïve and non-naïve Jaydess users are presented separately in **Tables 2 and 3**, respectively. Overall, the rate of comorbidities was low, with around 2% of non-naïve users having diagnoses of depression, anxiety, premenstrual syndrome, menorrhagia, or inflammatory diseases of female genital organs. Approximately 1% had gastrointestinal diseases, cervical intraepithelial neoplasia, or acne. Less than 1% had cardiovascular risk factors (hypertension, diabetes, or hyperlipidemia). Compared to non-naïve users, contraceptive naïve users had lower rates of inflammatory diseases of female genital organs, cervical intraepithelial neoplasia, and premenstrual syndrome.

Dispensations of selected medications in the year before the index date are reported in **Table 4 and 5** for contraceptive naïve and non-naïve Jaydess users, respectively. Naïve users and non-naïve users had similar rates of medication use including antibiotics (26-30%), antimigraine medication (16-18%), antidepressants (15-16%), analgesic drugs (10-13%) and NSAIDS (9-11%).

Stockholm Cohort Jaydess users in the Stockholm Cohort (n=13,123) were similar to the women in National Cohort with regards to the proportion of contraception naïve and non-naïve users, as well as mean and median age and country of birth, but had slightly higher levels of education and income (**Table 1b**). There were more women without recorded pregnancies in the 10 years prior to study start in the Stockholm versus National Cohort (72% vs 66%). Eighty percent were prescribed their

Jaydess from a midwife, and 80% of women in the Stockholm cohort dispensed their index Jaydess in the Stockholm region. The proportion of women in the Stockholm cohort with the selected comorbidities was similar to that in the National cohort (**Table 2 and 3**), as were the proportion of women using the selected medications (**Table 4 and 5**).

Objective 1b: To estimate the average duration of use of Jaydess.

National Cohort The end of Jaydess use was identified by a dispensing of another hormonal contraception for 63% of women, by pregnancy (resulting in a live birth) for 13%, an IUD removal procedure code for 6%, or by insertion of a copper IUD for 1.0%. Emigration and death ended the follow-up time for 1% and 0.1% of women, respectively. For 16% of women, there was no evidence of an event to signify the end of Jaydess use. Amongst the women where an event signifying the end of Jaydess use was identified, the duration of Jaydess use was estimated to be a mean and median of 26.2 (SD±14.7) and 31 months, respectively, with a range of 0.03 to 79 months (**Table 6a**).

There were fewer pregnancy events identifying the end of Jaydess use and more women without any event to signify end of Jaydess use in the naïve versus non-naïve users. Amongst those with an identified event signifying the end of Jaydess use, the mean duration of Jaydess for naïve users was two months longer (28.4, SD±14.6 months) than non-naïve users (26.0, SD±14.7 months). Amongst the non-naïve users, those with recent contraceptive use were more likely to have a dispensation of a hormonal contraceptive and less likely to have pregnancy signal the end of their Jaydess use compared to those with past contraceptive use.
Supplementary Table 6a reports the characteristics of the 6016 women where no event was identified to signify the end of use of their index Jaydess. Compared to the full National cohort, these women were older (mean age 30 versus 26 years), had higher levels of education, were more likely to be in a registered relationship and to have had children at index date, and also to have dispensed the index Jaydess in the last year (2016) of the study period (54 versus 47%).

Stockholm Cohort In the Stockholm cohort, the proportion of events signifying the end of Jaydess use and mean duration of use for all women and the naïve and non-naïve users were similar to the National Cohort (**Table 6b, Supplementary Table 6b**).

Medical Record Review In total, for 46% (n=78) of the Jaydess units reported in the medical records, there were either a missing insertion or removal date and therefore the duration of use could not be calculated (**Table 11**). Amongst those with data to calculate duration of use (n=91), the mean time between insertion and removal of Jaydess was 11.7 (SD ± 11.4) months with a range of 0 to 37 months. Overall, 23% of Jaydess were used for up to 6 months, 4.7% for 31 to 36 months, and only 2 women used Jaydess for longer than 3 years, with removal occurring the 37th month.

Objective 2a: To study contraceptive switching patterns among women using Jaydess, e.g. what are the hormonal contraceptive methods used before and what are the methods after discontinuing Jaydess.

National Cohort Amongst women with a recorded event indicating the end of Jaydess use, the contraceptive methods prior to and after Jaydess use are listed in **Table 7a.** The most common contraceptive use pattern was the use of progestogen-estrogen combined oral contraceptive pills before Jaydess with the use of a non-Jaydess hormonal IUD after Jaydess (10%). Another 10% of women used progestogen-estrogen combined oral contraceptive pills before and after Jaydess. For naïve users, **Table 8a** reports the type of contraception used after the first dispensation following the index Jaydess by age. With increasing age, larger proportions of women had no hormonal contraception dispensed after Jaydess, from 4% in the <15 age group to 67% in the 50+ age group. For all age groups, a hormonal IUD was the most common contraception used after Jaydess with over 50% of women under 20 and approximately 40% of women between 20 and 49 dispensing a subsequent IUD. The second most common type of contraception in all age groups was oral contraceptives, specifically combined tablets for women under 29 and progestogen only tablets for women between 30 and 49.

For non-naïve users, prior to use of the index Jaydess, oral contraceptives pills (combined or progesterone only tablets) were most commonly dispensed in all age groups (**Table 9a**). Similar to the naïve users, non-naïve users with a post-Jaydess dispensation of oral contraceptive pills or another IUD were the most common in all age groups. Most of the women who had been dispensed a new contraceptive returned to the method used prior to Jaydess.

Stockholm Cohort

In the Stockholm cohort, the dispensing patterns of hormonal contraception before and after Jaydess, overall and by age were similar to the National Cohort (**Table 7b, 8b, 9b**).

Objective 2b: To study off-label use of Jaydess:

- ***Use of Jaydess for a duration of more than 3 years***

In the National cohort, amongst the women that had an identifiable event signifying the end of Jaydess use (n=31,821), 9242 (29%) women had an estimated duration of Jaydess use of more than 3 years (**Table 10a**), with a mean and median length of use of 41.5 (SD±6.9) and 38.5 months, respectively, and a maximum of 79.6 months. Compared to the full National cohort (reported in Table 1a), women with an estimated Jaydess use longer than 3 years had the same characteristics including the same mean age but fewer were in the under 20 age categories and more had an IUD

removal procedure as the event to signify the end of Jaydess use (3% versus 6% in the full National cohort).

Similarly, in the Stockholm cohort, where, theoretically, more information is available regarding the stop date of Jaydess use via procedure codes from primary care, 30% (n=3268) of those with an identifiable end of Jaydess use also had an estimated duration of Jaydess use of more than 3 years (**Table 10b**). Mean and median length of use was 42.1 (SD±7.3) and 38.8 months, respectively, with a maximum of 78.6 months. Characteristics between the full Stockholm cohort (reported in Table 1b) and those with Jaydess use longer than 3 years were similar, with fewer women in the under 20 age categories.

- ***Use of Jaydess for indications other than contraception***

In the National Cohort, there were 49 women over the age of 55 years at the index date (**Table 10a**). Mean age was 60.5 (SD±5.42) years, of which 5 women aged were aged 66 years and above. Compared to the full National Cohort, these women had higher levels of education and income, and were more likely to be in a registered relationship. For 96% of this subset of women, the prescriber of Jaydess was a gynecologist.

In the Medical Record Review, the main indication written in the medical records for Jaydess use was contraception (87%), followed by endometriosis (4.1%), dysmenorrhea (2.4%), menorrhagia (2.4%), and for 1 woman the indication was hormone replacement therapy (**Table 12**). The indication was missing for 6 women (3.6%).

10.3 Outcome data

Only descriptive results reported. See Section 10.2

10.4 Main results

Only descriptive results reported. See Section 10.2

10.5 Other analyses

None.

10.6 Safety data (Adverse events/adverse reactions)

This is a descriptive utilization study and reporting of adverse events is not an included objective.

11. Discussion

11.1 Key results

The objectives of this report are to describe the characteristics of first-time users of Jaydess, their use of contraception before and after Jaydess, to estimate the duration of Jaydess use, as well as to identify possible off-label use.

Characteristics of Jaydess users

During the ascertainment period of the study (2014-2016), 38,864 women dispensed Jaydess for the first time in Sweden and 38,327 were included in this study. The study population reflects the population of Sweden in respect to income, education, country of birth. The study population in general was healthy. The most common disorders among both naïve and non-naïve users where mood disorders such as anxiety and depression. Two to three percent of the women had diagnoses for premenstrual syndrome or menorrhagia. The subset of women in the Stockholm cohort were better educated and had a higher income than women living elsewhere in Sweden. This is consistent with the demographics of the general population in Stockholm compared to the rest of Sweden.

In Sweden, contraceptives can be prescribed by both medical doctors and midwives. The majority of the prescriptions for Jaydess were issued by a midwife, which is to be expected. However, for women older than 55 years in the study population, almost all IUDs were prescribed by a doctor. This is interpreted as that older women are not using Jaydess for contraception, but rather for bleeding control or other indications. Note that in the 2018 interim report of this study, we erroneously reported that Jaydess was more commonly prescribed by gynecologists.

There was little difference in the characteristics between women who were hormonal contraception naïve and non-naïve Jaydess users. As expected, compared to non-naïve users, contraceptive naïve users had around half the rate of inflammatory diseases of female genital organs and cervical intraepithelial neoplasia, as would be expected based on the assumption that naïve hormonal contraceptive users having had less sexual activity.

While the prevalence of diagnoses related to inflammatory diseases of female genital organs may appear higher than expected in this population (2-3%), these diagnoses may be used in the outpatient clinic setting in cases of general reproductive tract pain until further clinical exploration is done. Of note, pelvic/genital inflammatory diagnoses are not a contraindication for IUD use and therefore the observed prevalence in this study population does not raise concern.

Duration of Use and Contraceptive Switching Patterns

Amongst the women where an event signifying the end of Jaydess use could be identified, the median duration of use for all Jaydess users during the study was 31 months. There was little difference in the median duration of time between naïve and non-naïve users. The maximum approved duration is 36 months, implying that many of the women are satisfied with their choice of Jaydess and do not have it removed prematurely. This interpretation is supported by the finding that 55% of the study participants who had the dispensation of a hormonal contraceptive signifying the

end of Jaydess use chose a hormonal IUD again as their next contraceptive method after the index Jaydess. Specifically, among the younger naïve users (age 15-19 years at index Jaydess use), 57% chose a new hormonal IUD as their next contraception and among the women 20-49 years of age at the time of the index Jaydess use around 42-44% chose a new hormonal IUD. The differences in age groups was less evident in the non-naïve users, where an IUD was selected as the hormonal contraceptive method after Jaydess for 42.5% of the women 15-19 years at the time of the index Jaydess use.

Approximately 30% of women with a recorded event signifying the end of Jaydess use had a duration of use of more than 36 months. However, amongst these women, the median duration was 3 years and 2 months, reflecting a short delay in scheduling an appointment for Jaydess removal and/or imprecision in the methods used to identify the end of Jaydess use. Additionally, there were fewer women with an IUD removal procedure signifying the end of Jaydess use amongst this subset with estimated duration of use of more than 3 years, further providing evidence that the imprecision of the estimated duration is an important factor. Overall, the results indicate that the majority of these women did not use Jaydess significantly longer than the approved duration of use.

The imprecision in the methods used to identify the end of Jaydess use are due to poor capture of IUD insertion and removal procedure codes in the register data. Therefore, the date of Jaydess dispensation was used as the start date of Jaydess use, where in reality the woman may have to wait some days or weeks to their appointment for Jaydess insertion. Further, the use of proxies for the end of Jaydess is likely to also result in an overestimation of the duration of use, especially when using the start date of pregnancy, where Jaydess was likely removed many months prior to conception.

Data on the duration of use was also extracted during the medical record review, but was only present for 54% of the Jaydess units included in the records. Amongst the women with information to calculate duration, the mean duration of use was only 11.7 months. This subset of women for which medical records were reviewed are not generalizable to the National or Stockholm cohorts (who primarily receive contraceptive care from midwives in a primary care setting) because they are receiving health care from gynecological clinics at teaching hospitals in Sweden, and therefore are likely to have more complex contraceptive and gynecological needs. Hence, even if these women had been linked to the national and regional health registers, information from this subset could not be used to determine the validity of our methods for identifying duration of use nor the magnitude of the over-estimation of duration by these methods in the full national and Stockholm cohorts. What can be concluded is that in this very small subset (n=91) duration of Jaydess use is short. The aim of the medical record review was primary to identify possible indications of off-label use of Jaydess. The majority of women in the subset were prescribed Jaydess for contraception (approximately 90%). It may be speculated that these women were less satisfied with Jaydess as their method of contraception and were possibly more prone to suffer from/ less capable to tolerate side effects. All this may contribute to a shorter duration of use compared to the majority of Jaydess users. Further, in approximately 10 % of the reviewed medical records the indication was not contraception, and

among these women it may very well be that the effect of Jaydess on, for example, endometriosis was not sufficient resulting in an early removal of the hormonal IUD.

In the national cohort, 6016 women (15.7%) had no identifiable event to indicate end of Jaydess use after the index date recorded in the national registers. This is not unexpected since the majority of IUD insertions and removals occurs in primary care. Therefore, in the regional cohort, national register data was supplemented with primary care data to better detect the end of Jaydess use via removal procedure codes. However, the Stockholm cohort had the same proportion of women (15.6%) without a certain stop date which was unexpected. It could be that some women had their Jaydess removed by a midwife in a 'drop-in clinic' where the visits are not recorded in the primary care data. This could occur, for example, if a woman planning to get pregnant asks the midwife to remove the IUD during a cervical screening appointment.

Evidence of off-label indications of use

Overall, few women were prescribed Jaydess for off-label indications. As the median age in menopause in Sweden is 51 years of age,(28) the use of hormonal contraception after this age implies an indication other than contraception. Only 49 women were older than 55 years when Jaydess was dispensed in the National cohort. Among the 168 women with their medical records reviewed, 9.5% of the women had an off-label indication for Jaydess, most commonly endometriosis followed by menorrhagia and dysmenorrhea. Jaydess is a smaller version of an IUD containing 52 mg (20 microgram/24h) Levonorgestrel (Mirena) available on the Swedish market. Mirena has the following indications in Sweden: contraception, menorrhagia, and endometrial protection during oestrogen substitution. Since some but not many of the women who were prescribed Jaydess for off-label indications in the medical record review received it for indications registered for Mirena, it may be assumed that the clinicians prescribing Jaydess perceive the product as less efficient than its larger counterpart for these off-label indications. As off-label indications of use of Jaydess is very low, it is likely not to pose clinical safety issues in the Swedish context.

11.2 Limitations

The study includes data from three different data sources: national register data, a regional primary care dataset, and medical records. The strengths include full coverage of the national and regional populations.

One limitation inherent to using dispensations of medication for identifying use is that having filled a prescription is not the same as actually using the medication. However, all women who are 23 years or older pay out-of-pocket around 100 Euro for Jaydess. It seems unlikely that a woman will pay this sum and not have it inserted. For women less than 23 years, the device is subsidized to a personal cost of approximately 10 Euro, hence failure to have the IUD inserted may be higher in the younger women.

Based on the potential misclassification of the estimated Jaydess start and end date (outlined in section 9.6) is it likely that the duration of Jaydess use is over- or -under-estimated in this study. Administration of LARCs is mostly done in primary care and therefore information concerning insertion and removal of these contraceptives is not fully covered in the NPR, which includes information from hospital-based care only. Those identified as having an IUD inserted or removed at the hospital are likely not representative of users of IUDs in general. Insertion at the hospital may be in connection with an abortion and a removal could be performed because of special complications, such as dislocation of the IUD. In order to get more complete data for IUD insertion and removal dates the study combined regional and national data registers for a subset of women in Stockholm County. The expanded dataset did not provide more information on the removal dates of the IUD. Other sources of information were used to determine the end of Jaydess use, including the start of pregnancy and the dispensation of another type of hormonal contraceptive. More than 60% of the events indicating the end of Jaydess use were a dispensation of a new hormonal contraceptive. However, the 2016 Pilot study shows that a dispensation of another contraceptive had low sensitivity for identifying IUD removal within 1 to 3 months. Additionally, pregnancy was the event which identified the end of Jaydess use for 13% of women, and the sensitivity of this method has not been validated. It is likely to be low since amongst women removing Jaydess with the intent to conceive will likely take many months to actually become pregnant. As discussed above, the duration of use could not be validated in the data collected from the medical chart review due to the non-generalizability of the women for which charts were requested compared to the larger study population of Jaydess users.

Ultimately, the study could estimate the duration of use of 83% of the women included in the National cohort , and the women where end of Jaydess could not be identified differed slightly in their sociodemographic characteristics including age, education, and parity.

Information included in the MBR before 2004 was not linked to the study dataset. Hence information on children born by women in the dataset before 2004 is missing, which is why all women older than 55 years appear to be nulliparous in the dataset.

The last year of follow-up for the study population was 2020 during which the COVID-19 pandemic began worldwide. In Sweden, there were significant changes in the volume of prescription medication dispensed at pharmacies during the month of March, overall suggestion stockpiling behavior, followed by a stabilization in volume dispensed throughout the rest of the year.(29) However, this is likely to have a negligible impact on this study.

11.3 Interpretation

The results of the report lie within an excepted range based on knowledge from clinical practice in the patient population. The socio-economic characteristics and clinical background of the participants reflect the general reproductive-aged female population in Sweden. The number of women included in the study population was higher than anticipated in the study protocol, reflecting

the observed market uptake after Jaydess launch in Sweden. There are no similar population studies on the use and characteristics of users of Jaydess in a real world setting. Published studies including randomized clinical trials and smaller clinical studies have shown high efficacy and safety of Jaydess, and that it is generally well tolerated in women of all ages and parity.(6-12) The current study support these findings, and also concludes that the off label use of Jaydess in the Swedish context is low.

11.4 Generalizability

In Part 1 of this study, the study population was identified by data from the Swedish National Registers. The criteria for an individual's data to be included in the national registers is the assignment of PIN which is assigned to all citizens and to residents staying at least 1 year in Sweden (further described in Section 9.5).(14, 15) The study population in Part 2 was identified based on primary care data from the Stockholm region. Characteristics between the National and Stockholm Cohort were similar. Therefore, the study findings are likely to be generalizable to all Jaydess users in Sweden and in similar settings.

The information about the indication for Jaydess use was investigated in Part 3 where data was collected from medical records based on visits to gynaecology clinics in teaching hospitals. As the prescribing, insertion, and removal of IUDs in Sweden is mainly performed in primary care by midwives, the women contributing data to Part 3 of the study are not representative of users of Jaydess or IUDs in general. Insertion and removal of an IUD at a hospital-based clinic could be done in connection with an abortion, due to of complications such as dislocation of an IUD, or in women with gynaecological conditions.

12. Other information

None.

13. Conclusion

In the current post-marketing study including more than 38,000 first time users of Jaydess in Sweden 2014-2016, we conclude that the users reflect the general population of Swedish women regarding sociodemographic factors. The participants were as expected in general good health with the most common medical conditions being mood disorders (2-3%). The duration of use was estimated in 83% of the study population and the median duration of use was 31 months. More than 50% of the women who continued with hormonal contraception after the index Jaydess chose a hormonal IUD, and among these half the women opted for a new Jaydess. The majority of women who chose another hormonal contraception other than an IUD returned to the method of contraception they used before Jaydess, the most common of which was combined oral contraception. Off-label use of the Jaydess is most likely negligible in clinical practice in Sweden.

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Appendices

Annex 1: List of stand-alone documents

Table 2: List of stand-alone documents

Document Name	Final version and date (if available)*
Jaydess Report Final Tables 2022 08 22	v.1.0, 22 AUGUST 2022

Annex 2 Additional information

<Not applicable>

Annex 3 Signature Pages

Please use the following Signature Page template to prepare signature pages for each OS Team member in accordance to their roles in the study (see also persons listed in section 3.1 (main responsible parties at Bayer)).

Please refer to the best practice document ***Guidance for the supplement OS*** **report** ***(secondary data collection)*** *for further guidance and information*

Signature Page – PPD

Title	Jaydess DUS/ Pharmacoepidemiological study (Drug Utilization Study) of JAYDESS use in routine clinical practice in Sweden.
Report version and date	Final Report v1.0, 22 AUGUST 2022
IMPACT study number	16903
Study type / Study phase	PASS
EU PAS register number	8498
Medicinal product / Active substance	Jaydess Intrauterine delivery system, 13.5 mg (ATC code G02BA03) / Levonorgestrel (ATC code G03AC03)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: PPD PPD

Signature Page – MAH contact person

Title	Jaydess DUS/ Pharmacoepidemiological study (Drug Utilization Study) of JAYDESS use in routine clinical practice in Sweden.
Report version and date	Final Report v1.0, 22 AUGUST 2022
IMPACT study number	16903
Study type / Study phase	PASS
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Medicinal product / Active substance	Jaydess Intrauterine delivery system, 13.5 mg (ATC code G02BA03) / Levonorgestrel (ATC code G03AC03)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: Dr PPD

PPD

Date, Signature: _____

Signature Page - PPD

Please insert information as per title page

Title:	Jaydess DUS/ Pharmacoepidemiological study (Drug Utilization Study) of JAYDESS use in routine clinical practice in Sweden.
Report version and date	Version 1.0, 22.08.2022
IMPACT study number	16903
Study type / Study phase	Observational <Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study)> <PASS> Joint PASS: ☐ YES ☒ NO
EU PAS register number	6498 in the EU PAS register
Medicinal product / Active substance / Medical Device / Combination Product	Jaydess Intrauterine delivery system, 13.5 mg (ATC code G02BA03)
Comparator / Reference therapy	n.a.
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: _____, PPD

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Report version and date	Version 1.0, 22.08.2022
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Study type / Study phase	Observational Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) <PASS> Joint PASS: ☐ YES ☒ NO
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Print Name: <Name Surname> PPD

Date, Signature: PPD PPD

Signature Page – PPD

Title:	Jaydess DUS/ Pharmacoepidemiological study (Drug Utilization Study) of JAYDESS use in routine clinical practice in Sweden.
Report version and date	Version 1.0, 22.08.2022
IMPACT study number	16903
Study type / Study phase	Observational Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) <PASS> Joint PASS: ☐ YES ☒ NO
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Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 29.9.2022, PPD

Signature Page – PPD

Title:	Jaydess DUS/ Pharmacoepidemiological study (Drug Utilization Study) of JAYDESS use in routine clinical practice in Sweden.
Report version and date	Version 1.0, 22.08.2022
IMPACT study number	16903
Study type / Study phase	Observational Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) <PASS> Joint PASS: ☐ YES ☒ NO
EU PAS register number	6498 in the EU PAS register
Medicinal product / Active substance / Medical Device / Combination Product	Jaydess Intrauterine delivery system, 13.5 mg (ATC code G02BA03)
Comparator / Reference therapy	n.a.
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: <Name Surname>

Date, Signature: PPD PPD