Post-Authorisation Safety Study Protocol

Version 2.0

A Drug Utilization Study of SEASONIQUE® in Europe

Non-interventional Phase IV study

Study: DR105-WH-50023

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Sponsor

Teva Branded Pharmaceutical Products R&D, Inc.

Post-Authorisation Safety Study Information

Title	A Drug Utilization Study of SEASONIQUE® in Europe
Protocol Version Identifier	Version 2.0
Protocol Last Version Date	12 January 2017
EU Post-Authorisation Study(PAS) Register Number	Study has not yet been registered. It will be registered prior to data collection.
Active Substance	0.15 mg levonorgestrel (LNG)/0.03 mg ethinyl estradiol (EE) for 84 days, followed by 0.01 mg EE for 7 days
Medicinal Product	SEASONIQUE®
Product Reference	N/A
Procedure Number	FR/H/0516/001
Marketing Authorisation Holder(s)	**FR**: Teva Sante, 100-110 Esplanade du Général de Gaulle, Paris la Défense Cedex, 92931, France **AT**: Ratiopharm Arzneimittel Vertriebs-GmbH **BE**, LU: Teva Pharma Belgium N.V **CZ**: Teva Pharmaceuticals CR s.r.o **DE**: Teva GmbH **DK, EE, FI, LV, NL**: Teva B.V. **ES**: TEVA PHARMA, S.L.U. **HR**: Pliva Hrvatska d.o.o **HU**: Teva Gyógyszergyár Zrt. **IT**: Teva Italia S.r.l. **PL**: Teva Pharmaceuticals Polska Sp. z o.o. PT: Teva Pharma – Produtos Farmacêuticos Lda **RO**: Teva Pharmaceuticals S.R.L. **SE**: Teva B.V. **SI**: Teva Pharma B.V. **SK**: Teva Pharmaceuticals Slovakia s.r.o. **UK**: Teva UK Limited **US**: Teva Branded Pharmaceutical Products R&D, Inc.
Joint Post-Authorization Safety Study	No

Post-Authorisation Safety Study Information (continued)

Research Question and Objectives	To characterize drug utilization patterns of SEASONIQUE® in European countries
Countries of Study	Belgium, France, and Italy
Author	Sigal Kaplan, PhD, B.Pharm Director, Epidemiology team leader Teva Pharmaceutical Industries E-mail: Sigalit.Kaplan@teva.co.il
Marketing Authorisation Holder(s)	**FR**: Teva Sante, 100-110 Esplanade du Général de Gaulle, Paris la Défense Cedex, 92931, France **AT**: Ratiopharm Arzneimittel Vertriebs-GmbH, Albert-Schweitzer-Gasse 3, 1140 Wien, Austria **BE, LU**: Teva Pharma Belgium N.V, Laarstraat 16, Wilrijk, 2610, Belgium **CZ**: Teva Pharmaceuticals CR s.r.o, Radlická 3185/1c, Prague, 150 00, Czech Republic **DE**: Teva GmbH, Graf-Arco-Str. 3, 89079 Ulm, Germany **DK, EE, FI, LV, NL, SE**: Teva B.V., Swensweg 5 Haarlem, 2031GA, The Netherlands **ES:** TEVA PHARMA, S.L.U., C/ Anabel Segura, 11, Edificio Albatros B, 1ª planta, Alcobendas, Madrid, 28108, Spain **HR**: Pliva Hrvatska d.o.o, Prilaz baruna Filipovića 25, 10 000 Zagreb, Croatia **HU**: Teva Gyógyszergyár Zrt., Debrecen, Pallagi út 13., H-4042, Hungary **IT**: Teva Italia S.r.l., Piazzale Luigi Cadorna, 4 - 20123 Milano, Italy **PL**: Teva Pharmaceuticals Polska Sp. z o.o., 53 Emilii Plater street, 00-113 Warsaw, Poland **PT**: Teva Pharma – Produtos Farmacêuticos Lda, Lagoas Park, Edifício 5 A, Piso 2, Porto Salvo, 2740-245, Portugal **RO**: Teva Pharmaceuticals S.R.L., Str.Domnita Ruxandra nr.12, parter, sector 2, Bucuresti, Romania **SI**: Teva Pharma B.V., Swensweg 5, 2031 GA Haarlem, The Netherlands **SK**: Teva Pharmaceuticals Slovakia s.r.o., Teslova 26, 821 02 Bratislava, Slovakia **UK**: Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, United Kingdom **US**: Teva Branded Pharmaceutical Products R&D, Inc., 41 Moores Rd., Frazer, PA 19355
Marketing Authorisation Holder(s) (MAH) Contact Person	Wendy Huisman EU QPPV Teva Pharmaceuticals Europe BV Swensweg 5 2031 GA Haarlem Netherlands Email: wendy.huisman@tevapharmachemie.com

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ATC	Anatomical Therapeutic Chemical
ATE	arterial thromboembolic event
BMI	body mass index
BP	blood pressure
CHC	combined hormonal contraceptive
CI	confidence interval
COC	combined oral contraceptive
CSD	Cegedim Strategic Data
CV	cardiovascular
CVA	cerebrovascular accidents
DUS	drug utilization study
DVT	deep venous thrombosis
EE	ethinyl estradiol
EMA	European Medicines Agency
EMR	electronic medical records
EU	Europe/European Union
GP	general practitioner
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IS	ischemic stroke
LNG	levonorgestrel
OC	oral contraceptive
PASS	post-authorisation safety study
PE	pulmonary embolism
RWD	real world data
SD	standard deviation
SOP	standard operating procedures
VTE	venous thromboembolic event

3. RESPONSIBLE PARTIES

Sponsor's Safety physician
Mihaela Dumistracel, MD
Global Patient Safety and Pharmacovigilance
Teva Pharmaceuticals
4-8 Nicolae Titulescu Blvd
Bucharest, 011141
Tel: 037-452-0799
Cel: 075-308-2931

Sponsor's Epidemiologist
Sigal Kaplan, PhD, B.Pharm
Director, Epidemiology team leader
Global Patient Safety & Pharmacovigilance
Teva Pharmaceutical Industries
16 Basel St., Petach-Tikva, Israel
E-mail: Sigalit.Kaplan@teva.co.il

Sponsor's Qualified Person Responsible for Pharmacovigilance (QPPV)
Wendy Huisman
European Union (EU) QPPV
Teva Pharmaceuticals Europe BV
Swensweg 5
2031 GA Haarlem, Netherlands
Email: wendy.huisman@tevapharmachemie.com

Sponsor's Global Medical Affairs Project Leader
Marie-Christine Micheletti, MD
Europe Women's Health Medical Manager
E-mail: Marie.Christine.Micheletti@Tevaeu.com

4. ABSTRACT

Title

A Drug Utilization Study of SEASONIQUE®[1] in Europe

Rationale and Background

SEASONIQUE is a novel extended oral contraceptive containing fixed-dose combination of 0.15 mg levonorgestrel (LNG)/0.03 mg ethinyl estradiol (EE) for 84 days, followed by 0.01 mg EE for 7 days. The extended-regimen combined oral contraceptives (COC) may improve compliance and reduce the risk of unwanted pregnancies by providing continuity and decreasing scheduled withdrawal bleeding to 4 episodes per year.

In the context of the regulatory submission for market authorization of SEASONIQUE in Europe, the European Medicines Agency (EMA) has requested a drug utilization study (DUS) to describe the utilization patterns of SEASONIQUE in Europe during routine clinical practice.

Research Question and Objectives

The primary objective is to characterize drug utilization patterns of SEASONIQUE in European countries

Study Design

This study will be a retrospective cohort study using a secondary database.

Setting and Study Population

The study will capture data from patients in the outpatient setting in selected European countries (Belgium, France, and Italy). The study population will consist of female patients receiving at least 1 prescription for SEASONIQUE during a 3-year time period after product launch in Europe.

Study participants will be followed from first SEASONIQUE prescription until the earliest of the following censoring dates: end of the study period or end of enrollment in the database.

Among the study population, a subset of patients with at least 6 months of continuous membership enrollment prior to the first SEASONIQUE prescription will be defined, if feasible, to obtain relevant data on the patients' medical history and prescriptions recorded in the databases.

Variables

Data on demographics, patient and treatment characteristics of SEASONIQUE use, and medical history will be extracted for each patient. Comorbidities and concomitant medications will be included as well.

Drug utilization patterns of SEASONIQUE will be described using all available data from the date of first prescription until the end of study period or end of enrollment in the database.

[1] SEASONIQUE® is a registered trademark of Teva Pharmaceutical Industries Ltd.

The following characteristics will be examined:

- duration of use
- indication of use
- use of previous COC and switch patterns

Exposure will be defined as one or more recorded written prescription for SEASONIQUE during the study period. If feasible, naïve users (starting use), new users, re-starters, and switchers will be further identified.

Data Sources

Data will be obtained from European Union (EU) automated healthcare databases, IMS electronic medical records (EMR), from 3 countries in which the product is marketed (Belgium, France, and Italy). The databases to be used collect information recorded by various panels of healthcare providers, such as primary care physicians and gynecologists in real-life setting.

Study Size

All SEASONIQUE prescriptions for female patients recorded during the study period in the selected databases will be included in the analysis. The sample size for this study depends on the data availability in the 3 IMS healthcare databases. The final number of women to be included in the study will be determined at the time of data extraction for the entire study period based on the data available in the country-specific databases.

During the period from product marketing until October 2016, the numbers of female patients receiving SEASONIQUE prescriptions were 30 in Belgium (primary care), 60 and 260 in France (primary care and gynecologist, respectively), and 100 in Italy (primary care). Based on these numbers and on the projected sales of this product, it is estimated that by 2018, the number of female patients treated with SEASONIQUE® by panel and country will be 88 in Belgium (primary care), 167 and 724 in France (primary care and gynecologist, respectively), and 134 in Italy (primary care). Therefore, in spite of the low use, most of the drug utilization data are expected to derive from France.

Data Analysis

The main analysis will be descriptive and will provide drug utilization of SEASONIQUE use, including duration of use and indication. The drug utilization patterns of SEASONIQUE will also describe patients characteristics/demographics and indication by physician panel in the outpatient settings (ie, primary care, gynecologists) in each of the 3 databases.

Milestones

The data collection will start 3.5 years after SEASONIQUE usage is first captured (eg, launch date) in EU databases to allow for accumulation of data in the databases and to take into account the time lag for data recording. End of data collection is expected 6 months after the start of data collection. The final study report will be submitted 12 months after the end of data collection.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

The drug utilization study will be conducted using 3 IMS European electronic medical records (EMR) databases. The milestones and dates are aligned with the data availability in the 3 country-specific databases (Belgium, France, and Italy) as well as with the proposed study period.

The study period will be from the time SEASONIQUE®[2] is first captured in the country-specific EU database (ie, around drug launch in 2015) for a period of 3 years. The product was launched in May, August, and September 2015 in Italy, Belgium, and France, respectively. Since SEASONIQUE is new in the EU market, a 3-year time period was selected to allow for accumulation of data on SEASONIQUE in the EU data source for describing utilization patterns. Moreover, this time period will also allow for obtaining study results in a reasonable time frame.

Data collection will start 3.5 years after SEASONIQUE is first captured in the EU databases to allow for 3 years' worth of data accumulation. The additional 6-month gap was added to account for the time lag until data are accumulated and available for extraction and analysis. End of data collection is expected 6 months after start of data collection.

Because of the small number of patients, ranging from 30 to 260 (in primary care or gynecologist settings) found in a preliminary patient count of SEASONIQUE users in each country for the period since product marketing until October 2016, an interim analysis will not be conducted.

A final analysis of the EU data will be conducted when data covering at least 3 years after launch are available, and the final DUS report will be submitted 12 months after end of data collection.

Study milestones along with planned dates for the databases are presented in Table 1.

Table 1: Milestones

Milestone	Planned date
Start of data collection	3.5 years after SEASONIQUE is first captured (eg, launch date) in European Union databases
End of data collection	6 months after start of data collection
Registration in the EU PAS register	Prior to data collection
Final report of study results	12 months after the end of data collection

[2] SEASONIQUE® is a registered trademark of Teva Pharmaceutical Industries Ltd.

7. RATIONALE AND BACKGROUND

SEASONIQUE is a 91-day extended combined oral contraceptive (COC), containing a fixed-dose combination of 0.15 mg of LNG and 0.03 mg ethinyl estradiol (EE) to be taken without interruption for 84 days, followed by 0.01 mg EE tablets for 7 days. The extended-regimen of SEASONIQUE is a modification of the standard 28-day cyclic regimen and is designed to increase the number of days of combined active tablets administration. Consequently, this regimen results in fewer scheduled withdrawal bleeding episodes per year than would regularly occur with conventional COCs. The extended-regimen COC may improve compliance and reduce the risk of unwanted pregnancies by providing continuity and decreasing scheduled withdrawal bleeding to 4 episodes per year.

The standard 28-day cyclic regimen, consisting of 21 days of active combination pills followed by 7 pill-free days or 7 days of placebo pills, was designed to induce withdrawal bleeding once every 28 days (13 times per year). The monthly bleeding concept was designed to imitate the normal menstrual cycle as it was presumed that regular withdrawal bleeding was essential to the acceptance of oral contraceptives (OCs) by women and society. However, this bleeding is not a physiologic menstrual period. Moreover, the presence of cyclic bleeding is not essential for the contraceptive action of OCs. Therefore, research was conducted to reduce the length of the hormone-free interval (HFI) in an attempt to decrease estrogen-related withdrawal symptoms associated with traditional OCs.

The marketing authorizations for SEASONIQUE were granted in Europe in various countries starting from 2015. The doses of this fixed-combination COC, ie, 0.15 mg LNG and 0.03 mg EE, are already approved and used in other COCs authorized in Europe. In Europe, the first extended-regimen OC has been authorized in 2012 (Yvidually, which contains drospirenone and ethinylestradiol, and intended to be taken up to 120 days continuously). SEASONIQUE is the first levonorgestrel-containing extended regimen approved in Europe. SEASONIQUE was approved in the United States in May 2006 and in Canada in March 2010.

Given that the clinical program does not necessarily reflect the actual utilization patterns of women treated with SEASONIQUE, utilization patterns of this new extended regimen in routine clinical practice are not entirely known. In the context of the regulatory submission for market authorization of SEASONIQUE in Europe, the European Medicines Agency (EMA) has requested a post-authorization safety study (PASS) to describe the drug utilization patterns with SEASONIQUE during routine clinical practice.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Primary Objective(s)

The primary objective is to characterize drug utilization patterns of SEASONIQUE in European countries

8.2. Secondary Objective(s)

None.

9. RESEARCH METHODS

9.1. Study Design

This will be a retrospective cohort study using secondary databases.

9.2. Setting and Study Population

The study will capture data from patients in the outpatient setting of primary care providers and specialists (gynecologists) in selected European countries (Belgium, France, and Italy). The countries were selected based on the product launch and availability of longitudinal secondary databases. The study population will consist of female patients receiving at least 1 prescription for SEASONIQUE during a 3-year period after product launch.

The study period will begin from the time the drug data are first captured in the database of the selected countries (at the earliest May, August, and September 2015 in Italy, Belgium, and France, respectively) until 3 years after product first captured. Since SEASONIQUE is new in the EU market, a 3-year time period was selected to allow for accumulation of data on SEASONIQUE in the EU data source for describing utilization patterns. Moreover, this time period will also allow for obtaining the study results in a reasonable time frame.

The date of receiving the first prescription of SEASONIQUE in the study period will be defined as the index date. Study participants will be followed from the index date until the earliest of the following censoring dates: end of the study period or end of enrollment in the database.

Among the study population who have at least 1 prescription record for SEASONIQUE during the study period, a subset of patients with at least 6 months of continuous membership enrollment prior to the first SEASONIQUE prescription will be defined, if feasible. A minimum of 6-month continuous enrollment/membership within the database before the index date will be used to obtain information about the relevant medical history and COC drugs before start of SEASONIQUE. A period of at least 6 months was selected to allow for an adequate number of patients in that subgroup without reducing precision significantly.

9.2.1. Inclusion Criteria

Patients will be included in the study only if they meet all of the following criteria:

- female
- have a record of at least 1 written prescription for SEASONIQUE during the study period

9.2.2. Exclusion Criteria

No exclusion criteria will be applied to examine SEASONIQUE use in real life.

9.3. Variables

9.3.1. Exposure

Exposure will be defined as 1 or more recorded written prescriptions for SEASONIQUE during the study period. By definition, the starters of this newly launched product would only include new users. SEASONIQUE prescriptions will be identified using the Anatomical Therapeutic Chemical (ATC) classification system code for SEASONIQUE. The date of first record of SEASONIQUE prescription (ie, exposure start date or cohort entry date) in the database during the study period will be defined as the index date. The duration of each prescription will be determined from the date of prescription and the total prescription quantity. The duration of use will be estimated based on all written prescriptions during the observation period.

Episodes of SEASONIQUE will be constructed using the prescription date and number of packages prescribed, if available. An episode of therapy will be defined as a period of continuous usage of 1 or a series of prescriptions for SEASONIQUE for the same patient. The first episode of therapy will begin on the cohort entry date. If a subsequent prescription fill is recorded within 30 days after the end of the preceding prescription's days of supply, then the therapy will be counted as continuous use and the subsequent prescription will be considered part of the continuous use related to the earlier prescription. This gap of 30-day grace period after the 90-day SEASONIQUE supply allows for some variability in fill date (Sikka 2005; Pittman 2010). An arbitrary gap's length of time is chosen to account for any potential lag in obtaining a new prescription and for defining whether or not COC was discontinued. A shorter gap of 7 days may be too short for defining a COC discontinuation in database settings. A sensitivity analysis will be performed to vary the gap length.

On the other hand, if a successive prescription for the same COC is filled during the time period of the previous prescription (resulting in an overlap), the assumption of using the drug regimen as prescribed will be examined. The group of patients with overlapping prescriptions will be identified.

If a new different COC is either added to or replaced by the initial drug (ie, new COC other than the drug used on the index date), the first ongoing prescription of 2 overlapping prescriptions will be truncated and will be considered discontinued on the date the new subsequent prescription is issued.

If the gap between adjacent prescriptions is longer than 30 days for SEASONIQUE, then the episode of therapy ends on the last day of the previous prescription. The consecutive prescription will be considered as the start of a new episode of exposure rather than as a continuation of the previous one. Patients may have several exposure episodes during the study period.

Examination of the entire medical history available prior to the index date (ie, 6 months of continuous enrollment or beyond) for COC use will allow for differentiation between various groups of users. The following definitions will be used to identify naïve users, new users, re-starters, and switchers in the subpopulation (Lidegaard 2011), if feasible:

- **Naïve users (starting use)** are defined as women with first-ever exposure to SEASONIQUE during the study period and no use of any dispensed combined hormonal contraceptive (CHC) prior to the index date.

- **New users** are defined as women starting use of SEASONIQUE after a break of at least 12 weeks for any prescription of CHC prior to the index date.
- **Re-starters** are defined as women who restart SEASONIQUE after a break of 4-11 weeks of using other CHC.
- **Switchers** are defined as women starting SEASONIQUE after a different CHC preparation with a break of less than 4 weeks.

9.3.2. Primary and Secondary Endpoints

To describe the drug utilization patterns of SEASONIQUE in the outpatient setting in Europe, the following parameters will be considered:

- duration of SEASONIQUE use (uninterrupted use)
- SEASONIQUE indication (diagnosis related to the SEASONIQUE prescription)
  - In general, a prescribed medication is systematically linked to a clinical diagnosis.
  - It is possible that the linked diagnosis does not reflect the specific treatment indication (eg, flu as a reason for the consultation).When prescriptions are not linked to a specific indication in a database, a proxy will be used to define the indication for prescribing the COC at index date. Diagnoses related to prescribing COC will be defined a priori using International Classification of Diseases, Ninth or Tenth Revisions, Clinical Modification (ICD-9-CM or ICD-10-CM) codes, as applicable, to represent the approved indications for COC (contraceptive management) and indications known to be potentially associated with COC. The list of diagnoses is based on the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on Noncontraceptive Uses of Hormonal Contraceptives (ACOG 2010). It lists some common potential non-contraceptive use including treatment of menstrual cycle irregularity, dysmenorrhea, acne, and premenstrual syndrome, and prevention of menstrual migraines (ACOG 2010). The ICD-10-CM diagnosis codes for defining the diagnoses related to prescribing COC are described in Annex 3.1. The diagnoses of SEASONIQUE prescriptions recorded in the database will be listed and grouped by ICD-10-CM codes (up to 4-digit code).
  - The indication is recorded using a country-specific proprietary diagnostic code thesaurus (France and Belgium) or ICD-9-CM classification (Italy) implemented as a pre-coded list (not free text) in the physician's software. However, the physician could elect to record any other associated diagnosis (according to an in-house thesaurus list). Proxies for indication will be created using computer algorithms based on appropriate diagnostic, procedural, and medication codes and be applied to identify potential on-label indications.
  - A time window of 1 month before or after the index date will be used. Therefore, any ICD-10-CM code for the pre-defined diagnosis potentially related to prescribing COC recorded in the ±1-month time window will be considered in the analysis as a potential reason for prescription.

- use of prior CHC before SEASONIQUE initiation
- switch patterns of patients using SEASONIQUE and changes to a different COC and concomitant use of other COC or other forms of contraception

9.3.3. Other Variables

Baseline characteristics and demographic information will be collected for each patient from the database during the period prior to the index date based on medical codes and terms and/or from detailed clinical data in the patient medical record, if available, including the following:

- demographic characteristics of SEASONIQUE users
  - age at index date
  - smoking status
  - height/weight (body mass index [BMI])
- information on type of prescriber (physician panel)
- medical history of the following diagnoses:
  - thromboembolic event
    - venous thromboembolic event (VTE), defined as deep venous thrombosis (DVT) and/or pulmonary embolism (PE)
      - The ICD-10-CM diagnosis codes for defining VTE outcomes are described in Annex 3.2.
    - arterial thromboembolic events (ATEs), including acute myocardial infarction (AMI), ischemic stroke (IS) and cerebrovascular accidents (CVA)
      - The ICD-10-CM diagnosis codes for defining ATE outcomes are described in Annex 3.3.
  - breast cancers and other gynecological cancers
    - Breast, cervical, endometrial, and ovarian cancers will be identified. ICD-10-CM diagnosis codes for defining gynecological cancers are described in Annex 3.4.
  - previous major surgery (including lower limb orthopedic surgery) or major lower extremity or pelvic trauma within 3 months before treatment initiation
  - chemotherapy
  - hypertension: uncontrolled or untreated hypertension diagnosis (or blood pressure [BP] measurements of systolic BP ≥ 140 mmHg or diastolic BP ≥90 mmHg) or use of antihypertensive drugs
  - diabetes mellitus: diagnosis or use of diabetes drugs
  - polycystic ovary syndrome (PCOS)
  - migraine

  - hyperlipidemia
  - diagnosis of systemic lupus erythematosus (SLE)
- data on concomitant medication use (including medications prescribed for the treatment of cardiovascular (CV) disease, diabetes, and other chronic medical conditions)
- pregnancy
  - Periods of pregnancy will be estimated by identifying ICD-10-CM diagnoses codes for pregnancy (Annex 3.5).
  - Pregnancy will be defined as follows, if feasible:
    - previous pregnancy: 3 months or longer before index date
    - recent pregnancy: within 3 months before index date
    - prospective pregnancy: after index date

The availability of key study variables in the proposed databases is provided in Table 2.

Table 2: Venous Thromboembolic Event Risk Factors Available in IMS Electronic Medical Record Databases

Variables	France IMS EMR GPs	France IMS EMR Gynecologists	Belgium IMS EMR GPs	Italy IMS EMR GPs
Age	Yes	Yes	Yes	Yes
Gender	Yes	Yes	Yes	Yes
Weight	Yes[a]	Yes[a]	Yes[a]	Yes[a]
Height	Yes[a]	Yes[a]	Yes[a]	Yes[a]
BMI	Yes[a]	Yes[a]	Yes[a]	Yes[a]
Smoking	Yes[a]	Yes[a]	Yes[a]	Yes[a]
DVT/PE	Yes	Yes	Yes	Yes
AMI	Yes	Yes	Yes	Yes
Stroke	Yes	Yes	Yes	Yes
IS	Yes	Yes	Yes	Yes
CVA	Yes	Yes	Yes	Yes
Pregnancy	Yes[a]	Yes	Yes[a]	Yes[a]
Breast cancer	Yes	Yes	Yes	Yes
Chemotherapy	No	No	No	No
Previous major surgery	Yes[a]	Yes[a]	Yes[a]	Yes[a]
Diabetes	Yes	Yes	Yes	Yes
Polycystic ovary syndrome	Yes	Yes	Yes	Yes
Hypertension	Yes	Yes	Yes	Yes
Dyslipidemia	Yes	Yes	Yes	Yes
Systemic lupus erythematosus	Yes	Yes	Yes	Yes
Migraine	Yes	Yes	Yes	Yes

[a] The variable is only partially available, because of suboptimal recording of the information in the patient file.
EMR=electronic medical records; GP=general practitioner; BMI=body mass index; DVT=deep venous thrombosis; PE=pulmonary embolism; AMI=acute myocardial infarction; IS=ischemic stroke; IS=ischemic stroke; CVA=cerebrovascular accident.

9.4. Data Sources

All patient information on exposure and outcomes will be obtained from existing European real world data sources. IMS Health® IMS Real World Data (RWD) EMR, longitudinal patient-level databases, in outpatient setting of primary care providers and specialists (gynecologists) in Belgium, France, and Italy will be used.

- Belgium - IMS RWD EMR Belgium (formerly Cegedim Strategic Data [CSD] Longitudinal patient database) provides a nationally representative sample of about 300 primary care physicians
- France - IMS RWD EMR France (formerly CSD Longitudinal patient database) provides a nationally representative sample of two panels of interest, about 1200 primary care physicians and 120 gynecologists
- Italy - IMS RWD EMR Italy (formerly CSD Longitudinal patient database) provides a nationally representative sample of about 900 primary care physicians (560 practices)

The databases consist of data collected from primary care practices and specialists on encounters of healthcare providers with patients in real-life setting. The characteristics of patients and practices within each database are representative of the primary care practices in the respective country (Becher 2009). Information on events deemed necessary by the physician will be recorded in the patient's EMR. However, complete records of diagnoses or events requiring hospitalization are not available in the databases. Information on the variables collected in the IMS databases are provided in Annex 3.6.

Information on patient demographics, medical diagnoses, laboratory test results, and drug therapy are directly obtained from the practice computer system of the healthcare providers during daily recording. The therapeutic classifications in the database are mapped to the ATC classification system. Signs, symptoms, diagnoses, and diagnostic tests are mapped to ICD codes. To ensure confidentiality of patient information, the data are anonymized at the collection stage using encrypted identifiers for the physician and individual. Contributor physicians receive advisory feedback on the quality of data collection in their practice with individual feedback reports on data reported by the practice compared to data from other practices. Information on the general characteristics of the databases in Belgium, France, and Italy are provided in Table 3.

Existing automated healthcare databases were selected for this drug utilization study, as at least partial data are readily available, allowing obtaining the study results in a reasonable time frame. In addition, the breadth of information on drug use makes these data most suitable for examining drug utilization patterns in routine clinical practice setting.

Table 3: General Characteristics of the Databases

Characteristics	France	France	Belgium	Italy
Physician panel	IMS EMR GPs	IMS EMR Gynecologists	IMS EMR GPs	IMS EMR GPs
Data collection methodology	Physicians' software	Physicians' software	Physicians' software	Physicians' software
Panel size (number of physicians)	1,200 GPs	120 GYN	300 GPs	900 GPs
National coverage	~2.0% of all GPs	~2.5% of gynecologists	~2.4% of all GPs	~2.0% of all GPs
Number of active patients	1,800,000	240,000	370,000	750,000
Average length of enrollment in database	7-8 years	4 years	8 years	10 years
Patient ID unique cross physicians panel (GPs and gynecologists)	No	No	N/A	N/A
Diagnostic coding system	ICD-10-CM	ICD-10-CM	ICD-10-CM	ICD-9-CM

EMR=electronic medical records; GP=general practitioner; GYN=gynecologists; ICD=International Classification of Diseases.

9.5. Study Size

The primary objective of this study is to describe drug utilization patterns among women treated with SEASONIQUE in outpatient settings in selected European countries. All SEASONIQUE prescriptions for female patients recorded in primary care practice and gynecologists in the selected databases during the study period will be included in the analysis. Hence, the sample size for this study depends on the data availability in the 3 IMS healthcare databases. It also depends on the number of prescriptions of SEASONIQUE in Europe, which is currently low. The final number of women to be included in the study will be determined at the time of data extraction for the entire study period based on the data available in the country-specific databases.

For each country-specific database and setting, a preliminary number of female patients treated with SEASONIQUE by panel and country was conducted (Table 4). These numbers were 30 in Belgium (primary care), 60 and 260 in France (primary care and gynecologist, respectively), and 100 in Italy (primary care) for the period since product marketing until October 2016. Based on these numbers and on the projected sales of this product, it is estimated that by 2018, the number of female patients treated with SEASONIQUE® by country and setting will be 88 in Belgium (primary care), 167 and 724 in France (primary care and gynecologist, respectively) and 134 in Italy (primary care). Therefore, in spite of the low use, most of the drug utilization data are expected to derive from France. Overall, the estimated total number of users in the study databases is approximately 1110.

Table 4: Total Number of Unique Users of SEASONIQUE Since Launch Date until October 2016 (by Outpatient Settings and Country), IMS Health® IMS RWD EMR

Setting	SEASONIQUE users (Total)		
	France	**Belgium**	**Italy**
	Total GPs (N=1200)/ Gynecologist (N=120)	**Total GPs (N=300)**	**Total GPs (N=900)**
Primary care	60	30	100
Gynecologists	260	N/A	N/A

Note: Launch period: Italy, May 2015; Belgium, August 2015; France, September 2015.
RWD=Real World Data; EMR=Electronic Medical Records; GP=general practitioner.

Based on the study primary objective, sample size was calculated for the proportion of female patients' prior use of CHC medication before SEASONIQUE initiation in each country. Since no relevant background/historical data are available from which to derive this proportion in advance, it is assumed that among all patients using this drug in each country, the expected proportion (p) of female patients with prior use of CHC medication before SEASONIQUE initiation is 50%. Given this assumption (ie, p= 0.5, which will yield the largest sample size per country), confidence interval of 95% and margin of error of 5%, the required sample size, using the following formula,

$$n = t^2 . \frac{p.(1-p)}{e^2}$$

would be 385 users per country, ie, a total sample size of approximately1155 female patients.

The precision achieved with various assumptions was calculated; results are provided in Table 5.

Table 5: Sample Sizes for Different Estimates of Proportions and Varying Precisions of the Estimates

	Proportion of users					
	0.01	**0.02**	**0.05**	**0.1**	**0.2**	**0.5**
Precision=0.01	381	753	1825	3458	6147	9604
Precision=0.02	96	189	457	865	1537	2401
Precision=0.05	16	31	73	139	246	385
Precision=0.1	4	8	19	35	62	97
Precision=0.2	1	2	5	9	16	25

9.6. Data Management

The study will use existing healthcare claims databases with anonymized information on the individual patients. The study will be conducted according to IMS Health standard operating procedures (SOPs). SAS software will be utilized for access to the raw data to manage the

analytic datasets and to conduct data analysis. Oversight for data analyses will be coordinated by the country-specific IMS Health Real World Evidence Central team. A lead statistician will work with the relevant multi-country databases to ensure homogeneity in data extraction. The data will be accessed and extracted by trained employees of IMS, and queries, extraction, and analyses will be conducted on IMS (password-protected) computers only. Datasets extracted from each database will be stored at the database level to allow future analysis, if needed.

This study will follow the relevant data management guidelines in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Conference on Harmonisation (ICH).

9.7. Data Analysis

9.7.1. General Considerations

The main study analysis will describe the prescribing patterns among females treated with SEASONIQUE in outpatient setting in selected European countries to meet the study objective. The analysis will be descriptive in nature. Descriptive statistics will be provided for demographics and other patient characteristics of patients prescribed SEASONIQUE, treatments, and diagnosis characteristics, including duration of use, indication, and type of prescriber. Categorical variables will be summarized as counts (n), percentages (%), and confidence intervals (CIs) when relevant. Continuous variables will be summarized using counts, means, standard deviations (SD), medians, minimums, and maximums, as summary statistics. The distribution of the number of prescriptions, frequency, duration of use, by physician panel (primary care, gynecologists) and country (ie, database) will be descriptively summarized, as appropriate.

A subset of patients with at least 6 months of continuous membership/enrollment within the database prior to first SEASONIQUE prescription (ie, index date) will be examined. If preliminary counts indicate a large population with at least 6 months of history, this group would be the main analysis group.

Analyses of exposure will be conducted on patient level and on prescription level, as appropriate. On the patient level, the statistical unit will be the patient for information such as demographical and clinical characteristics and medical history. On the prescription level, the statistical unit will be SEASONIQUE prescription for information such as all diagnoses related to the SEASONIQUE prescriptions, number of prescriptions, and treatment duration. Percentage of prescriptions with the relevant indications will be estimated. The analysis will be done separately per database in the target country and by physician panel in the outpatient settings (ie, primary care, gynecologists). The analysis will be performed separately per database and target country. Results will be harmonized into a common multi-county study report. Data coming from different databases will not be pooled, but the confidence interval for each country will be calculated separately. It is not recommended pooling the data coming from different databases in this study, as they generally reflect different sampling methods, coverage levels and data structure. All analyses will be performed using SAS software version 9.3 or higher (SAS Institute Inc., Cary, NC).

9.7.2. Handling of Missing Data

Missing values for the variables will be reported as missing and no imputation will be conducted.

9.8. Quality Control

All key study documents, such as the statistical analysis plan and study reports, will undergo quality control and scientific review. Data quality control is conducted at several levels. At the study level, IMS SOPs will be used to guide the conduct of the study. These procedures include internal quality audits of the data, accuracy, and consistency of collected data, validation of coding, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. At the database level, the quality unit of IMS production department continuously verifies the quality of its numerous physician panels in terms of panel representativeness, consistency of collected data, and validation of coding of physicians' verbatim.

All programming code developed for this study by the executing researcher will be reviewed independently by a senior researcher. All key study documents, such as the statistical analysis plan and study reports, will undergo quality control and senior scientific review. The study will be executed in line with the data vendor's quality management system.

9.9. Limitations of the Research Methods

This study will be conducted to characterize the utilization of SEASONIQUE in routine care settings using existing longitudinal EU healthcare databases. The use of these databases will ascertain a geographically and demographically diverse cohort of SEASONIQUE users in selected number of countries in Europe. Health information recorded in population-based data sources that collect and record data on a regular basis minimize bias related to differential reporting of prescriptions or impacts of contacts with patients and healthcare professionals. Although misclassification of clinical indication is recognized as a potential issue for all these data sources, studies evaluating data already collected may be the most efficient way to accurately assess drug utilization patterns. In a prospective study with data specifically collected for this goal, clinicians may be more inclined to align diagnoses with approved indications than when documenting diagnosis during routine clinical practice.

Given the use of health care database, the study has several limitations. Because of the nature of selected secondary databases that capture only reimbursed drugs, the number of European countries where SEASONIQUE, which is a non-reimbursed product, could be captured is very limited. As a result, the selection of the countries was based on product launch and availability of longitudinal secondary databases. While the 3 chosen countries may not be representative of COC prescription habits in Europe, they are representative of SEASONIQUE drug utilization in the EU.

The French database would be the only data source providing data on SEASONIQUE prescriptions by gynecologists as well as primary care providers. A gynecologist panel is not available in Italian or Belgian databases, and thus data on SEASONIQUE use will be obtained only from primary care provider panels in these 2 databases. The lack of data from

SEASONIQUE-prescribing gynecologists in Belgium and Italy will limit to some extent the generalizability of the study results.

Misclassification of exposure or outcome is a potential limitation of observational studies. Assessment of SEASONIQUE exposure is based on the electronic medical records of written prescriptions rather than information on dispensed prescriptions (days of supply) or actual intake. The duration of SEASONIQUE treatment (in days) will be evaluated using the number of packages prescribed. In cases where this information is not available, the treatment duration cannot be exactly determined. In addition, when treatment patterns suggest that the actual treatment duration may be shorter compared with the length of the prescribing recommendations (by physician or labeling), the reason (eg, stockpile or potential misuse) cannot be discerned. Thus, patients may be classified as exposed when they have actually stopped taking the drug. In this manner, prescription duration may not be necessarily identical to actual use and consumption behavior, and may result in apparent shorter or longer treatment durations. While electronic medical records data may not represent the actual consumption of the medications, these data have been extensively studied and provide sound and fairly unbiased information on medication use from real world data.

Another caveat is related to the longitudinal description of SEASONIQUE duration of use. Given the nature of these databases where anonymized patients cannot be tracked across panels, practices or specialties, detailed information on duration of SEASONIQUE use may be limited. Specifically, differentiation between various groups of users examining history of CHCs before SEASONIQUE start (new users, restarters, switchers, etc) relies on complete prescription information. However, only prescriptions from the participating physicians can be tracked. Therefore, even if women take SEASONIQUE without interruption, gaps between prescriptions are expected to be observed whenever women change prescriber and get prescribed elsewhere, even if only temporarily. Such limitation in the drug use pattern may lead to contamination and misclassification of SEASONIQUE exposure.

Misclassification may also occur due to underreporting of diagnoses or events in the databases, because these databases were not designed for research purpose. Another reason for underreporting may result from unrecorded information on diagnoses from other physician panel or inpatient diagnoses, deaths, or date transferred out of the system. Moreover, acute events (ie, myocardial infarction) can be missing for some patients or not correctly reported in the EMR data. This information is recorded by the physician in the patient's EMR only as deemed necessary.

Indications for the use of SEASONIQUE can be reported only if the respective conditions (diagnoses) are documented in EMR by the physician. While a clinical diagnosis is systematically associated with specific courses of medications, it may not necessarily reflect the treatment indication (eg, flu [reason for the consultation]) associated with contraception. Moreover, for SEASONIQUE, which is usually intended for long-term use, the indication for use may not be directly available in the medical records. The physician may not document the indication for which the drug is prescribed every time a prescription is issued. Lack of recording of drug indication or diagnosis is more likely to occur for conditions that are chronic or drugs that are prescribed for chronic use, as is the case for SEASONIQUE. For this reason an underestimation of indications for use can be assumed for long-term–use medication such as SEASONIQUE. This underreporting may limit the accuracy for assigning indication of use. In

addition, the actual indication may change over time. It should be noted that, as the indication of use may not be recorded for most of the prescriptions, the indication will be inferred from medical diagnoses recorded around the time of the written prescription to allow for a wide window to capture the indication. Nonetheless, since the study is conducted in EMR databases from the time SEASONIQUE is launched in Europe, it is expected that the indication for which the drug is prescribed is more readily available. Overall, the information from the medical history is useful for the description of indications for use and also for key variables and risk factors for VTE/ATE, but results should be interpreted with some caution, depending on the availability of medical history for patients in the databases.

Detailed information on duration of use may be lacking to some extent. Patients seeking care outside the EMR practice setting will not have that medical information or drug utilization recorded in the database. In addition, in the IMS® RWD EMR, anonymized patients cannot be tracked across panels, practices or specialties. Therefore, double counting of patients cannot be completely ruled out when analyzing more than 1 panel. Furthermore, if patients are receiving their prescriptions from various specialties, even without interruption, gaps between prescriptions are expected to be observed whenever women change of prescriber, even if only temporarily.

The availability on some lifestyle variables in IMS longitudinal databases depends on physician reporting. Some variables provided in the protocol may be available, yet are reported to only a certain extent. For example, weight is more likely to be recorded if abnormal (eg, overweight/underweight patients). Therefore, these variables will be used to describe characteristics based on their availability.

The duration of SEASONIQUE treatment (in days) will be evaluated using the number of packages prescribed. In cases where this information is not available, the treatment duration cannot be exactly determined. Therefore, it is possible that if patients are misusing the drug, the actual treatment duration should be shorter compared to the length of the prescribing recommendations (by physician or labeling).

Information on pregnancy is expected to be limited. Since the drug is prescribed for 3 months, there is no way to know whether the woman stopped taking the drug during those 3 months (information on drug consumption is not available). In addition, the date of conception may not be recorded in the database. Consequently, it will not be possible to estimate accurately whether a patient is still taking the drug while pregnant.

9.10. Other Aspects

None.

10. PROTECTION OF HUMAN SUBJECTS

This study will be conducted in accordance with the 2016 Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies (EMA 2016, module VIII), the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE) (ISPE 2016), and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP 2016).

All data used for the study will be de-identified with no breach of confidentiality with regard to personal identifiers and health information. The database research vendor will apply for an independent ethics committee review and/or other approvals according to national guidelines and local regulations. Processes assuring data security for abstraction of medical records will be employed during data extraction, storage, and back-up to ensure that the confidentiality of the records of the study patients remains protected. The data and all study documents will be kept until written notification from the Marketing Authorisation Holder (MAH) that records may be destroyed. The legislation on data protection will be followed in accordance with national regulations on the protection of individuals with regard to the processing of personal data.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), individual reporting of adverse reactions is not required for non-interventional study designs that are based on secondary use of data (EMA GVP 2014 module VI). No expedited reporting of adverse events or reactions is required.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Common study protocol, study status, and report(s) will be included in regulatory communications in line with the risk management plan (RMP), Periodic Safety Update Report (PSUR), and other regulatory milestones and requirements. When results of this study are reported, the appropriate STROBE checklist (STROBE 2007) will be followed.

Study results will be considered for publication and will follow the International Committee of Medical Journal Editors (ICMJE 2015) guidelines. In addition, communication in appropriate scientific meetings will be considered.

13. REFERENCES

American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 110: noncontraceptive uses of hormonal contraceptives. Obstet Gynecol 2010;115(1):206-18.

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Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423.

Pittman ME, Secura GM, Allsworth JE, Homco JB, Madden T, Peipert JF. Understanding prescription adherence: pharmacy claims data from the Contraceptive CHOICE Project. Contraception 2011;83(4):340-5. [Epub] Accessed September 17, 2010.

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Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). STROBE statement—Checklist of items that should be included in reports of cohort studies. Version 4;2007. Available at: http://strobe-statement.org/fileadmin/Strobe/ uploads/checklists/STROBE_checklist_v4_cohort.pdf.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

A copy of the ENCePP Checklist for Study protocols available at http://www.encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.
The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.
In question 9.5 of the Checklist, Revision 1:
"Study start" means "Start of data collection"
"Study progress" means "Progress report(s)"
"Study completion" means "End of data collection"
"Reporting" means "Final report of the study results"

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A Drug Utilization Study of SEASONIQUE® in Europe

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[3]	☒	☐	☐	6
1.1.2 End of data collection[4]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	

[3] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[4] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2
4.2.2 Age and sex?	☒	☐	☐	9.2
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2 9.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2 9.3.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health-care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2, 9.4
9.1.3 Covariates?	☒	☐	☐	9.3.3, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2, 9.4
9.3.3 Covariates?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.3 Are stratified analyses included?	☐	☐	☒	9.7.1
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	9.7.2
10.6 Is sample size and/or statistical power estimated?	☐	☒	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.2, 9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Sigal Kaplan

Date: 11/1/2017

Signature:

ANNEX 3. ADDITIONAL INFORMATION

1. POSSIBLE INDICATION RELATED TO COMBINED ORAL CONTRACEPTIVE USE

Below is list of diagnoses related to prescribing COC based on the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on Noncontraceptive Uses of Hormonal Contraceptives.

Diagnoses related to prescribing combined oral contraceptives	
	ICD-10-CM codes:
Contraceptive management	
Z30.xx	Encounter for general counseling and advice on contraception (excluding Z30.2 Encounter for sterilization)
Menstrual cycle (ir)regularity (cycle control)	
N92.x	Excessive, frequent and irregular menstruation
Treatment of menorrhagia	
N92.x	Excessive and frequent menstruation with regular cycle
Treatment of dysmenorrhea	
N94.4	Primary dysmenorrhea
N94.5	Secondary dysmenorrhea
N94.6	Dysmenorrhea, unspecified
Inducing amenorrhea for lifestyle considerations	
N91.0	Primary amenorrhea
N91.1	Secondary amenorrhea
N91.2	Amenorrhea, unspecified
Treatment of premenstrual syndrome	
N94.3	Premenstrual tension syndrome
Prevention of menstrual migraines	
G43.82x	Menstrual migraine, not intractable
G43.83x	Menstrual migraine, intractable
Decrease in risk of endometrial cancer, ovarian cancer, and colorectal cancer	
C54.1	Malignant neoplasm of endometrium
C56	Malignant neoplasm of ovary
C18.7	Malignant neoplasm of colon
C20	Malignant neoplasm of rectum
Treatment of acne or hirsutism	

L70	Acne
L68.0	Hirsutism
Improved bone mineral density	
M81.0	Osteoporosis
Treatment of bleeding due to leiomyomas	
D25.x	Leiomyoma of uterus
Treatment of pelvic pain due to endometriosis	
N80.x	Endometriosis of uterus
E28.2	PCOS (polycystic ovarian syndrome)

2. VENOUS THROMBOEMBOLISM OUTCOME DEFINITIONS

Patients will be identified as having a VTE outcome if they had at least 1 of the diagnosis codes that also met the corresponding place of service and diagnosis location criteria.

Venous Thromboembolic Event (VTE)

VTE, defined as deep venous thrombosis (DVT) and/or pulmonary embolism (PE)

ICD-10-CM codes:

Deep Venous Thrombosis (DVT)	
I80.1	Phlebitis and thrombophlebitis of femoral vein
I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
I80.3	Phlebitis and thrombophlebitis of lower extremities, unspecified
Pulmonary Embolism (PE)	
I26	Pulmonary Embolism

3. CARDIOVASCULAR (CV) OUTCOME DEFINITIONS

Patients will be identified as having a CV outcome if they had at least one of the diagnosis codes that also met the corresponding place of service and diagnosis location criteria.

Arterial Thromboembolic Events (ATEs)

Arterial thromboembolic events (ATEs), including acute myocardial infarction (AMI), ischemic stroke (IS) and cerebrovascular accidents (CVA)

ICD-10-CM codes:

Acute myocardial infarction (AMI)	
I21	Acute myocardial infarction
Stroke	
I60	Subarachnoid hemorrhage
I61	Intracerebral hemorrhage

I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction

4. GYNECOLOGICAL CANCER DEFINITIONS

Gynecological cancers will be identified for women if they had the following diagnosis codes, or procedures.

Gynecological Cancers	
	ICD-10-CM codes:
Breast cancer	
C50	Malignant neoplasm of breast
Cervical cancer	
C53	Malignant neoplasm of cervix uteri
Endometrial cancer	
C54.1	Malignant neoplasm of corpus uteri, Endometrium
Ovary cancer	
C56	Malignant neoplasm of ovary

5. PREGNANCY IDENTIFICATION AND OUTCOME DEFINITIONS

Pregnancy and pregnancy outcomes will be identified for women if they had at least 1 of the diagnosis codes, or procedures.

Pregnancy Identification &Outcomes	
	ICD-10-CM codes:
Pregnancy diagnosis codes	
Z32.1	Pregnancy confirmed
Z34.X	Supervision of normal pregnancy
Z35.X	Supervision of high-risk pregnancy
Z36.X	Antenatal screening
Z37.X	Outcome of delivery
Z38.X	Liveborn infants according to place of birth
Delivery diagnosis codes	
080-084	Outcome of delivery
Pregnancy with abortive outcome	
000	Ectopic pregnancy
001	Hydatidiform mole
002	Other abnormal products of conception

003	Spontaneous abortion
004	Medical abortion
005	Other abortion
006	Unspecified abortion
007	Failed attempted abortion
008	Complications following abortion and ectopic and molar pregnancy

6. VARIABLES COLLECTED IN IMS DATABASES

Characteristics	**Variable**	**Collected in database (Y/N/partial)**
Demography	Year of birth	Y
	Age (year) at index date	Y
	Sex	Y
	Ethnicity	N
	Socioeconomic status	Partial
	Marital status	Partial
Clinical data	Height	Partial
	Weight	Partial
	BMI	Partial
	Blood pressure (diastolic. systolic)	Partial
	Heart rate	Partial
	Waist circumference	Partial
Risk factor assessments	Smoking status	Partial
	Number of cigarettes / day	Partial
	Alcohol drinker	Partial
	Level of alcoholism	Partial
Treatment prescriptions	National codification for drug code	Y
	Brand name	Y
	Strength	Y
	Molecule	Y
	ATC Code	Y
	NB dose/pack	Y
	Date of prescription	Y
	Treatment duration in days OR Treatment duration in packs	Y

Characteristics	**Variable**	**Collected in database (Y/N/partial)**
	renewals prescriptions	Y
	Daily dose	Y
Diagnosis and medical history	Diagnosis linked to the prescription	Y
	Date of diagnosis	Y
	Comorbidities	Y
	Patient medical and family medical history	Y
Healthcare utilization	Referrals to specialist care	Y[a]
	Hospitalization (for any cause)	Y[a]
	Cause of hospitalization	Y[a]
Laboratory tests	Prescriptions	Y
	Test results	Y[a]
Imaging	Prescriptions	Y[a]
	Test results	N
Death	Death date	N
	Cause of death	N
Physician	Physician age	N
	Physician gender	Y
	Physician practice region	Y

[a] Not mandatory.