A Retrospective Longitudinal Cohort Study Assessing the Safety of SEASONIQUE® Use: A Post-marketing Authorization Safety Study (PASS) to Assess the Risk of Venous Thromboembolic Events (VTE) in Women Exposed to SEASONIQUE®

Study No. DR105-WH-50015

Revised Final Report

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A Report by Optum Epidemiology

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PASS information

Title	A Retrospective Longitudinal Cohort Study Assessing the Safety of SEASONIQUE® Use: A Post-marketing Authorization Safety Study (PASS) to Assess the Risk of Venous Thromboembolic Events (VTE) in Women Exposed to SEASONIQUE®
Version Identifier of the Final Study Report	1
Date of Last Version of the Final Study Report	Not applicable
EU PAS Register Number	EUPAS18976
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	SEASONIQUE® NL42237
Procedure Number	FR/H/0516/001
Marketing Authorisation Holder(s)	Theramex Ireland Limited, 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin 1 D01YE64, Ireland
Joint PASS	No
Research Question and Objectives	**Primary objective**: to compare incidence rates of VTE in women exposed to SEASONIQUE® with women exposed to 28-day cycle LNG-containing combined oral contraceptives (COC_{LNG}) **Secondary objectives**: to compare users of SEASONIQUE ® to users of 28-day cycle COC_{LNG} with regard to the following events of interest: arterial thromboembolism (ATE), including acute myocardial infarction (AMI) and cerebrovascular accidents (CVA), pregnancy outcomes, breast cancers, and other gynaecological cancers.
Country(-ies) of Study	US
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1. Abstract

Title

A retrospective longitudinal cohort study assessing the safety of SEASONIQUE use: a post-marketing authorization safety study (PASS) to assess the risk of venous thromboembolic events (VTE) in women exposed to SEASONIQUE

Keywords

Extended oral contraceptive, combined hormonal contraceptive, combined oral contraceptive, levonorgestrel, venous thromboembolism

Rationale and Background

SEASONIQUE is an extended combined oral contraceptive (COC) containing levonorgestrel (LNG). The extended-regimen may improve compliance and reduce the risk of unwanted pregnancies.

The European Medicines Agency (EMA) has requested a PASS to assess the cardiovascular risk associated with SEASONIQUE during standard clinical practice.

Research Question and Objectives

Primary objective: To compare incidence rates (IRs) of VTE in women exposed to SEASONIQUE with women exposed to 28-day cycle COC_{LNG}.

Secondary objectives: To compare users of SEASONIQUE to users of 28-day cycle COC_{LNG} with regard to the following events of interest: arterial thromboembolism (ATE) including acute myocardial infarction (AMI) and cerebrovascular accidents (CVA), pregnancy outcomes, breast cancers and other gynaecological cancers.

Study Design

This was a retrospective longitudinal cohort study.

Setting

The study period began on 01 January 2006 and ended on 30 June 2017.

Subjects and Study Size, Including Dropouts

The study included 147,390 women (176,323 treatment episodes) with at least one dispensing of SEASONIQUE or 28-day cycle COC_{LNG}. Each SEASONIQUE user was matched with up to four 28-day cycle COC_{LNG} users. Follow-up was examined independently for each of the study outcomes.

Variables and Data Sources

Data were obtained from an existing United States (US) automated health care claims database. Exposure was defined as a dispensing of SEASONIQUE or 28-day cycle COC_{LNG} and the treatment length was determined by the days' supply and the number of consecutive dispensings. Within the SEASONIQUE and 28-day cycle COC_{LNG} cohorts, users were further categorized as

naïve users, new users, re-starters or switchers to account for variable effects of COCs on VTE risk over time.

Covariates derived from the database included VTE risk factors, medications, demographics, lifestyle factors, and empirically identified covariates.

The primary outcome was VTE, defined as deep venous thrombosis (DVT) and/or pulmonary embolism (PE). Secondary outcomes were ATE (including AMI and CVA), fertility, delayed pregnancy detection, breast cancer, and other gynaecological cancers.

Results

Results from this study suggest that current SEASONIQUE use (versus current 28-day cycle COC_{LNG} use) was not associated with a significantly increased risk of VTE among naïve and new users (hazard ratio [HR] 1.40, 95% confidence interval [CI] 0.90 to 2.19), although some sensitivity analyses suggested a possible increased risk among naïve users. Findings for the secondary outcome ATE were similar (HR 1.21, 95% CI 0.58 to 2.53).

SEASONIQUE discontinuers tended to have lower pregnancy rates compared to 28-day cycle COC_{LNG} discontinuers. Based on timing of the first prenatal care visit relative to the estimated pregnancy start date, there was no suggestion of delayed pregnancy detection among SEASONIQUE users as compared to 28-day cycle COC_{LNG} users. However, using the estimated SEASONIQUE/28-day cycle COC_{LNG} treatment end date and estimated pregnancy start date, naïve and new SEASONIQUE users tended to have an additional eight days of treatment on average during the first trimester.

There were no consistent associations between SEASONIQUE use and risk of breast cancer and there were too few cervical, endometrial, and ovarian cancers cases to draw conclusions.

Discussion

These results do not suggest an association between SEASONIQUE and risk of VTE, ATE, fertility, or delayed pregnancy detection. Further analyses among naïve users may aid in interpreting the statistically significant increased VTE and ATE risk observed in some sensitivity analyses.

Marketing Authorisation Holder(s)

Theramex Ireland Limited

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2. List of Abbreviations

AMI	Acute Myocardial Infarction
ATE	Arterial Thromboembolism
CHC	Combined Hormonal Contraceptive
CI	Confidence Interval
COC	Combined Oral Contraceptive
COC_{LNG}	Levonorgestrel-containing Combined Oral Contraceptives
COX	Cyclooxygenase
CMS	Centers for Medicare & Medicaid Services
CPT	Current Procedural Terminology
CVA	Cerebrovascular Accident
DVT	Deep Venous Thromboembolism
EE	Ethinyl Estradiol
EMA	European Medicines Agency
EU	European Union
GPP	Good Pharmacoepidemiology Practices
HCFA	Health Care Financing Agency
HCPCS	HCFA Common Procedure Coding System
HR	Hazard Ratio
ICD-10	International Classification of Diseases, 10th Revision
ICD-9	International Classification of Diseases, 9th Revision
IQR	Interquartile Range
IR	Incidence Rate
IRB	Institutional Review Board
KDE	Kernel Density Estimate
LNG	Levonorgestrel
MAH	Marketing Authorization Holder
mg	Milligrams
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OC	Oral Contraceptive
ORD	Optum Research Database
PASS	Post-authorization Safety Study
PE	Pulmonary Embolism
PII	Patient-identifiable Information
PPV	Positive Predictive Value
PS	Propensity Score
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
UB	Uniform/Universal Billing
US	United States
VTE	Venous Thromboembolic Event

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5. Milestones

Milestone	Planned Date	Actual Date	Comments
Start of Data Collection	3 Months After Protocol Approval	21-Jul-17	
End of Data Collection	18 Months After Start of Data Collection	18-May-18	
Registration in the EU PAS Register	Prior to Data Collection	6-Aug-17	
Initial IRB Approval		19-May-17	
IRB Amendment Approval		21-Jul-17	Revised Protocol
IRB Renewal Approval		20-Apr-18	
IRB Renewal Approval		22-Apr-19	
Draft 1 Report	18-Jun-19	18-Jun-19	
Draft 2 Report	20-Aug-19	20-Aug-19	
Final Report of Study Results	18-Sep-19	18-Sep-19	
Revised Final Report	23-Sep-19	23-Sep-19	Minor Modifications Requested

6. Rationale and Background

SEASONIQUE is a 91-day extended COC, containing a fixed-dose combination of 0.15 mg LNG and 0.03 mg ethinyl estradiol (EE) taken without interruption for 84 days, followed by 0.01 mg EE for seven days (1). The doses of this COC (0.15 mg LNG and 0.03 mg EE) are already used in other COCs authorized in Europe (2). The standard COC 28-day cyclic regimen consists of 21 days of active combination pills followed by seven pill-free days or seven days of placebo pills. This hormone-free interval was designed to induce withdrawal bleeding once every 28 days (13 times per year), imitating the normal menstrual cycle, as it was presumed that regular withdrawal bleeding was essential for the acceptance of oral contraceptives (OCs) by women. 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 in an attempt to decrease oestrogen-related withdrawal symptoms associated with traditional OCs (3, 4).

The extended-regimen of SEASONIQUE was designed to eliminate the withdrawal bleeding that regularly occurs with conventional COCs once every 28 days. This extended COC may improve compliance and reduce the risk of unwanted pregnancies by providing continuity and decreasing scheduled withdrawal bleeding to four episodes per year. The first extended-regimen OC, Seasonale®, was approved in the US in 2003 and in Canada in 2007. Seasonale is a 91-day extended-regimen contraceptive with 84 days of active combination tablets (0.15 mg LNG and 0.03 mg EE) and seven placebo tablets. SEASONIQUE was developed as a successor to Seasonale and approved in the US in 2006 and in Canada in 2010. LoSeasonique® is similar to SEASONIQUE but with a lower dose of LNG and EE and was approved in the US in 2008. In Europe, the first extended-regimen OC was authorized in 2012 (Yvidually®, which contains drospirenone and EE, and is taken up to 120 days continuously).

Evidence suggests that oral combined hormonal contraceptives (CHCs) containing low dose EE and a second generation progestin (conventional 28-day cycle regimen) are associated with a higher risk of VTE with an IR of six to 10 events per 10,000 person-years (5-7). In comparison, VTE rates are two to four per 10,000 person-years among women not using CHCs (5, 7). During the clinical development of SEASONIQUE, few adverse events of medical relevance to OC use were reported. One case of deep vein thrombosis (DVT) and one case of ATE were reported among the non-SEASONIQUE treatment group.

Sex-hormone-related malignancies were also examined during the clinical development of SEASONIQUE as breast cancer and other gynaecological cancers may be hormone-sensitive. One case of ovarian cancer was reported in a woman randomized to the non-SEASONIQUE treatment group one year after the first dose of treatment. From the data submitted, there were no cases of breast cancer or hepatocarcinoma reported with SEASONIQUE during the clinical program.

Given the limited number of women treated with SEASONIQUE in the clinical program as well as the limited length of exposure (one year for the pivotal study and four years for the extension study, but with a very small population), the safety profile of this extended-cycle contraceptive regimen in terms of VTE risk is not entirely known. We expected that the risk of VTE and other cardiovascular and cancer outcomes would be the same between SEASONIQUE and standard 28-day cyclic regimens with combined LNG/EE. In the context of the regulatory submission for market authorization of SEASONIQUE in Europe, the EMA requested a PASS to assess the cardiovascular risk associated with SEASONIQUE during standard clinical practice.

7. Research Question and Objectives

7.1. Primary Objective

The primary objective of this study was to compare the IRs of VTE in women exposed to SEASONIQUE with women exposed to 28-day cycle COC_{LNG}.

7.2. Secondary Objectives

The secondary objectives of this study were to compare users of SEASONIQUE to users of 28-day cycle COC_{LNG} with regard to the following events of interest:

- ATE, including AMI and CVA
- Pregnancy outcomes
- Breast cancer and other gynaecological cancers

8. Amendments and Updates

Not applicable.

9. Research Methods

9.1. Study Design

This was a retrospective cohort study comparing women exposed to SEASONIQUE to women exposed to 28-day cycle COC_{LNG} with respect to the risk of VTE, ATE, pregnancy outcomes, and select gynaecological cancers.

9.2. Setting

The study population included women identified from the Optum Research Database (ORD), a US-based automated healthcare claims database. The ORD collects information submitted for reimbursement by various healthcare providers such as physicians, pharmacies, and hospitals in real-life settings and comprises a large number of patients. It is therefore suitable for investigating relatively rare outcomes in routine clinical practice settings.

9.3. Subjects

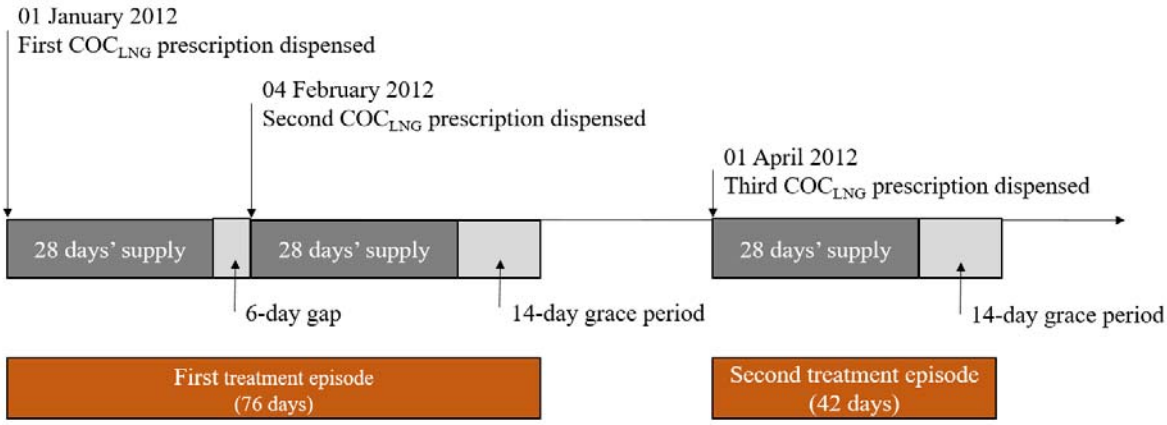
9.3.1. Base Population

The base population for this study consisted of females aged 12 years or older who used SEASONIQUE or a 28-day cycle COC_{LNG} between 01 January 2006 and 30 June 2017. The minimum age requirement of 12 years was empirically defined based on the distribution of observed age at each SEASONIQUE or 28-day cycle COC_{LNG} dispensing.

9.3.2. Treatment Episodes

Treatment episodes of SEASONIQUE or 28-day cycle COC_{LNG} were constructed using the dispensing date and the number of days' supply from the drug dispensing claims. An episode of therapy was defined as a period of continuous usage of one or a series of dispensings for SEASONIQUE or 28-day cycle COC_{LNG} for the same woman. The first episode of therapy began on the date of dispensing and continued through the days' supply of the dispensing (91 days for SEASONIQUE and 28 days for 28-day cycle COC_{LNG}), plus 30 days for SEASONIQUE and 14 days for 28-day cycle COC_{LNG} (the grace period). If a subsequent dispensing was recorded within 30 days (SEASONIQUE) or 14 days (28-day cycle COC_{LNG}) after the end of the preceding dispensing's days' supply, then the therapy was considered continuous and the subsequent dispensing was considered part of the same treatment episode (Figure A). The treatment period included any gaps between dispensings that were within the grace period. If the gap between adjacent dispensings was longer than 30 days for SEASONIQUE (or 14 days for 28-day cycle COC_{LNG}), then the episode ended on the last day of the days' supply of the previous dispensing, plus 30 (or 14) days.

Figure A. Example 28-day COC_{LNG} Treatment Episodes



The inclusion of a 30 (or 14) day grace period between dispensings better reflects the true exposure period, as some women may be delayed in refilling their prescriptions (8). These gaps allowed for some variability in fill date versus first use of that particular dispensing (8, 9). The estimation of exposure as treated (as opposed to intention-to-treat) enabled a more realistic time-to-event analysis especially with potential drug switching.

Subsequent dispensings that occurred after the end of the treatment episode (if any) were considered new treatment episodes and exposure time was reset to zero at the start of each new episode. In both groups, the treatment episode ended if a woman received a dispensing for any OC other than their treatment episode drug. If the new OC was a study drug (i.e., SEASONIQUE or 28-day cycle COCLNG), then a new episode began.

A woman in the base population could have contributed several exposure episodes to the analysis, with the beginning of each treatment episode set as a new index date. Each treatment episode created a separate record in the analytic dataset, and was the unit of observation in the analysis. Each SEASONIQUE treatment episode was matched to up to four 28-day cycle COC_{LNG} episodes on propensity score (PS) and these matched episodes were included in the main analysis.

9.3.2.1. Inclusion Criteria

Treatment episodes were included in the study if they met the following criteria:

- At least 12 months of continuous health plan enrolment prior to the start of the SEASONIQUE or 28-day cycle COC_{LNG} treatment episode/index date.
    - The 12 months of continuous enrolment in the health plan before the start of each treatment episode was defined as the baseline period for that particular treatment episode, with the start of the treatment episode (index date) defined as the last day of the baseline period. This period was required to obtain information about each woman's relevant medical history before the start of drug exposure. This eligibility requirement increased the length of time available to observe baseline covariates (increasing validity) but decreased the number of eligible women (reducing precision). Therefore, in a sensitivity analysis, outcome rates were examined among qualifying episodes with a minimum of six months of continuous health plan enrolment before the index date.
- 12 years of age or older at the start of the SEASONIQUE or 28-day cycle COC_{LNG} treatment episode.
- For the analysis of pregnancy outcomes, the analysis was further restricted to those age 45 years or younger at the start of the treatment episode.

9.3.2.2. Exclusion Criteria

Treatment episodes were excluded if any of the following were present:

- One or more codes for breast cancer, cervical cancer, endometrial cancer, or ovarian cancer using the codes (three-digit level) listed in Annex 4 *Breast Cancers and Other Gynaecological Cancers* within the 12 months (baseline period) before and including the start of the treatment episode (index date).
    - In a sensitivity analysis, women with any cancer (including non-gynaecological cancer) in the baseline period (including the index date) were excluded.
- Chemotherapy during the baseline period (including the index date).
- A cancer diagnosis (see Section 9.3.3 *Follow-up*) during a previous episode: if an episode was censored due to a cancer diagnosis, all subsequent episodes were excluded from the analysis.
- A pregnancy period that overlapped one or more days with the three months before and including the index date, based on the pregnancy outcome definition described in Section 9.4.2.2.2 *Pregnancies*.
- Previous major surgery (including lower limb orthopaedic surgery) or major lower extremity or pelvic trauma within three months before and including the index date.

9.3.3. Follow-up

Each woman could have contributed more than one eligible treatment episode to the analysis, and the analysis was conducted at the treatment episode level rather than the person level. Follow-up of eligible women (treatment episodes) started on the day after the index dispensing of SEASONIQUE or 28-day cycle COC_{LNG}. For each treatment episode, follow-up for each study outcome ended at the earliest of the following dates:

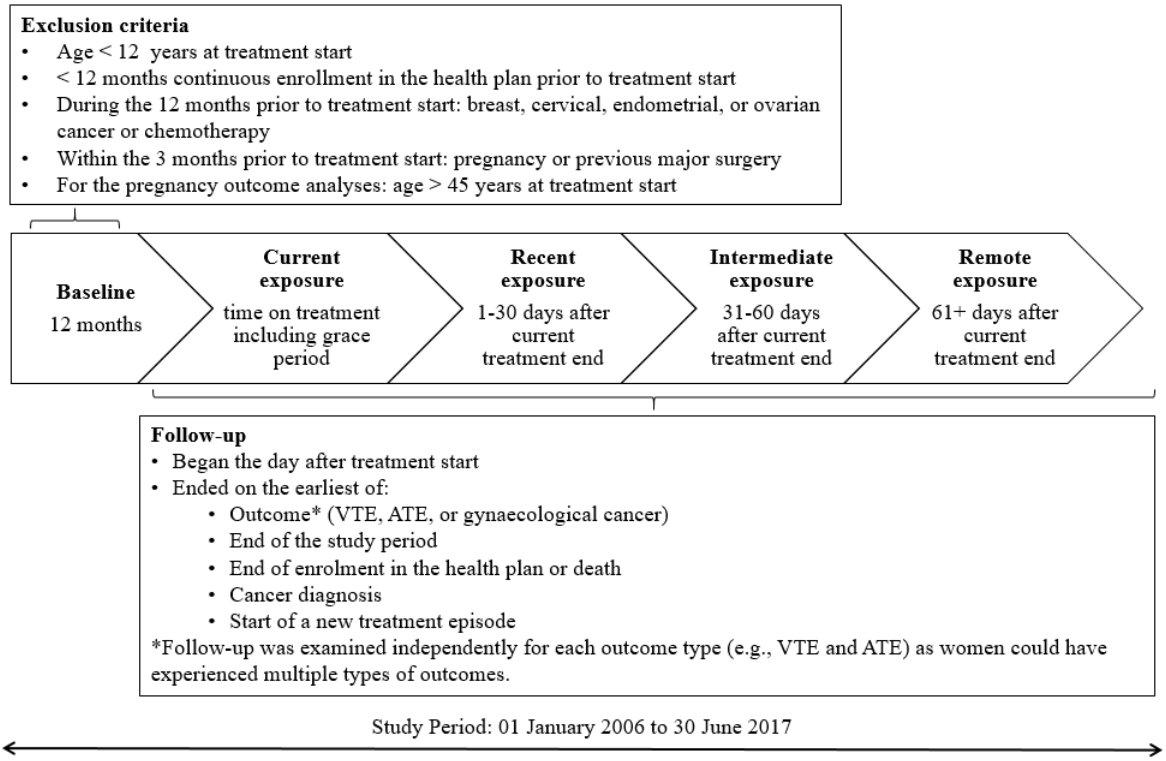
- Occurrence of the study outcome (see Section 9.4.2 *Outcomes*)
- End of the study period
- End of enrolment in the health plan (last date of continuous membership)
- Death
- Cancer diagnosis (see Annex 4 for International Classification of Disease, 9th Revision [ICD-9] and International Classification of Disease, 10th Revision [ICD-10] codes; censoring for cancer diagnosis required at least two ICD codes that were identical at the three-digit level and that occurred at least seven days but no more than 90 days apart [from any site of care, in any position]) or chemotherapy
- Start of a new SEASONIQUE or 28-day cycle COC_{LNG} treatment episode

Women could have experienced more than one outcome (e.g., two VTEs) and follow-up for a study outcome was censored after the earliest qualifying outcome date (the earliest VTE). Women could also have experienced multiple types of study outcomes (e.g., VTE and ATE). In these scenarios, follow-up was examined separately for each outcome. Take, for example, a woman who had two treatment episodes, experienced a VTE between the first and second treatment episode, and experienced an ATE after the second treatment episode. The woman's second treatment episode would be excluded from the analysis of VTE whereas both treatment episodes would be included in the analysis of ATE. Therefore, the occurrence of one study outcome (e.g., VTE) did not censor follow-up for other types of study outcomes (e.g., ATE). Furthermore, since follow-up began the day after the index date, in the unlikely event that a woman had an event on the index day, that event was considered part of the covariate (baseline) data and not an outcome event.

Patterns of drug use were explored to examine the possibility that some women in the 28-day cycle COC_{LNG} group received continuous hormonal exposure by consuming the 21 days of active pills and immediately starting a subsequent pill pack, thereby omitting the seven-day hormone-free interval. In particular, women with three or more overlapping dispensings (defined as having two or more consecutive dispensings that occurred at least seven days prior to the end of the days' supply of the prior dispensing) were identified. Follow-up and contribution of person-time for these women was censored on the date of the second consecutive dispensing that was at least seven days early.

Note: The study protocol stated the following (Annex 5, Section 9.2.2 *Exclusion Criteria*), "Other conditions known to substantially modify the VTE risk occurring during the follow-up will be examined. Patients with these conditions, including surgery/injury, and pregnancy, will not be censored. While these events are risk factors for VTE, they may occur after the index date and thus are in the causal pathway. Therefore, these conditions will be addressed in the analysis using techniques such as stratification." Since surgery/injury are not likely to be in the causal pathway because they are not likely to be affected by contraceptive use, we performed a stratified analysis as described in the Section 9.9.2.3 *Analysis of Outcomes*. In addition, when following women for the VTE outcome, we did not censor by pregnancy during follow-up but rather flagged these women and stratified follow-up by pregnancy status. Figure B presents an overview of the study design.

Figure B. Overview of Study Design



9.4. Variables

9.4.1. Exposure

9.4.1.1. SEASONIQUE and 28-day Cycle COC_{LNG}

SEASONIQUE use included all generic equivalents (i.e., 91-day extended COC products, containing a fixed-dose combination of 0.15 mg LNG and 0.03 mg EE, taken without interruption for 84 days followed by 0.01 mg EE tablets for seven days). All 28-day cycle LNG-containing COC products were included in the comparator group (all doses and combinations of LNG and EE). LoSeasonique® (91-day extended COC products, containing a fixed-dose combination of 0.1 mg LNG and 0.02 mg EE, taken without interruption for 84 days followed by 0.01 mg EE tablets for seven days) and its generics were excluded from the SEASONIQUE cohort as were Seasonale (91-day extended COC products, containing a fixed-dose combination of 0.15 mg LNG and 0.03 mg EE, taken without interruption for 84 days followed by placebo tablets for seven days) and its generics.

9.4.1.2. Exposure Classification

9.4.1.2.1. Exposure Classification of Treatment Episodes: Prior CHC Use

Treatment episodes were categorized based on exposure to CHCs prior to the index date as follows: naïve users, new users, re-starters and switchers. This categorization aimed to reduce the misclassification of new users that could potentially occur when comparing a new treatment with an established one. In addition, it is important to differentiate between these groups as the timing of prior CHC use may affect VTE risk (7, 10).

Combined hormonal contraceptives were defined as all combined oestrogen and progestin contraceptives, including LNG plus EE-containing emergency contraceptives as women exposed to these products cannot be considered CHC-naïve; CHCs excluded postmenopausal hormone products. The list of CHCs included COCs as well as injectables, patches, and rings. The following definitions were used for exposure categorization:

- **Naïve users** were defined as women with first ever exposure to SEASONIQUE or 28-day cycle COC_{LNG} during the study period and no dispensing or evidence of use (including device implantation or removal) of any CHC during baseline (i.e., the index date dispensing was the first observed dispensing).
- **New users** were defined as women starting use of SEASONIQUE or 28-day cycle COC_{LNG} after a break of at least 12 weeks from any CHC prior to the index date (i.e., no dispensing of any CHC with a days' supply that covered any part of the 84-day period preceding the index date but one or more dispensing of any CHC in the baseline period with a days' supply that ended prior to this period; or device removal more than 84 days prior to index date).
- **Re-starters** were defined as women with a dispensing of SEASONIQUE or 28-day cycle COC_{LNG} after a break of 4-11 weeks from any COC prior to the index date (i.e., no dispensing of any COC (defined as the subset of CHCs in oral dosage forms) with a days' supply that covered any part of the 27-day period preceding the index date but one or more dispensings of any COC with a days' supply that covered at least one day in the period spanning 28 to 83 days preceding the index date).
    - This definition includes the timing of prior COC use rather than CHC use because the study drugs of interest (SEASONIQUE and 28-day cycle COC_{LNG}) are limited to oral CHCs.
    - Re-starters could have re-started the same COC or a different COC.
- **Switchers** were defined as women starting SEASONIQUE or 28-day cycle COC_{LNG} after a different CHC preparation with a break of less than four weeks (i.e., one or more dispensings of any CHC other than the index CHC with a days' supply that covered at least one day in the 27-day period preceding the index date; or device removal within the 27-day period preceding the index date).

The primary analysis combined the naïve and new user groups, representing incident users with a minimum wash-out period of 12 weeks from prior exposure to CHCs. Separate analyses were also performed within each of the four user groups individually.

9.4.1.2.2. Current, Recent, Intermediate, and Remote Exposure

To reduce misclassification, exposure periods thereafter were further classified to account for any remaining pharmacological and physiological effects of COCs on cardiovascular risk (e.g., increased coagulability):

- **Current exposure**: the beginning of the treatment episode (SEASONIQUE or 28-day cycle COC_{LNG} index date or start of therapy) to the last day of the treatment episode, including the grace period. As stated in the statistical analysis plan (SAP, Annex 6), the main analysis of VTE events was conducted among the combined group of naïve and new users during current exposure.

- **Recent exposure**: from the end of current exposure (end of the treatment episode) to 30 days later (from one to 30 days after the end of SEASONIQUE or 28-day cycle COC_{LNG} treatment course).
- **Intermediate exposure**: from the end of recent exposure to 30 days later (from 31 to 60 days after the end of SEASONIQUE or 28-day cycle COC_{LNG} treatment course).
- **Remote exposure**: from the end of intermediate exposure (from 61 days after the end of SEASONIQUE or 28-day cycle COC_{LNG} treatment course to the end of follow-up).

9.4.1.3. Sensitivity Analyses Relating to Exposure

A sensitivity analysis that extended the grace period to 60 days for SEASONIQUE users and 28 days for 28-day cycle COC_{LNG} users was performed. In a second sensitivity analysis, women in the 28-day cycle COC_{LNG} group identified as skipping their placebo weeks were not censored at the second consecutive early dispensing. Instead, the start date of each refill was modified to correspond to the day after the end of the days' supply of the preceding dispensing. In this analysis, all subsequent refills (including dispensings with overlapping days' supply) were counted towards the days on treatment. This process was repeated until the end of the treatment episode.

9.4.2. Outcomes

Since the study period spanned 01 October 2015, the date on which the US converted from ICD-9 to ICD-10, both ICD-9 (prior to 01 October 2015) and ICD-10 (starting on 01 October 2015) codes were used to define outcomes.

9.4.2.1. Primary Outcomes

The primary outcome was VTE, defined as PE and/or DVT.

- PE was defined as an inpatient diagnosis (including emergency departments) of PE (at least one of the corresponding ICD-9 or ICD-10 codes in Annex 4 in the primary position). The diagnosis code listed in the primary position of a medical claim is the principal diagnosis, which is the condition that has been determined to be chiefly responsible for the admission.
- DVT was defined as:
    - a DVT diagnosis (at least one of the corresponding ICD-9 or ICD-10 codes in Annex 4 in the primary position) in an inpatient setting, including emergency departments; or
    - a DVT diagnosis (at least one of the corresponding ICD-9 or ICD-10 codes in Annex 4) in an outpatient setting in conjunction with an anticoagulant or alteplase dispensing during the 30-day period following the date of DVT diagnosis. Anticoagulants included low molecular weight heparins (i.e., enoxaparin, dalteparin, tinzaparin), apixaban, argatroban, bivalirudin, dabigatran, desirudin, drotrecogin alfa, danaparoid, edoxaban, fondaparinux, lepirudin, rivaroxaban, or warfarin. Note that heparin was excluded from a DVT outpatient diagnosis because it is only administered in an inpatient setting.

In addition, the dispensing of an anticoagulant that was not associated with an outcome as defined above (i.e., inpatient PE diagnosis in the primary position, inpatient DVT diagnosis in the primary position, or outpatient DVT diagnosis in combination with use of an anticoagulant/alteplase within 30 days) was also identified. Women with these dispensings were considered for medical record review. As it is unlikely for a woman of child-bearing age to receive an anticoagulant for conditions other than VTE, this helped ensure the sensitivity of the primary outcome definitions.

Based on previous claims database studies, potential misclassification of VTE may occur as a result of unconfirmed diagnoses (5, 11); therefore a medical record validation study was performed for a sample of VTE cases as described in Section 9.5 *Data Sources and Measurement*.

9.4.2.1.1. Sensitivity Analyses Relating to Primary Outcomes

As a sensitivity analysis, we used alternative algorithms for PE and DVT (12). The VTE sensitivity definition was as follows:

- PE was defined as an inpatient diagnosis (including emergency departments) of PE (at least one of the corresponding ICD-9 or ICD-10 codes in Annex 4 in the primary position) in conjunction with a first dispensing of anticoagulant (including heparin) during the 30-day period following the date of PE diagnosis. This sensitivity PE definition was more restrictive than the main analysis definition as it also required an anticoagulant dispensing within 30 days.
- DVT was defined as a DVT diagnosis (at least one of the corresponding ICD-9 or ICD-10 codes in Annex 4 in any position) in either outpatient or inpatient settings, in conjunction with a first dispensing for an anticoagulant (including heparin) during the 30-day period following the date of DVT diagnosis. As compared with the main analysis definition, the sensitivity DVT definition was more inclusive because it allowed an ICD code in any position in the inpatient setting but also more restrictive as it required an anticoagulant dispensing within 30 days in inpatient settings.

9.4.2.2. Secondary Outcomes

The secondary outcomes were ATE, pregnancy outcomes (fertility and delayed pregnancy detection), breast cancer, cervical cancer, endometrial cancer, and ovarian cancer.

9.4.2.2.1. ATE

Arterial thromboembolic events, defined as AMI or CVA, were identified based on inpatient codes only. Ischaemic and haemorrhagic strokes were included in the definition of CVA. Women were defined as having an ATE outcome if they had at least one of the corresponding ICD-9 or ICD-10 diagnosis codes in Annex 4 on an inpatient claim. Codes for CVA (but not AMI) were required to be in the primary position.

9.4.2.2.2. Pregnancies

Pregnancies were assessed in the subset of women with a maximum age of 45 years at the beginning of the treatment episode. A maximum age limit was applied because women over age 45 have a low likelihood of becoming pregnant (13). The calculation of the pregnancy period began with the identification of pregnancy outcomes from claims with codes for pregnancy terminations and deliveries. For each delivery, a period of pregnancy was estimated as the 270 days prior to the date of delivery. For each abortion, a period of pregnancy was estimated as the 120 days prior to the date of the abortion.

Delivery was defined by the presence of any of the corresponding diagnosis or procedure codes in Annex 4 for delivery in any position on an inpatient claim. Pregnancy with an abortive outcome was defined by the presence of one of the corresponding diagnosis or procedure codes in Annex 4 for abortive outcome in any position on either inpatient or outpatient claims (14).

Note: there were some differences between the code lists used for the pregnancy baseline exclusion as compared with the identification of pregnancies. First, ICD-9 74.3 (removal of extratubal ectopic pregnancy) was moved from the delivery code list to the termination code list. Second, the following Current Procedural Terminology (CPT) codes were removed for specificity in the identification of pregnancies as they may be related to postpartum care for pregnancies that ended prior to the index date: 59400 (routine obstetric care including antepartum care, vaginal delivery [with or without episiotomy, and/or forceps] and postpartum care), 59510 (routine obstetric care including antepartum care, caesarean delivery, postpartum care), 59610 (routine obstetric care including antepartum care, vaginal delivery [with or without episiotomy, and/or forceps] and postpartum care, after previous caesarean delivery), and 59618 (routine obstetric care including antepartum care, caesarean delivery, and postpartum care, following attempted vaginal delivery after previous caesarean delivery).

9.4.2.2.2.1. Fertility

Fertility was assessed among women who stopped taking SEASONIQUE or 28-day cycle COC_{LNG} and did not switch to any other contraceptive. Women contributed person-time following the discontinuation of SEASONIQUE or 28-day cycle COC_{LNG} (end of the treatment episode) until they either became pregnant, resumed contraception as evidenced by a new contraceptive dispensing or device implantation, or follow-up ended. The codes specified for delivery and pregnancy with abortive outcome were used to define pregnancy. The fertility rate was estimated as the number of pregnancies per 1,000 person-years. Because the women who contributed to the fertility analysis were a subgroup of the primary analysis cohort (i.e., those who stopped SEASONIQUE or 28-day cycle COC_{LNG} and did not switch to any other contraceptive), we assessed covariate balance between the two groups (i.e., those who stopped SEASONIQUE and those who stopped 28-day cycle COC_{LNG}) and adjusted for individual variables that were unbalanced in this subgroup by including them in the outcome regression models.

9.4.2.2.2.2. Delayed Pregnancy Detection

Delayed pregnancy detection was assessed during current exposure in two ways. First, the earliest encounter for prenatal care following the estimated start of pregnancy was identified (the start of pregnancy was defined according to Section 9.4.2.2.2 *Pregnancies*). The time between the estimated start of the pregnancy and the first encounter for prenatal care was measured. The mean (SD) and median (interquartile range [IQR]) time between these two dates were compared between SEASONIQUE and 28-day cycle COC_{LNG} groups using t-tests and Wilcoxon rank sum tests, respectively.

Second, the time between estimated pregnancy start and the estimated end date of SEASONIQUE or 28-day cycle COC_{LNG} exposure was estimated. The mean (SD) and median (IQR) time between these two dates were compared between SEASONIQUE and 28-day cycle COC_{LNG} groups using t-tests and Wilcoxon rank sum tests, respectively. Because the days' supply of SEASONIQUE (i.e., 91 days) is longer than 28-day cycle COC_{LNG}, we conducted a sensitivity analysis restricting this analysis to only those pregnancies with estimated start dates that occurred within the last 28 days' supply of a dispensing.

9.4.2.2.3. Breast Cancer and Other Gynaecological Cancers

Breast, cervical, endometrial, and ovarian cancers were identified using the corresponding ICD-9 or ICD-10 diagnosis codes in Annex 4, requiring at least two ICD codes that were identical at the three-digit level and that occurred at least seven days but no more than 90 days apart (from any setting, in any position).

9.4.3. Covariates

We accounted for potential differences in outcome risk between users of SEASONIQUE and 28-day cycle COC_{LNG} through evaluation and adjustment for a broad range of baseline characteristics. The list of pre-specified covariates is summarized in Table A. These characteristics include demographics, known VTE risk factors, and factors that may be associated with the use of SEASONIQUE as opposed to 28-day cycle COC_{LNG} (15). These covariates were included in the PS model, as described in Section 9.9.2.2 *PS Modelling and Matching*.

Table A. Pre-specified Covariates

Variable(s)	Details	Assessment Date/Period
Age (continuous), in years	(Index date – date of birth) / 365.25	Index date
Age (categorical), in years	12 to < 15; ≥ 15 to ≤ 35; > 35 to ≤ 50; > 50	Index date
US geographic region	Northeast, South/Southeast, Midwest, West	Index date
Calendar month	1-12	Index date
Cardiac dysrhythmia	0= No 1=Yes	12-mo. baseline period, including index
Cerebrovascular or coronary artery disease	0= No 1=Yes	12-mo. baseline period, including index
Coagulation defects (that can result in either thrombotic or haemorrhagic disorders)	0= No 1=Yes	12-mo. baseline period, including index
Chronic obstructive pulmonary disease (COPD)*	0= No 1=Yes	12-mo. baseline period, including index
Diabetes mellitus Type 1	0= No 1=Yes	12-mo. baseline period, including index
Diabetes mellitus Type 2 (including gestational)	0= No 1=Yes	12-mo. baseline period, including index
Hyperlipidaemia	0= No 1=Yes	12-mo. baseline period, including index
Hypertension	0= No 1=Yes	12-mo. baseline period, including index
Overweight and obesity	0= No 1=Yes	12-mo. baseline period, including index
Pregnancy	0= No 1=Yes	90 to 365 days before index

Variable(s)	Details	Assessment Date/Period
Prior VTE	0= No 1=Yes	12-mo. baseline period, including index
Prior ATE	0= No 1=Yes	12-mo. baseline period, including index
Tobacco use (smoking-related diagnoses, smoking cessation medications, counselling)	0= No 1=Yes	12-mo. baseline period, including index
Unstable angina	0= No 1=Yes	12-mo. baseline period, including index
Vascular disease, including peripheral vascular disease and varicose veins of lower extremity	0= No 1=Yes	12-mo. baseline period, including index
Combined Charlson-Elixhauser comorbidity score	Continuous	12-mo. baseline period, including index
Anovulation	0= No 1=Yes	12-mo. baseline period, including index
Asthma	0= No 1=Yes	12-mo. baseline period, including index
Dysmenorrhea	0= No 1=Yes	12-mo. baseline period, including index
Epilepsy	0= No 1=Yes	12-mo. baseline period, including index
Gynaecological disorders, including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum; and uterine leiomyoma	0= No 1=Yes	12-mo. baseline period, including index
Hepatitis C	0= No 1=Yes	12-mo. baseline period, including index
History of abortion	0= No 1=Yes	90 to 365 days before index
Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS)	0= No 1=Yes	12-mo. baseline period, including index
Liver failure	0= No 1=Yes	12-mo. baseline period, including index
Migraine	0= No 1=Yes	12-mo. baseline period, including index
Polycystic ovary syndrome	0= No 1=Yes	12-mo. baseline period, including index
Renal failure (acute or chronic)	0= No 1=Yes	12-mo. baseline period, including index
Thyroid disorder	0= No 1=Yes	12-mo. baseline period, including index
Prior use of other forms of contraception, including intrauterine devices, patches, and depot injections	0= No 1=Yes	12-mo. baseline period, including index

Variable(s)	Details	Assessment Date/Period
Prior time on CHCs	Categorical: 0, 1-90, 91-180, 181-270, 271-365 days	12-mo. baseline period, including index
Number of prior CHCs (unique dispensings, except for naïve users)	Categorical: 0, 1, ≥ 2	12-mo. baseline period, including index
Anticoagulants	0= No 1=Yes	12-mo. baseline period, including index
Angiotensin converting enzyme inhibitors/angiotensin II receptor blockers	0= No 1=Yes	12-mo. baseline period, including index
Benzodiazepines	0= No 1=Yes	12-mo. baseline period, including index
Beta-blockers	0= No 1=Yes	12-mo. baseline period, including index
Calcium channel blockers	0= No 1=Yes	12-mo. baseline period, including index
Cyclooxygenase (COX)-2 inhibitors	0= No 1=Yes	12-mo. baseline period, including index
Diabetes medications	0= No 1=Yes	12-mo. baseline period, including index
Non-steroidal anti-inflammatory drugs (NSAIDs) other than COX-2 inhibitors	0= No 1=Yes	12-mo. baseline period, including index
Spironolactone	0= No 1=Yes	12-mo. baseline period, including index
Selective serotonin reuptake inhibitors/tricyclic antidepressants**	0= No 1=Yes	12-mo. baseline period, including index
Statin/fibrate	0= No 1=Yes	12-mo. baseline period, including index
Number of outpatient visits	Categorical: 0, 1-2, ≥ 3	12-mo. baseline period, including index
Number of emergency room visits	Categorical: 0, 1, ≥ 2	12-mo. baseline period, including index
Number of hospitalizations	Categorical: 0, 1, ≥ 2	12-mo. baseline period, including index

* COPD is rare in young women of reproductive age. However, it may serve as a proxy for smoking which may not be captured adequately in the database.

**Includes selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tetracyclics, and tricyclics.

Descriptive statistics were examined for all covariates. Continuous variables were categorized, either using pre-defined categories or based on quantiles as appropriate based on the distribution of values for each variable.

9.4.3.1. Empirically-defined Covariates

Additional baseline covariates were defined based on the most frequently occurring diagnoses, procedures, and medications observed in the 12-month baseline period (Supplemental Tables 1-3). The 100 most frequently observed baseline diagnoses were derived using individual codes (e.g., ICD-9 codes at the three-digit level) with the exception of the last calendar block which included ICD-9 and ICD-10 codes, where the 200 most frequently observed baseline diagnoses/procedures/medications were identified. The top 100/200 most frequently dispensed/administered medications were identified at the therapeutic class level. Healthcare utilization variables such as the number of drugs dispensed and the number of ICD diagnoses (at the three-digit level) were also considered for entry into the PS model, as described in Section 9.9.2.2 *PS Modelling and Matching*. The goal of additionally including these empirically-defined covariates was to further reduce confounding (16).

9.5. Data Sources and Measurement

This study used the ORD, formerly the Optum Life Sciences Research Database, which contains health insurance claims and enrolment data dating back to 1993. The database includes data from over 59.5 million individuals with pharmacy and medical benefits; an additional 40.5 million enrolees with medical benefits only are available. On average, individuals are enrolled in the health plan for 2.6 years. For 2015, data relating to approximately 13.5 million individuals with both medical and pharmacy benefit coverage were available. An additional 11.5 million enrolees with medical benefits only were available. Of the 13.5 million individuals, race/ethnicity, and financial resource information is available for approximately 75% of the individuals. The data undergo regular audits and quality control procedures by the insurer and are updated monthly. The insured population from which the data are drawn is geographically diverse across the US and comprises approximately three to four percent of the US population.

Accessible information from the ORD includes demographics, pharmacy use, and medical and facility claims, which provide data on services, procedures, and their accompanying diagnoses. Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The claims history is a profile of outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days' supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications.

Medical claims or encounter data are collected from various health care sites (inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.) for virtually all types of provided services, including specialty, preventive, and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers (i.e., physicians) use the Health Care Financing Agency (HCFA)-1500 or Centers for Medicare & Medicaid Services (CMS)-1500 formats. Claims for facility services submitted by institutions (i.e., hospitals) use the Uniform/Universal Billing (UB)-82, UB-92, UB-04, or CMS-1450 formats. Medical claims include: multiple diagnoses recorded with ICD-9 diagnosis codes prior to October 2015 and ICD-10 codes since October 2015; procedures recorded with ICD-9 procedure codes prior to October 2015 and ICD-10 afterward; CPT, or Healthcare Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include medications dispensed in hospital. Pharmacy claims are added to the research database within six weeks of dispensing.

Optum utilized de-identified data from the ORD. For a subset of women in the ORD with administrative approval from the health plan, patient-identifiable information (PII) was accessed for medical record review. Medical records (PII) were accessed after approval of the study protocol by the Western

Institutional Review Board. All data access conformed to applicable Health Insurance Portability and Accountability Act (HIPAA) policies.

9.5.1. Medical Record Outcome Confirmation

For the subset of women with administrative approval from the health plan, Optum attempted to obtain medical records to confirm VTE. Medical records were requested for women who met the primary VTE case definition and a sample of women who received an anticoagulant dispensing during follow-up but did not meet the primary VTE case definition. Optum worked with an outside clinical consultant to perform a detailed review of the chronological listing of relevant claims (i.e., clinical profile) for each of the potential cases to determine the medical site most likely to yield medical records with the necessary information to confirm case or non-case status.

Optum developed an abstraction checklist of medical record elements to be obtained for review and an adjudication form to be used by the clinical consultants to confirm the case status and date of VTE diagnosis (when applicable). Consensus was required between the two clinical adjudicators and any discrepancies were flagged by the research team and then discussed and resolved by the two adjudicators.

9.6. Bias

SEASONIQUE treatment episodes were matched to 28-day cycle COC_{LNG} treatment episodes on PS to balance patient characteristics between the two cohorts and reduce confounding bias. The matching was performed separately within approximately two-year calendar blocks to account for any differences in prescribing patterns over time. Any characteristics that remained unbalanced after matching were included in the multivariable outcome models.

The claims-based VTE algorithm was validated using medical records from a subset of claims-identified cases. Trained abstractors blinded mentions of study drugs in the medical records prior to review by the clinical adjudicators to reduce the possibility for differential outcome misclassification bias.

9.7. Study Size

The sample size calculation assumed a background IR of six VTE per 10,000 person-years among 28-day cycle COC_{LNG} users (5, 6). The study was designed to demonstrate non-inferiority of SEASONIQUE in terms of VTE risk versus the comparator (28-day cycle COC_{LNG}) with the ability to detect a 50% increase in risk (i.e., hazard ratio [HR] of 1.5) with an alpha of 0.05 and 80% power. As described in the study protocol (Annex 5), at least 100,000 women (with a matching ratio of 1:2 or more for SEASONIQUE and comparators) followed for approximately 200,000 person-years would therefore yield 120 VTE cases.

9.8. Data Transformation

Data transformations have been described in Sections 9.4 *Variables* and 9.9 *Statistical Methods*.

9.9. Statistical Methods

9.9.1. Main Summary Measures

Categorical variables were summarized using frequencies and percentages and continuous variables were summarized using mean and standard deviation (SD) or median and IQR as appropriate. Standardized differences were used to assess covariate balance after matching. Incidence rates were calculated by exposure group and IR differences compared SEASONIQUE to 28-day cycle COC_{LNG} users, with corresponding 95% CIs. Relative risks were estimated using HRs and corresponding 95% CIs derived

from Cox proportional hazards models where 28-day cycle COC_{LNG} use served as the reference group. Ninety-five percent CIs were presented rather than p-values as the 95% CI provides information on statistical significance as well as precision of the effect estimates.

9.9.2. Main Statistical Methods

9.9.2.1. Descriptive Analysis

Descriptive statistics were summarized for baseline characteristics of SEASONIQUE and 28-day cycle COC_{LNG} users separately for the four user groups (i.e., naïve users, new users, re-starters and switchers), as well as for the combined group of naïve and new users (the primary analysis). Characteristics among the subset of women who stopped SEASONIQUE or 28-day cycle COC_{LNG} were also described to aid in interpreting the fertility analysis results which were limited to such discontinuers.

9.9.2.2. PS Modelling and Matching

9.9.2.2.1. Overview of the PS Model

The purpose of the PS was to address differential selection of women into the SEASONIQUE vs. comparator (28-day cycle COC_{LNG}) cohort (i.e., differences between women dispensed SEASONIQUE vs. dispensed a 28-day cycle COC_{LNG}). Propensity score models were built separately within each approximately two-year study block to account for evolving prescribing practices over time and the transition from ICD-9 to ICD-10 on 01 October 2015. The six calendar blocks were 01 January 2006 to 31 December 2007, 01 January 2008 to 31 December 2009, 01 January 2010 to 31 December 2011, 01 January 2012 to 31 December 2013, 01 January 2014 to 30 September 2015, and 01 October 2015 to 30 June 2017. The outcome of each PS model was the use of SEASONIQUE or 28-day cycle COC_{LNG} and predictors included the pre-specified (Table A) and empirical covariates. Episodes of SEASONIQUE and 28-day cycle COC_{LNG} were matched by PS to produce balance between treatment groups on all variables that were included in the PS model. We evaluated balance before and after matching for each covariate. Any covariates that remained unbalanced after matching were included in the outcome (Cox) models. Propensity score model building, matching, and balance assessment was performed according to standard practice (17-20).

9.9.2.2.2. Building the PS Model

To reduce multicollinearity, the correlations between each pair of pre-specified and empirical covariates were assessed. For variable pairs with a correlation coefficient > 0.9, one variable was eliminated according to the following criteria:

- If one variable was pre-specified, this pre-specified covariate was retained and the other eliminated.
- If both or neither variables were pre-specified, the variable with the higher prevalence was retained and the other eliminated.
- After a variable was eliminated, it was not re-considered for model inclusion.

Empirical variable identification may identify correlates of exposure that are not risk factors for the outcome (and hence, not confounders); therefore, the list of empirical variables was manually reviewed by the study team (including an epidemiologist and pharmacist) to identify and remove such variables. Univariate c-statistics were evaluated for each of the remaining empirical variables (modelling SEASONIQUE or 28-day cycle COC_{LNG} treatment status as the dependent variable). Variables with the highest c-statistics had the greatest individual discrimination between SEASONIQUE and 28-day cycle

COC_{LNG} OC use. Any individual variable with a c-statistic value > 0.95 was evaluated by the research team for possible coding errors and clinical plausibility. If the variable was deemed to represent a surrogate of exposure and not a confounder (not a likely risk factor for VTE events), it was removed from the variable list.

The PS models were unconditional logistic regression models of SEASONIQUE use relative to 28-day cycle COC_{LNG} use (the outcome or dependent variable). From the remaining variables (after assessing high correlations and univariate c-statistics), the following variables were forced into the PS models: the pre-specified covariates listed in Table A, indicators for the four user groups (naïve user, new user, re-starter, switcher), the 10 empirical variables with the highest c-statistics, and interactions between the four user groups and the five empirical variables with the highest c-statistics. The interaction terms were included to ensure that the balance would remain when stratifying the analysis by user group. In addition to the forced variables, the remaining empirical variables were eligible for inclusion in the PS model through the stepwise automatic forward selection procedure. With this procedure, each remaining, eligible variable was considered for inclusion in the model in a sequential manner. A variable was entered into the model if it had a bivariate p-value ≤ 0.10. Variables that met the ≤ 0.10 threshold for model entry remained in the model unless their p-value became larger than 0.30, at which point the variable was dropped from the model and excluded from further consideration.

A PS was calculated for each treatment episode using the final calendar block PS models. As women may have had multiple treatment episodes, a unique PS was calculated for each episode. The distribution of PSs was reviewed for potential coding errors, outliers, and to identify any women with a missing PS.

9.9.2.2.3. PS Matching

SEASONIQUE episodes were matched to 28-day cycle COC_{LNG} episodes by PS separately within the calendar time blocks with the goal of matching up to four 28-day cycle COC_{LNG} episodes to each SEASONIQUE episode. Matching on the PS was expected to balance SEASONIQUE and 28-day cycle COC_{LNG} episodes across all variables included in the PS model. Unmatched SEASONIQUE episodes were retained and followed for outcomes separately.

9.9.2.2.4. Assessing Covariate Balance After Matching

Through an iterative process, post-matching covariate balance among the matched episodes was reviewed and the need for any further adjustment of PS models was assessed. To assess whether PS estimation and matching achieved a suitable covariate balance, we compared baseline covariates between SEASONIQUE and 28-day cycle COC_{LNG} users before and after matching. Weighted standardized differences were calculated to quantitatively assess differences between groups. Standardized differences were calculated using the following equations (in which $\overline{X}$ represents the mean of the covariate and $\hat{p}$ represents the prevalence of the covariate):

Continuous variables:

$$d = \frac{\overline{X}_{treatment} - \overline{X}_{control}}{\sqrt{(s^2{}_{treatment} + s^2{}_{control})/2}}$$

Binary variables:

$$d = \frac{\hat{p}_{treatment} - \hat{p}_{control}}{\sqrt{(\hat{p}_{treatment}(1 - \hat{p}_{treatment}) + \hat{p}_{control}(1 - \hat{p}_{control}))/2}}$$

The weighted standardized difference weights all SEASONIQUE episodes as one, all 28-day cycle COC_{LNG} episodes matched 1:1 as one, all 28-day cycle COC_{LNG} episodes matched 1:2 as 1/2, all 28-day cycle COC_{LNG} episodes matched 1:3 as 1/3, and all 28-day cycle COC_{LNG} episodes matched 1:4 as 1/4 (21). Variables with a standardized difference ≤ 0.1 were considered well balanced (22). If a variable had a standardized difference > 0.1, it was included in the Cox proportional hazards models.

The final PS model was then re-run among all matched episodes to evaluate the ability of the model to discriminate between SEASONIQUE use relative to 28-day cycle COC_{LNG} use. This model was run five times (once for each user group: naïve + new users, naive users, new users, re-starters, switchers) to calculate a final pooled c-statistic for each user group. This post-matching, pooled c-statistic was used to evaluate overall covariate balance and the need for any further adjustment. Re-running the final PS model within the matched cohorts provided an assessment of the remaining differences across all variables rather than individual variables. The desired result is a c-statistic close to 0.5, which would imply no remaining imbalance of baseline covariates between the matched cohorts. A c-statistic ≥ 0.8 suggests important remaining imbalance and reconsideration of the PS models (23).

As an additional diagnostic evaluation of the PS matching, we plotted the PS distributions as kernel density estimates (KDEs, the probability density functions of the PSs) pre- and post-matching. The KDEs for SEASONIQUE and 28-day cycle COC_{LNG} plotted on the same figure provided a visual assessment of the extent of overlap in PSs before and after matching. The area of overlap denotes the population from which study inferences may be drawn and generalizations made (i.e., external validity). A high degree of overlap implies exchangeability (similarity in covariate patterns) of women between treatment groups. Areas of non-overlap indicate women in one treatment group who, based on their covariate profiles, did not have comparable women in the other treatment group.

9.9.2.3. Analysis of Outcomes

9.9.2.3.1. Estimation and Comparison of IRs

Crude IRs of VTE and secondary outcomes of interest were estimated along with corresponding 95% CIs calculated using exact confidence limits. Incidence rates were calculated by summing the number of cases and dividing by the number of person-years of follow-up, presented as the number of cases per 1,000 person-years. Differences in IRs and 95% CIs were also calculated comparing SEASONIQUE users to 28-day cycle COC_{LNG} users.

9.9.2.3.2. Modelling of Outcomes

The main analysis was conducted in the combined cohort of naïve and new users comparing current SEASONIQUE use to current 28-day cycle COC_{LNG} use. Relative risks were estimated using Cox proportional hazard models and corresponding HRs. Separate models were created for each outcome. Because SEASONIQUE users were matched to comparators overall and not within user group (naïve user, new user, re-starter, switcher), stratifying the analysis by user group effectively broke this matching and therefore the PS was included in each Cox model as a single continuous variable. Any variables that remained unbalanced after PS matching were included in the models as well. The Cox models were

stratified by matching ratio and used a robust variance estimator to take into account the correlation between exposure episodes among women contributing more than one episode to the analysis.

The proportional hazards assumption was assessed in two ways: first, using a graphical approach that compared the log-log survival curves by exposure group and second, using the goodness-of-fit test (likelihood ratio test) comparing models with and without cross-product terms between treatment and time. Additionally, for each outcome, the cumulative probability of survival by exposure group was depicted using Kaplan-Meier plots.

9.9.2.3.3. Subgroup Analyses

In addition to the main analyses, women in the following subgroups were analysed separately (current exposure only): age group (12 to < 15, ≥ 15 to ≤ 35, > 35 to ≤ 50, or > 50, in years); overweight or obese (yes/no, i.e., codes for overweight or obese); tobacco user (yes/no, i.e., codes for smoking-related diagnoses, smoking cessation medications, or procedures); smoking-by-age interaction (tobacco users age > 35 years, tobacco non-users age > 35 years, tobacco users age 12 to ≤ 35 years, tobacco non-users age 12 to ≤ 35 years); prior VTE or anticoagulant use (yes/no); and surgery/injury during follow-up (yes/no). The age categories were divided between women over and under age 35 as "advanced maternal age" is typically defined as age 35 years or older. Note that although surgery/injury was assessed during follow-up, we did not expect that stratifying by surgery/injury in follow-up would introduce bias because it is unlikely to be affected by prior exposure.

9.9.3. Missing Values

Missing values were reported as missing and no imputation was conducted (for example, geographic region, and days' supply). This study is based on an analysis of automated medical and prescription claims, supplemented by information abstracted from medical records. We applied the standard approach in claims data analyses and assumed that the presence of a medication or disease claim indicated the use of that medication or the presence of that disease and conversely, the absence of a medication or disease claim indicated the absence of use of that medication or a diagnosis of that disease.

9.9.4. Sensitivity Analyses

As described in Section 9.3 *Subjects*, a sensitivity analysis requiring a minimum of six (instead of 12) months of continuous health plan enrolment within the database before the index date for the primary analysis of the VTE outcome was performed.

As described in Section 9.3.2.2 *Exclusion Criteria*, women with any cancer in baseline (not just gynaecological cancers) were excluded for the primary analysis of VTE.

As described in Section 9.4.1 *Exposure*, while the primary analysis was limited to women currently exposed to SEASONIQUE and 28-day cycle COC_{LNG}, sensitivity analyses compared SEASONIQUE vs. 28-day cycle COC_{LNG} users with recent, intermediate, and remote exposure.

As described in Section 9.4.1. *Exposure*, the grace period was extended to 60 (instead of 30) days for SEASONIQUE users and 28 (instead of 14) days for 28-day cycle COC_{LNG} users.

As described in Section 9.4.1. *Exposure*, women who appeared to be continuously exposed to COC by consuming only the 21 active pills before starting a new pack were not censored. In this sensitivity analysis, women were presumed to be taking their 28-day cycle COC_{LNG} as prescribed and the start date of each refill was modified to correspond to the day after the end of the days' supply of the preceding dispensing.

As described in Section 9.4.2.1 *Primary Outcomes*, the PE definition was modified to require a first dispensing of an anticoagulant within 30 days. The DVT definition was modified to include an inpatient DVT diagnosis in any position (instead of the primary position) and required a first dispensing of an anticoagulant within 30 days in the inpatient (as well as the outpatient) setting.

As described in Section 9.4.2.2.2 *Pregnancies*, the delayed pregnancy detection analysis was restricted to only those pregnancies with an estimated start date within the last 28 days' supply of a dispensing to take into account the extended days' supply of SEASONIQUE (i.e., 91 days) compared to 28-day cycle COC_{LNG}.

As described in the protocol (Annex 5), it is possible that naïve users could have had prior CHC use more than 365 days before the index date. In three sensitivity analyses, we increased the minimum CHC-free baseline period as follows: (1) women with at least 24 months of prior continuous enrolment and no CHC use in this period; (2) women with 24 to 36 months of prior continuous enrolment and no CHC use in this period; and (3) women with at least 36 months of prior continuous enrolment and no CHC use in this period.

As described in Section 10.4.4 *Ad Hoc VTE Results*, an ad hoc sensitivity analysis was conducted to explore differences between ICD-9 and ICD-10 algorithms for VTE. This analysis calculated the PPV separately by ICD period. The two periods were the ICD-9 era (before 01 October 2015) and the ICD-10 era (on or after 01 October 2015).

As described in Section 10.4.4 *Ad Hoc VTE Results*, an ad hoc sensitivity analysis utilizing the chart confirmed cases was conducted to further explore the main VTE results. This analysis was limited to confirmed cases of VTE among naïve and new users during current exposure. For comparability, the analysis was restricted to the subset of naïve and new user episodes that were chart-eligible as only chart-eligible episodes had the opportunity to become chart-confirmed cases. In the analysis of confirmed VTE events, claims-based VTE occurrence was ignored: follow-up was not censored at the claims-based VTE occurrence for episodes with a non-confirmed VTE.

9.9.5. Amendments to the Statistical Analysis Plan

There are no deviations from the final SAP dated 18 June 2019 (Annex 6).

9.10. Quality Control

All key study documents, such as the SAP and study reports, underwent quality control and scientific review. Standard operating procedures (SOPs) were used to guide the conduct of the study. These procedures included 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.

The following steps were undertaken to ensure quality and accuracy of all programming:

- Data for analysis was extracted by a competent Optum Analyst.
- The SAP and table shells were reviewed and approved by the Optum Senior Scientist.
- All programming code developed for this study was validated by a senior Optum Analyst.
- The study report including results and tables were reviewed by the Optum Senior Scientist.

Procedures were consistent with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) (24).

10. Results

10.1. Participants

A total of 147,390 women with a dispensing of SEASONIQUE or a 28-day cycle COC_{LNG} between 01 January 2006 and 30 June 2017 were included in the base population (35,464 SEASONIQUE users and 113,761 comparators). The number of SEASONIQUE users and comparators sum to more than the total number of women as some women used both SEASONIQUE and the comparator 28-day cycle COC_{LNG} (albeit at different time points) during the study period. Among them, 176,323 treatment episodes (44,078 SEASONIQUE users and 132,245 PS-matched comparators) were included in the analysis. Of these matched episodes, 58% were included in the main analysis of naïve and new users (25,587 SEASONIQUE users and 76,575 comparators) (Table 1). The majority of episodes were classified as naïve users (34% of SEASONIQUE users and 40% of comparators) and about a fifth each were classified as new users, re-starters, or switchers in both cohorts.

SEASONIQUE users tended to have slightly longer treatment episodes relative to comparators. Naïve and new SEASONIQUE users had a median of one dispensing (IQR one to three) and a median of 121 days' supply (IQR 121 to 303) including the 30-day grace period. Naïve and new comparators had a median of two dispensings (IQR one to six) and a median of 105 days' supply (IQR 42 to 263) including the 14-day grace period. This represents the current exposure period, the at-risk period for the main analysis of VTE.

A similar proportion of SEASONIQUE users and comparators were censored due to the occurrence of cancer, end of the study period, end of enrolment or death, or the start of a new treatment episode. The most common reasons for censoring were end of enrolment in the health plan and the start of a new treatment episode. While health insurance claims data do not always differentiate disenrolment due to changing health plans versus death, it is expected that among these young, healthy women, the majority disenrolled because they changed health plans. About three percent of naïve and new comparators were censored due to continuous use (i.e., had three or more consecutive early dispensings).

10.2. Descriptive Data

The majority (91%) of SEASONIQUE users were matched to at least one comparator and included in the main analysis of naïve and new users (Table 2a). The unmatched naïve and new SEASONIQUE users were similar to those who were matched, with the exception that the unmatched users were slightly older (median age 33 versus 29 years), were more likely to have migraines (15% versus 8%), had a lower prevalence of gynaecological disorders (22% versus 27%), and had used CHCs for more days (median 182 versus 0 days). These differences were more pronounced among naïve users (Table 2b). Among new users, re-starters, and switchers, the main differences between matched and unmatched SEASONIQUE users were age and history of migraine (Tables 2c to 2e).

Note that the total number of matched episodes in Tables 2a to 2e differed from those in Table 1. This is because Tables 2a to 2e included all matched episodes whereas Table 1 described the average treatment length and reasons for censoring among those episodes included in the main VTE analysis. Hence, the number of matched episodes is slightly higher in Tables 2a to 2e as a handful of women had multiple episodes and experienced a VTE in an earlier episode; for these women, the later episodes were not included in the VTE analysis described in Table 1.

Among matched naïve and new users, general characteristics and the prevalence of VTE risk factors among SEASONIQUE users and comparators were similar. The median age among SEASONIQUE users was 29 years (IQR 22 to 37) and among comparators 28 years (IQR 20 to 36) (Table 2a). The majority of women resided in the South and Southeast (52% of SEASONIQUE users and 46% of comparators) and had a low (< 6%) prevalence of VTE and cardiovascular risk factors. The most common comorbidities

were gynaecological disorders (27% of SEASONIQUE users and 27% of comparators) and dysmenorrhea (10% of SEASONIQUE users and 11% of comparators). The most commonly used drugs were antidepressants including selective serotonin reuptake inhibitors and tricyclics (20% of SEASONIQUE users and 18% of comparators), NSAIDs other than COX-2 inhibitors (19% of SEASONIQUE users and 18% of comparators), and benzodiazepines (12% of SEASONIQUE users and 10% of comparators). SEASONIQUE users had a median of five outpatient visits and comparators four outpatient visits in the 12 months of baseline.

Overall, the PS-matching was successful and the vast majority of baseline characteristics were well-balanced between the SEASONIQUE and comparator cohorts. The only exceptions were the number of prior CHCs in baseline (standardized difference 0.19) and the number of days of prior CHC use in baseline (standardized difference 0.19). However, the standardized mean is not ideal for assessing differences in count data. Although the median (and IQR) number of prior CHCs was the same across the two groups, SEASONIQUE users had a mean of 0.4 (SD 0.6) and comparators a mean of 0.3 (SD 0.5) prior CHCs. SEASONIQUE users and comparators both had a median of zero days on CHCs, but the range was larger among SEASONIQUE users (IQR 0 to 112) versus comparators (IQR 0 to 91). All baseline characteristics were balanced among naïve users alone (Table 2b), new users alone (Table 2c), re-starters (Table 2d), and switchers (Table 2e) with the exception of prior number of days on CHCs among re-starters. The pooled c-statistics (indicating the ability of the PS to predict type of treatment) for matched episodes (across all user groups and calendar time blocks) were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Only women who discontinued their COC use were included in the fertility analysis. Therefore, we re-assessed the balance achieved by PS matching among this subset of women. Among naïve and new discontinuers, there were no differences in baseline characteristics between the matched SEASONIQUE and comparator groups (Table 2f.1). With the exception of prior number of days on CHCs among re-starters, which was slightly lower for SEASONIQUE users versus comparators, there were no imbalances in baseline characteristics among naïve users alone, new users alone, re-starters, and switchers included in the fertility analysis (Table 2f.2).

10.3. Outcome Data

For the main analysis of VTE among naïve and new users during current exposure, there were a total of 35 cases during 16,867.6 person-years of follow-up among the SEASONIQUE users yielding an IR of 2.07 per 1,000 person-years (95% CI 1.45 to 2.89) (Table 3a). Among comparators, there were a total of 68 cases during 46,462.3 person-years of follow-up with a corresponding IR of 1.46 per 1,000 person-years (95% CI 1.14 to 1.86). Among the 2,652 unmatched naïve and new SEASONIQUE users during current exposure, the VTE IR was 1.38 (95% CI 0.28 to 4.03) per 1,000 person-years.

10.4. Main Results

10.4.1. VTE (Primary Definition)

Although VTE IRs were higher among SEASONIQUE users versus comparators in the main analysis of naïve and new users during current exposure, the IR difference was not statistically significant (0.61 per 1,000 person-years, 95% CI -0.16 to 1.38) (Table 3a). The PS-adjusted HR for VTE comparing SEASONIQUE users to comparators was 1.40 but not statistically significant (95% CI 0.90 to 2.19). With additional adjustment for the number of CHCs and days on CHCs in baseline, the two variables that remained unbalanced after PS-matching, these results were essentially unchanged (HR 1.41, 95% CI 0.91 to 2.19). Hence, the remaining results discussed pertain to the HRs adjusted for PS only.

10.4.1.1. Sensitivity and Subgroup Analyses

Few cases of VTE were observed among naïve and new users during the recent (1-30 days after treatment end) and intermediate (31-60 days after treatment end) exposure periods. The majority of VTE events occurred during the remote exposure period (61 or more days after treatment end): 41 events among SEASONIQUE users and 74 among comparators (Table 3a). The VTE IRs tended to decrease somewhat after treatment ended in both study groups. In the remote exposure period, the IRs were lower in both groups (1.55 per 1,000 person-years among SEASONIQUE users and 0.95 per 1,000 person-years among comparators) but the magnitude of the IR difference (0.60 per 1,000 person-years) was similar to that of the current exposure period, yet did not include the null value of zero (95% CI 0.08 to 1.12).

With so few events in the recent and intermediate exposure periods, the HR 95% CIs were very wide and consistent with a wide range of hypotheses, so are not discussed further. During the remote exposure period, the association between SEASONIQUE use and risk of VTE was stronger than that observed during current exposure and statistically significant (HR 1.66, 95% CI 1.12 to 2.45).

A similar non-statistically significant positive association during current exposure and statistically significant positive association during remote exposure were observed among naïve users alone (Table 3b). Among new users alone (Table 3c), re-starters (Table 3d), and switchers (Table 3e), there were no statistically significant associations between SEASONIQUE use and risk of VTE during current or remote exposure.

In a sensitivity analysis that extended the grace period from 30 to 60 days for SEASONIQUE users and from 14 to 28 days for comparators, the association was similar but the confidence interval did not include the null value of one among naïve and new users during current exposure (HR 1.53, 95% CI 1.01 to 2.31) (Table 3f.1). With this extended grace period, more cases were attributed to the current exposure period in both SEASONIQUE users and comparators. In the remote exposure period, the extended grace period yielded similar results as the main analysis (HR 1.63, 95% CI 1.09 to 2.43).

In a sensitivity analysis of naïve and new users that did not censor comparators with continuous use, the results were similar to the main analysis. During current exposure, there was no association between SEASONIQUE use and risk of VTE (HR 1.32, 95% CI 0.84 to 2.06). During remote exposure the association was essentially unchanged (HR 1.65, 95% CI 1.12 to 2.42) (Table 3f.2).

Three sensitivity analyses extended the length of the required CHC-free prior continuous enrolment beyond 12 months for naïve users, thereby selecting women that were more likely to have never used CHC in the past as per the naïve user definition. Among naïve users with at least 24 months of CHC-free prior continuous enrolment, results were similar during current exposure (HR 1.32, 95% CI 0.67 to 2.60) and similar but no longer statistically significant during remote exposure (HR 1.60, 95% CI 0.97 to 2.62) (Table 3f.3). Among naïve users with > 24 to 36 months of CHC-free prior continuous enrolment, there was no association between SEASONIQUE use and risk of VTE during current exposure (HR 0.55, 95% CI 0.11 to 2.80) but a positive association that was larger in magnitude during the remote exposure period (HR 2.99, 95% CI 1.23 to 7.24) (Table 3f.4). Among naïve users with a minimum of 36 months of CHC-free prior continuous enrolment, the association between SEASONIQUE use and risk of VTE was stronger in magnitude during current exposure and statistically significant (HR 2.35, 95% CI 1.05 to 5.24); there was no association during remote exposure (HR 0.94, 95% CI 0.46 to 1.93) (Table 3f.5).

In a sensitivity analysis of naïve and new users that shortened the required prior continuous enrolment period from 12 to six months, the association between SEASONIQUE use and risk of VTE was similar but statistically significant during current exposure (HR 1.53, 95% CI 1.03 to 2.28) (Table 3f.6). Among this larger group of women, the association during remote exposure was similar (HR 1.50, 95% CI 1.04 to 2.16). Note that this analysis included additional women whose data were not included in the creation of the PS scores. For these women with six to < 12 months prior continuous enrolment, a PS was calculated

using the final PS models created among women in the main analysis (with a minimum 12 months of continuous enrolment).

In subgroup analyses of naïve and new users during current exposure, results were generally similar across age groups, among normal weight versus overweight women, among smokers versus non-smokers, among women with and without prior VTE, and among women with and without surgery/injury during follow-up (Table 3f.7). However, the association between SEASONIQUE use as compared to 28-day cycle COC_{LNG} and risk of VTE was stronger among younger women age ≥ 15 to ≤ 35 years (HR 2.05, 95% CI 1.00 to 4.22) compared to older women age > 35 to ≤ 50 years (HR 0.95, 95% CI 0.52 to 1.75), athough the CIs overlapped (Table 3f.7).

In a sensitivity analysis of naïve and new users that excluded all cancer in baseline (in addition to gynaecological cancer and chemotherapy), the association between SEASONIQUE use and risk of VTE was essentially the same: HR 1.46 (95% CI 0.93 to 2.30) during current exposure and HR 1.66 (95% CI 1.12 to 2.45) during remote exposure (Table 3g).

10.4.2. VTE Adjudication Results

A total of 619 women were identified as having a VTE according to the primary VTE definition. Of these, 166 (27%) were eligible for medical record retrieval. Of these, 123 were part of the matched cohorts and medical records were sought for each of these 123 women. Medical records were received for 89 women (72%) that had sufficient information for confirmation of case or non-case status (Table 4). Sixty-eight of these 89 women were confirmed by the adjudicators as having had VTE, yielding a positive predictive value (PPV) of 76% (95% CI 66 to 85%). The PPV was higher among SEASONIQUE users (85%; 95% CI 68 to 95%) versus comparators (71%; 95% CI 58 to 83%). As expected, the PPV was much lower among women who did not meet the criteria for VTE but had an anticoagulant dispensing (as described in Section 9.5.1 *Medical Record Outcome Confirmation*): PPV 40% (95% CI 16 to 68%). For time efficiency, medical records were sought before matching and applying all censoring criteria. Therefore, not all cases included in Table 4 were part of the analysis.

10.4.3. VTE (Sensitivity Definition)

The sensitivity VTE definition identified fewer cases as compared with the primary definition, yet the observed associations with SEASONIQUE use were generally similar among naïve and new users (albeit slightly larger in magnitude): HR 1.61 (95% CI 0.98 to 2.63) during current exposure and HR 1.80 (95% CI 1.17 to 2.78) during remote exposure (Table 3a). Using the sensitivity VTE definition, the association between SEASONIQUE use and risk of VTE was statistically significant among naïve users alone during current and remote exposure (Table 3b). No association was observed during either exposure period among new users alone (Table 3c), re-starters (Table 3d), or switchers (Table 3e).

When the grace period was extended, the association remained similar but statistically significant among naïve and new users during the current (HR 1.67, 95% CI 1.05 to 2.66) and remote exposure periods (HR 1.80, 95% CI 1.15 to 2.82) (Table 3f.1). When comparators with continuous use were not censored, the results were similar among naïve and new users during current exposure (HR 1.45, 95% CI 0.89 to 2.38) and remote exposure (HR 1.78, 95% CI 1.16 to 2.73) (Table 3f.2). Hence, the same results were observed with the main and sensitivity VTE definitions when the grace period was extended.

Among naïve users with at least 24 months of CHC-free prior continuous enrolment (Table 3f.3) and with > 24 to ≤ 36 months of CHC-free prior continuous enrolment (Table 3f.4), the associations were similar. Among naïve users with a minimum of 36 months CHC-free prior continuous enrolment, the association between SEASONIQUE use and risk of VTE was greater in magnitude during current exposure (HR 2.67, 95% CI 1.07 to 6.64) relative to the primary definition; no association was observed during remote

exposure (HR 1.17, 95% CI 0.54 to 2.54) (Table 3f.5). Overall, the same results were observed when extending the CHC-free enrolment period to a minimum of 36 months for both the main and sensitivity VTE definitions.

When naïve and new users with six to < 12 months of prior continuous enrolment were additionally included in the analysis, the association between SEASONIQUE use and risk of VTE was greater in magnitude during current exposure (HR 1.68, 95% CI 1.10 to 2.58) and similar during remote exposure (HR 1.67, 95% CI 1.12 to 2.50) (Table 3f.6). These results are consistent with those observed using the main VTE definition. Finally, results within each of the various patient subgroups were very similar using the sensitivity VTE definition as compared to the main VTE definition (Table 3f.7).

10.4.4. Ad Hoc VTE Results

There may be some differences in the capture of VTE by ICD-9 and ICD-10 codes as ICD-9 codes may not translate perfectly to ICD-10 codes and vice versa. We stratified the PPV results by eras corresponding to use of ICD-9 and ICD-10 to assess their comparability. Among all user groups and during all exposure time, the PPV was 76.9% (95% CI 66.0 to 85.7%) during ICD-9 and the PPV was 72.7% (95% CI 39.0 to 94.0%) during ICD-10.

To further investigate the main VTE results, an ad hoc analysis was performed that was limited to confirmed cases of VTE. This analysis included a total of 9,179 naïve and new SEASONIQUE episodes and 29,003 naïve and new 28-day cycle COC_{LNG} episodes. A total of 10 confirmed VTE events were observed among SEASONIQUE users and six confirmed VTE events among 28-day cycle COC_{LNG} users during current exposure, yielding a PS-adjusted HR of 4.78 with wide confidence limits (95% CI 1.57 to 14.50).

10.4.5. Summary of VTE Results

Table B presents a summary of the main and sensitivity VTE results for naïve and new users. The association between SEASONIQUE use and risk of VTE was not statistically significant among naïve and new users during current exposure, with the exception of the analysis that extended the grace period from 14 to 28 days for 28-day cycle COC_{LNG} users and from 30 to 60 days for SEASONIQUE users. However, the HR estimates from the various sensitivity analyses (HRs 1.32 to 1.61) are similar to those from the main analysis (HR 1.40) and all 95% CIs overlapped.

Analyses that shortened the baseline period to six months observed a similar association as the main analysis during current exposure (HR 1.53) (Table B). Although the association using six months of baseline was statistically significant, the CIs overlapped substantially as compared to the main analysis. Among naïve and new users, SEASONIQUE use was consistently associated with an increased risk of VTE in the remote exposure period across all sensitivity analyses of naïve and new users (HRs from 1.63 to 1.80).

Table B. Summary of VTE Results (HR [95% CI] SEASONIQUE Versus Comparator), Naïve and New Users, Primary VTE Definition, Adjusted for PS

	Main Results	Sensitivity VTE Definition*	Extended Grace Period	Not Censoring Comparators with Continuous Use	No History of Any Cancer in Baseline	6 Instead of 12 Months of Prior Continuous Enrolment
Current Exposure	1.40 (0.90 - 2.19)	1.61 (0.98 - 2.63)	1.53 (1.01 - 2.31)	1.32 (0.84 - 2.06)	1.46 (0.93 - 2.30)	1.53 (1.03 - 2.28)
Remote Exposure	1.66 (1.12 - 2.45)	1.80 (1.17 - 2.78)	1.63 (1.09 - 2.43)	1.65 (1.12 - 2.42)	1.66 (1.12 - 2.45)	1.50 (1.04 - 2.16)

*Sensitivity instead of primary VTE definition.
Abbreviations: CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; PS, propensity score; VTE, venous thromboembolism.

Table C presents a summary of results for naïve users. Varying the baseline period from 12 to at least 36 months of CHC-free continuous enrolment in the health plan did not produce any discernible trends and all such analyses have overlapping 95% CIs. Analyses using the sensitivity (rather than primary) VTE definition observed a similar association during current exposure: HR 1.57 using the primary definition and HR 1.84 using the sensitivity definition, with overlapping 95% CIs.

Table C. Summary of VTE Results (HR [95% CI] SEASONIQUE Versus Comparator), Naïve Users, Primary VTE Definition, Adjusted for PS

	Main Results	At Least 24 Months CHC-free Prior Continuous Enrolment	> 24 to ≤ 36 Months of CHC-free Prior Continuous Enrolment	Minimum of 36 Months of CHC-free Prior Continuous Enrolment	Sensitivity VTE Definition*
Current Exposure	1.57 (0.95 - 2.61)	1.32 (0.67 - 2.60)	0.55 (0.11 - 2.80)	2.35 (1.05 - 5.24)	1.84 (1.05 - 3.24)
Remote Exposure	1.74 (1.12 - 2.70)	1.60 (0.97 - 2.62)	2.99 (1.23 - 7.24)	0.94 (0.46 - 1.93)	1.85 (1.13 - 3.03)

*Sensitivity instead of primary VTE definition.
Abbreviations: CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; PS, propensity score; VTE, venous thromboembolism.

10.4.6. ATE

Among naïve and new users, a total of 13 ATE events were observed among SEASONIQUE users and 28 among comparators during current exposure. During remote exposure, 30 ATE events were observed among SEASONIQUE users and 54 among comparators (Table 3a). There were few events during the recent and intermediate exposure periods; therefore, these results discuss the current and remote exposure periods only. No statistically significant associations were observed between SEASONIQUE use and risk of ATE during current (HR 1.21, 95% CI 0.58 to 2.53) or remote exposure (HR 1.56, 95% CI 0.99 to 2.47) (Table 3a). Analyses that adjusted for prior CHC use, in addition to PS, were essentially the same as those that adjusted for PS only; hence, the results discussed pertain to HRs adjusted for PS only.

Among naïve users alone, there was no association between SEASONIQUE and risk of ATE during current exposure (HR 1.36, 95% CI 0.55 to 3.38) but there was an increased risk with remote exposure

(HR 1.99, 95% CI 1.20 to 3.30) (Table 3b). There was no association between SEASONIQUE use and risk of ATE among new users alone (Table 3c), re-starters (3d), or switchers (3e) during the current or remote exposure periods.

When the grace period was extended, there was no association between SEASONIQUE use and risk of ATE among naïve and new users during current or remote exposure (Table 3f.1). When comparators with continuous use were not censored, there was no association between SEASONIQUE and risk of ATE during current exposure and a borderline statistically significant increased risk during remote exposure (HR 1.59, 95% CI 1.00 to 2.51) (Table 3f.2).

Among naïve users with at least 24 months CHC-free prior continuous enrolment, there was no association between SEASONIQUE and risk of ATE during current exposure but there was an increased risk during remote exposure (HR 1.91, 95% CI 1.01 to 3.63) (Table 3f.3). Among naïve users with > 24 to ≤ 36 months or a minimum of 36 months CHC-free prior continuous enrolment, there was no association between SEASONIQUE and risk of ATE during current or recent exposure (Tables 3f.4 and 3f.5).

When naïve and new users with six to < 12 months of prior continuous enrolment were additionally included in the analysis, there was no association between SEASONIQUE and risk of ATE during current exposure but SEASONIQUE was associated with an increased risk of ATE during remote exposure (HR 1.64, 95% CI 1.07 to 2.52) (Table 3f.6). SEASONIQUE was not associated with risk of ATE in any of the subgroups presented in Table 3f.7.

10.4.7. Breast Cancer

A total of 92 breast cancers occurred among SEASONIQUE users and 193 among comparators during the study period. There were very few events during the recent and intermediate exposure periods; hence, only results from the current and remote exposure periods are discussed. Among naïve and new users, SEASONIQUE was not associated with risk of breast cancer: HR 1.57 (95% CI 0.79 to 3.10) during current exposure and HR 1.37 (95% CI 0.91 to 2.08) during remote exposure (Table 3a). SEASONIQUE was also not associated with risk of breast cancer among naïve users alone (Table 3b), new users alone (Table 3c), re-starters (Table 3d), or switchers (Table 3e) during current or remote exposure.

When the grace period was extended, SEASONIQUE was associated with an increased risk of breast cancer among naïve and new users during current exposure (HR 1.82, 95% CI 1.03 to 3.22) but not remote exposure (HR 1.38, 95% CI 0.91 to 2.10) (Table 3f.1). When comparators with continuous use were not censored, SEASONIQUE use was not associated with risk of breast cancer among naïve and new users during current or remote exposure (Table 3f.2).

Among naïve users with at least 24 months CHC-free prior continuous enrolment, SEASONIQUE was associated with an increased risk of breast cancer during remote exposure (HR 1.75, 95% CI 1.02 to 3.00) (Table 3f.3). However there was no association between SEASONIQUE and breast cancer among naïve users with > 24 to ≤ 36 months or a minimum of 36 months CHC-free prior continuous enrolment (Tables 3f.4 and 3f.5). Likewise, there was no association between SEASONIQUE and breast cancer among the larger patient population that included naïve and new users with a minimum of six months continuous enrolment (Table 3f.6). There were also no associations between SEASONIQUE and breast cancer in any of the subgroups presented in Table 3f.7.

10.4.8. Cervical Cancer

Across all naïve users, new users, re-starters, and switchers, there were a total of six cervical cancers among SEASONIQUE users and 12 among comparators. Among naïve users alone (Table 3b), new users alone (Table 3c), re-starters (Table 3d), and switchers (Table 3e), there was no suggestion of an

association between SEASONIQUE use and risk of cervical cancer. There were too few cervical cancers to draw conclusions from the sensitivity analyses (Tables 3f.1 to 3f.7).

10.4.9. Endometrial Cancer

There were too few cases of endometrial cancer (three among SEASONIQUE users and 12 among comparators) to draw conclusions from these results (Table 3a).

10.4.10. Ovarian Cancer

There were too few cases of ovarian cancer (two among SEASONIQUE users and 15 among comparators) to draw conclusions from these results (Table 3a).

10.4.11. Fertility

Across all user groups (naïve users, new users, re-starters, and switchers), SEASONIQUE users tended to have lower pregnancy rates as compared with comparators (Table 5a). Pregnancy rates ranged from 50 to 75 per 1,000 person years among SEASONIQUE users and from 67 to 106 per 1,000 person-years among comparators. These differences were statistically significant among naïve users and switchers, with IR 95% CIs that did not overlap. Results were generally the same with an extended grace period, without censoring comparators with continuous use, and among naïve users with longer CHC-free continuous enrolment (Table 5b). There were no obvious differences or trends across the various pre-specified subgroups (Table 5c).

10.4.12. Delayed Pregnancy Detection

10.4.12.1. Time from Pregnancy Start to First Prenatal Encounter

Among pregnancies that occurred during current exposure, there were no statistically significant differences between SEASONIQUE users and comparators in terms of time from estimated pregnancy start to first prenatal encounter (Table 6a). Results were similar among naïve and new users with an extended grace period, without censoring comparators with continuous use, and among naïve users with longer CHC-free continuous enrolment (Table 6b). There was no suggestion of a difference in time from pregnancy start to first prenatal care encounter among any of the various patient subgroups (Table 6c).

10.4.12.2. Time from Pregnancy Start to Current Treatment End

Based on estimated treatment end, naïve and new SEASONIQUE users were exposed to treatment for an average of eight days longer after estimated pregnancy start than naïve and new comparators (mean 61.8 days versus 53.7 days, p-value 0.03). No differences in timing were observed among new users alone, re-starters, or switchers (Table 7a). Results were similar for naïve and new users with an extended grace period and without censoring comparators with continuous use (Table 7b). As the CHC-free continuous enrolment period was extended for naïve users, this difference was no longer statistically significant.

To take into account the different days' supply of the two study drugs (91 versus 28), we examined time from pregnancy start to current exposure end among the subset of discontinuers with a pregnancy that started within the last 28 days of a dispensing. Among this subset of women, there was no statistically significant difference in time between pregnancy start and current exposure end (Table 7b).

When younger (age 12 to ≤ 35 years) and older (age > 35 to < 46 years) women were analysed separately, the difference in time between conception and end of exposure for SEASONIQUE users versus comparators was only observed among the younger women (mean 62.4 days versus 53.6 days, p-value

0.03 and not the older women (mean 56.7 days versus 54.0 days, p-value 0.76) (Table 7c). Only pregnancies with prenatal care codes were included in Table 6a whereas Table 7a included pregnancies with and without prenatal care codes. Therefore the total number of pregnancies was different between the two tables.

10.5. Other Analyses

There was a high degree of overlap between treatment groups in the KDE plots of PS distributions, suggesting good exchangeability (similar covariate patterns) of women in the two treatment groups (Figure 1). Among naïve and new users, for each outcome and during each exposure period, the cumulative probability of survival for the two study cohorts is graphically compared in Figures 2 to 8. The proportional hazards assumption checks, including the log-log survival curves and cross-product terms (SEASONIQUE versus comparator by time) are presented in the same figures. In no instances did the log-log survival curve cross *and* the cross-product term reach statistical significance in any one exposure period for any outcome. Therefore, we concluded that the proportional hazards assumption held for all analyses.

10.6. Adverse Events/Adverse Reactions

Not applicable.

11. Discussion

11.1. Key Results

11.1.1. VTE

11.1.1.1. VTE Rates

Prior studies have reported a background VTE incidence rate of 0.2 to 0.4 per 1,000 person-years among women not using CHCs and 0.6 to 1.0 per 1,000 person-years among women using conventional, 28-day cycle oral CHCs containing low dose EE and a second generation progestin (5-7). We observed an IR of 2.07 per 1,000 person-years among naïve and new SEASONIQUE users and an IR of 1.46 per 1,000 person-years among naïve and new 28-day cycle COC_{LNG} users in the matched cohorts. Our results are similar to a recent study that observed an IR of 1.23 per 1,000 person-years among naïve new 28-day cycle COC users where naïve new users were defined as having no prior CHC use during the six month baseline period (25). The IRs observed in this study and by Li et al. (25) may be similar because both used healthcare claims data and unconfirmed events.

11.1.1.2. Analyses of Current Exposure

Current SEASONIQUE use (versus current 28-day cycle COC_{LNG} use) was not associated with an increased risk of VTE in the main analysis of naïve and new users (HR 1.40, 95% CI 0.90 to 2.19). The same was true among naïve users alone (HR 1.57, 95% CI 0.95 to 2.61), new users alone (HR 1.07, 95% CI 0.45 to 2.53), re-starters (HR 1.12, 95% CI 0.55 to 2.28), and switchers (HR 0.64, 95% CI 0.28 to 1.43). While the HR estimates were generally consistent and elevated (except among switchers) and highest among naïve users, all 95% CIs included the null value of one and therefore chance is a plausible explanation for these associations.

In the sensitivity analyses conducted among naïve and new users during the current exposure period, the HR estimates for the association between SEASONIQUE use and risk of VTE were similar in magnitude

to the HR from the main analysis, and all CIs overlapped. The HRs reached statistical significance in some sensitivity analyses (for example, when the continuous enrolment period was relaxed to six [instead of 12] months [HR 1.53, 95% CI 1.03 to 2.28], and when the grace period was extended [HR 1.53, 95% CI 1.01 to 2.31]). However, the observed differences in the magnitude of HRs across the various analyses and slight shifts in CIs likely reflect the instability of the HR estimates (due to the reclassifying of person-time and/or events across the exposure windows, etc.) rather than true differences in risk. Within the pharmacy claims data, we are unable to determine whether patients began taking their medication immediately following their COC dispensing, or delayed the start of their medication use. Hence it is challenging to determine the grace period length that accurately reflects the patient's true exposure period. Previous studies have used 30-days for extended oral contraceptives (25) and 28-days for transdermal or oral contraceptives (26). A 14-day grace period may be more reasonable for shorter (e.g., 28-day) prescriptions.

In some secondary analyses restricted to naïve users, the CIs excluded the null, including the analysis using the VTE sensitivity definition (HR 1.84, 95% CI 1.05 to 3.24) and when the analysis was limited to those with a minimum of 36 months CHC-free continuous enrolment prior to treatment initiation (HR 2.35, 95% CI 1.05 to 5.24). Hence, due to the higher HRs, the association between SEASONIQUE use and risk of VTE appears somewhat different among the subgroup of naïve users. Overall, naïve SEASONIQUE users had similar distributions of measured baseline characteristics as naïve 28-day cycle COC_{LNG} users but there were some small differences (e.g. SEASONIQUE users were two years older on average) that taken together may indicate a slightly less healthy SEASONIQUE group. In addition, some unmeasured factors may have biased the observed results. In an ad hoc analysis of naïve and new users during current exposure where the outcomes were restricted to the 16 medical record-confirmed VTE cases, a higher HR of 4.78 (95% CI 1.57 to 14.50) was observed. These results are difficult to interpret as this study was not powered to examine confirmed events. While the 95% CI excluded the null value of one, the CI was wide, indicating an unstable HR estimate, and overlapped with the 95% CI from the main analysis (0.90 to 2.19). The difference in magnitude of the HR observed in the main analysis and this ad hoc analysis may be related to the confirmed cases not being a random sample of all cases: more SEASONIQUE users with a claims-identified VTE were eligible for medical records (47% versus 39%), more SEASONIQUE medical records were received (77% versus 70%), and more SEASONIQUE cases were confirmed (85% versus 71%). Further analyses are needed to interpret these ad hoc results.

11.1.1.3. Analyses of Recent, Intermediate, and Remote Exposure Periods

In addition to current exposure, the analysis examined risk of VTE during the recent (1-30 days after treatment end), intermediate (31-60 days after treatment end), and remote (> 60 days after treatment end) exposure periods. There were too few events during the recent and intermediate exposure periods to draw conclusions about the presence or lack of associations. With so few events, even combining these periods into one 60-day interval would not yield interpretable estimates of association. On the other hand, the majority of VTE events were observed in the remote exposure period during which we observed an increased risk of VTE among SEASONIQUE users versus comparators: HR 1.66 (95% CI 1.12 to 2.45) among naïve and new users. This increased risk was present among naïve users (HR 1.74, 95% CI 1.12 to 2.70) but not new users (HR 1.43, 95% CI 0.64 to 3.19) re-starters (HR 1.20, 95% CI 0.62 to 2.33) or switchers (HR 1.39, 95% CI 0.67 to 2.87).

The current literature suggests that VTE risk is highest in the first few months of COC use (19, 27, 28) and a break of four or more weeks in COC use results in a higher VTE risk, whereas switching to a different COC within four weeks does not increase risk (27). Therefore, the current exposure period was pre-specified as the main analysis, as in other literature (19). However, it is possible that some women could have had anywhere from one to several months of current exposure before contributing to the recent,

intermediate, and remote exposure periods, making results arising from these non-current exposure periods challenging to interpret.

In the main analysis of naïve and new users, the current exposure duration among the SEASONIQUE users (median 121 days, IQR 121-303) was higher than that among the comparators (median 105 days, IQR 42-263). Therefore, it is possible that events occurring within the first few months after COC initiation tended to be more often observed during the current exposure period among SEASONIQUE users than comparators. This could have biased findings from the current exposure period in a positive direction away from the null, resulting in an observed HR of greater magnitude. To reduce the potential for this bias, future analyses could examine follow-up time in terms of days since COC initiation as well as classified as current, recent, intermediate, or remote exposure.

The remote exposure results are less relevant than the current exposure results because SEASONIQUE is no longer in the system 60 days after treatment end; the terminal half-life of LNG with a single dose of SEASONIQUE is about 34 hours (1), so it should be fully eliminated in about a week. Even if the biologic activity of LNG as it relates to VTE risk extends beyond the time it can be measured, 60 days is likely to represent an adequate washout period. Hence, associations observed in the remote exposure period are unlikely to be due to the study drug. Instead, they may be a result of differential loss to follow-up, treatment discontinuation, or other mechanisms that would lead to differences between cohorts in this remote exposure period. On the other hand, if some stockpiling of COCs was missed and women filled their prescriptions more than two months before taking the first pill, it is possible that some of the remote exposure period was misclassified.

11.1.1.4. Varying The Definition of Naïve Use

The variable results across different definitions of the CHC-free baseline period for naïve COC users are difficult to interpret as there were no clear trends. Furthermore, the CIs overlapped substantially for these sensitivity analyses suggesting that any differences could be due to chance.

11.1.1.5. VTE Algorithm Performance

Our medical record confirmation of VTE outcomes suggested that the claims-based main VTE definition performed well, with a PPV of 76% (95% CI 66 to 85%), indicating that 76% of cases identified in the analysis were true cases. Our PPV is similar to that of other claims-based VTE algorithms (12, 29, 30). If the PPVs were the same in the SEASONIQUE and comparator groups, we would expect that the resulting relative risk estimates (HRs) would be somewhat less precise (with a PPV < 100%) but nevertheless unbiased because of non-differential misclassification of exposure. However, the PPV was unexpectedly higher among SEASONIQUE users (85%; 95% CI 68 to 95%) versus comparators (71%; 95% CI 58 to 83%), although the 95% CIs overlapped suggesting that this difference may not be statistically significant. Given that the adjudicators were blinded to exposure status during case confirmation, we interpret this difference as due to chance. Even if it were not due to chance, it would not explain the observed, elevated HRs because more events among comparators would be false positives. Analyses stratified by ICD-9 versus ICD-10 indicated that there were no important differences in algorithm performance between the two time periods: the PPV 95% CIs for the VTE algorithm overlapped completely for the two time periods.

11.1.1.6. Previous Literature

Our main analysis results are similar to a recent study by Li et al. which compared extended COCs to traditional 28-day COCs (25). Li et al. used a similar study population drawn from a commercially insured population, including some women from the ORD, and used a claims algorithm to identify cases of VTE.

Among naïve new users, this study observed a similar VTE IR difference of 0.64 per 1,000 person-years (IR 1.87 versus 1.23 per 1,000 person-years) and a PS-adjusted HR of 1.49 (95% CI 1.17 to 1.92). Li et al. did not analyse current, recent, intermediate, and remote exposure time separately. When all COC users were included in the analysis (not only naïve new users), Li et al. observed a smaller VTE IR difference of 0.35 per 1,000 person-years (IR 1.44 versus 1.09 per 1,000 person-years) and a PS-adjusted HR of 1.32 (95% CI 1.07 to 1.64). They concluded that due to the small absolute risk difference and potential residual confounding, these results did not provide strong evidence for a difference in VTE risk between extended and traditional 28-day COC use.

11.1.2. ATE

Among naïve and new users, current SEASONIQUE (versus current 28-day cycle COC_{LNG}) use was not associated with risk of ATE (HR 1.21, 95% CI 0.58 to 2.53). The same, null association was observed among naïve users alone, new users alone, re-starters, and switchers. The association remained null when the grace period was extended, when comparators with continuous use were not censored, when the CHC-free period for naïve users was lengthened, and when the continuous enrolment period was shortened to six months. Hence, these results were consistent across several sensitivity analyses.

As with the VTE analysis, too few ATE events were observed in the recent and intermediate exposure periods to draw conclusions. During the remote exposure period, among naïve and new users, the association between SEASONIQUE use and risk of ATE was not statistically significant (HR 1.56, 95% CI 0.99 to 2.47). However, among naïve users alone, this association reached statistical significance, suggesting a 2-fold increase in ATE risk (HR 1.99, 95% CI 1.20 to 3.30). There was no evidence of an association among new users alone, re-starters, or switchers. The same association reached borderline statistical significance among naïve and new users when comparators with continuous use were not censored. The association reached statistical significance when the baseline period was shortened to six months and when the CHC-free period was lengthened to at least 24 months for naïve users, but not when the CHC-free period was lengthened to > 24 to ≤ 36 months or a minimum of 36 months for naïve users.

Overall, the observed ATE associations appeared similar to the VTE associations where the positive associations were stronger and statistically significant during the remote exposure period and this positive association was mainly observed among the naïve users. Given that SEASONIQUE is fully metabolized within 60 days following the last dose, these results are difficult to interpret. These findings may be due to differences between SEASONIQUE users and comparators in follow-up such as differential discontinuation or switching to non-study contraceptives.

The definition of ATE included both ischaemic and haemorrhagic strokes. Of the 126 ATEs reported in Table 3a among naïve and new users, 23 (18%) were due to a haemorrhagic code only. Hence, the results may have been different if the analysis excluded haemorrhagic events.

11.1.3. Breast Cancer and Other Gynaecological Cancers

SEASONIQUE use was not associated with risk of breast cancer among naïve and new users combined, naïve users alone, new users alone, re-starters, or switchers. When the grace period was extended, SEASONIQUE was associated with an increased risk of breast cancer among naïve and new users during current exposure (HR 1.82, 95% CI 1.03 to 3.22) but not remote exposure (HR 1.38, 95% CI 0.91 to 2.10). This may be due to the reclassification of more breast cancers to the current exposure period with the extended grace period.

These results are difficult to interpret for multiple reasons. First, if SEASONIQUE truly increased the risk of breast cancer, we might expect to observe a stronger association during remote exposure compared to current exposure given that the current exposure period was a median of three to four months in both

cohorts and cancer typically develops over a longer period of time. Hence, the remote exposure period may be the most relevant exposure period for these particular gynaecological cancers. Second, the separation of follow-up time across the current, recent, intermediate, and remote exposure periods was relevant for the analysis of the acute outcome VTE, but is less relevant for the analysis of cancer. It may be more informative to assess the association between SEASONIQUE use and risk of breast cancer across all person-time combined. Third, the analysis was done at the episode level, censoring women who began a new treatment episode. Analysing at the person-level would be more appropriate for the cancer outcomes. Fourth, any associations observed during current exposure may represent reverse causality, where symptoms related to the cancer lead to prescribing of an OC (e.g., early signs of endometrial cancer are misinterpreted as endometriosis), because it is unlikely that short-term exposure (three to four months) would lead to cancer, particularly solid tumours. A lagged analysis that excludes the first few months of follow-up after exposure starts may be more appropriate for the cancer endpoints.

No associations were observed between SEASONIQUE use and risk of cervical cancer among naïve users alone, new users alone, re-starters, or switchers. Of the six cervical cancers observed in SEASONIQUE users and 12 in comparators, four were diagnosed during current exposure among naïve and new SEASONIQUE users and one during current exposure among naïve and new comparators, yielding an HR of 12.01 (95% CI 1.39 to 104.03). The wide CI for this estimate indicates that it is likely a chance finding and the separation of follow-up time into the current, recent, intermediate, and remote exposure periods is less relevant for non-acute outcomes like cervical cancer. There were too few endometrial or ovarian cancers to draw inference from these results; however, there was no suggestion of an association between SEASONIQUE versus 28-day cycle COC_{LNG} use and risk of either cancer.

11.1.4. Fertility

Across all user groups (naïve users, new users, re-starters, and switchers), SEASONIQUE discontinuers had fewer pregnancies than 28-day cycle COC_{LNG} discontinuers. This may be expected given that women planning to conceive in the near future may be less likely to choose a long-term contraceptive like SEASONIQUE. In terms of the potential for infertility, these results are difficult to interpret as the claims data do not capture information on whether women are trying to conceive, whether women are sexually active, and whether women are using non-prescription contraceptives (e.g., condoms). Without this information, it is uncertain whether the SEASONIQUE and comparator groups were balanced across such highly relevant factors.

Furthermore, fertility analyses often focus on whether women successfully become pregnant within a year but the majority of women who discontinued SEASONIQUE or comparator treatment were followed for less than a year. Overall, fertility rates in both groups were comparable to rates observed in a similar population of women of reproductive age, about four to five per 100 women per year (31, 32).

11.1.5. Delayed Pregnancy Detection

We observed no difference between SEASONIQUE users and comparators in terms of days from pregnancy start to first prenatal care code. However, comparing pregnancy start to the end of current treatment, naïve and new SEASONIQUE users had approximately eight additional days of current exposure compared to naïve and new comparators. There were no significant differences in either metric among new users alone, re-starters, or switchers. The observed delayed pregnancy detection using the latter metric could potentially be a result of SEASONIQUE users having less opportunity to observe early pregnancy signs such as a missed period because they only experience bleeding four times per year. However, if this were the case, we could expect to see differences across all user groups, not just naïve users.

The results based on the first prenatal care code may have less potential for misclassification as they rely on the date of a prenatal care visit claim and the estimated date of conception, while the comparison of time from pregnancy start to the end of treatment relies on two estimated dates: date of conception and the end of treatment. The same pregnancy period algorithms were applied for SEASONIQUE users and comparators; therefore, any errors associated with the estimated pregnancy start would not be expected to produce a spurious difference between cohorts. On the other hand, the end of treatment was defined by including the grace period at the end of the last consecutive dispensing's days' supply. Since the grace period was longer for SEASONIQUE (30 days as opposed to 14 days among comparators), this remains a possible explanation for some of the observed difference.

11.2. Limitations

This study was based on an analysis of automated medical and prescription claims, supplemented by information abstracted from medical records. While claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, health care resource utilization, and costs, all claims databases have certain inherent limitations because the claims are collected for the purpose of payment and not research. Medications filled over-the-counter or provided as samples by the physician are not observed in the claims data. The presence of a claim for a filled prescription does not indicate that the medication was actually taken or that it was taken as prescribed, which may result in exposure misclassification. For example, women may be classified as exposed when they have actually stopped taking the drug. In addition, it is possible that the 28-day cycle COC_{LNG} is used continuously, without a hormone-free interval (for several packages or even indefinitely) until breakthrough bleeding occurs. This may be especially true for monophasic COCs. Such continuous 28-day cycle COC_{LNG} users were censored from the main analysis. A sensitivity analyses did not censor these women, but assumed that they used their COC as prescribed (i.e., did not skip the placebo week).

In healthcare claims data, the presence of a diagnosis code on a medical claim may not represent the true presence of a disease, as the diagnosis code may be incorrect or included as rule-out criteria (to justify a work up, screening procedure, etc.) rather than actual disease. Indeed, our claims-based definition of VTE was associated with a PPV of 76%. While this PPV was acceptable, it indicated that about a quarter of cases identified may be false positives in studies that rely on the claims-based algorithm. For this particular VTE algorithm, a broad range of codes were included to improve its sensitivity, at the cost of the PPV. With any algorithm, there is always the risk of missing some cases (false negatives) due to the exclusion of particular codes. However, patients presenting with events like VTE may be expected to have a spectrum of corresponding VTE codes, including some that were part of our VTE algorithm, thereby decreasing the likelihood of false negatives. Despite these potential limitations, the algorithm performed well compared to existing claims-based algorithms (12). The inclusion or exclusion of specific codes would have resulted in non-differential misclassification of VTE as the same algorithm was used for both the SEASONIQUE users and comparators. This type of misclassification would not affect the HR estimates but would lead to less precise (wider) CIs.

In our study, we observed a slightly higher PPV for VTE among SEASONIQUE users as compared with the PPV observed among 28-day cycle COC_{LNG} users, although the CIs overlapped. If SEASONIQUE use was indeed associated with an increased risk of VTE, this PPV difference may have biased the positive association towards the null because fewer 28-day cycle COC_{LNG} events would represent actual events as compared to SEASONIQUE events. Indeed, an ad hoc analysis limited to confirmed cases produced a much higher HR of 4.78 comparing naïve and new users during current exposure. However, this estimate was unstable and difficult to interpret due to an extremely wide CI. Furthermore, this ad hoc analysis included a non-random sample of claims-identified events that favoured the confirmation of more SEASONIQUE events than comparator events, biasing the positive association further from the null.

The ATE and cancer analyses were limited to claims-identified cases only. Without corresponding PPVs, it is more difficult to interpret these results. In addition, the ATE algorithm included both ischaemic and haemorrhagic strokes; future studies may prefer to include only ischaemic strokes as they are most relevant for studying risk of ATE. Lastly, the claims data lacked information on some important gynaecological cancer risk factors such as genetics, family history, and reproductive history and we cannot determine if these risk factors were balanced between the two study groups.

Despite the success of the PS matching, some residual confounding is possible due to unmeasured or imprecisely measured confounders. For example, the claims data has limited information on smoking, obesity, personal and family history of thrombosis, and lifetime use of hormonal contraceptives. While information on potential confounders such as smoking and obesity are often missing in claims data, we performed subgroup analyses among women with codes for these factors, in which we expected the impact of residual confounding to be less, and observed similar results albeit with much smaller sample sizes and significantly less precision.

Confounding by indication was not expected in this study as both SEASONIQUE and 28-day cycle COC_{LNG} contain similar active ingredients (LNG combined with EE) and thus a physician's decision to prescribe SEASONIQUE vs. a 28-day cycle COC_{LNG} is not expected to be based on risk of VTE. However, in the overall database (before matching), SEASONIQUE users had a higher prevalence of migraine and a slightly higher prevalence of dysmenorrhea versus comparators in baseline suggesting that women with such comorbidities may be more likely to use an extended COC. Furthermore, confounding could occur if physicians tended to prescribe SEASONIQUE to women with specific characteristics that may also be risk factors for VTE, and if these characteristics were not captured in the database and hence, were not accounted for in the statistical analysis. Some VTE risk factors that are less well-captured in claims data are body mass index, smoking, family history of thrombosis, and lifetime use of hormonal contraceptives. To the extent possible, we used diagnosis and procedure codes to assess these potential confounders. We also assessed variables related to general health (e.g. number of prescriptions, diagnoses, and hospitalizations). Overall, all assessed potential confounders were well-balanced across the two study cohorts.

The 28-day cycle COC_{LNG} cohort had various strengths and combinations of COCs. If the mechanism linking extended COC use and risk of VTE is cumulative oestrogen exposure, such an association may have been missed as the actual doses of oestrogen between cohorts were not explored. It is also possible that there was differential censoring or exposure to other contraceptives during follow-up between the study cohorts. For example, when women started a non-study CHC, their current exposure period was censored but their follow-up continued. Follow-up was only censored when starting a new study COC. Hence, exposures in follow-up may not be comparable between the study cohorts, especially during the remote exposure period.

Delayed pregnancy detection may not be accurately estimated. Each SEASONIQUE pack includes 91 days of pills, but it is not possible to know based on the claims whether a woman stopped taking the drug before the end of the pill pack. In addition, date of conception is not recorded in the database and was estimated using an average pregnancy period of 270 days for deliveries and 120 days for terminations. As such, whether women are still using the drug when they become pregnant cannot be determined with certainty. Furthermore, the definition of fertility assumes that women are sexually active and not using other forms of contraception that are not captured by claims (i.e., condoms).

In addition, fertility relates to actively trying to conceive and it is unclear which identified pregnancies were planned. Women wishing to receive a long-term CHC, such as SEASONIQUE, may be more likely to be trying to prevent pregnancy in the next several months than women using shorter-duration 28-day cycle COC_{LNG}. Therefore the relative fertility rates comparing SEASONIQUE to 28-day cycle COC_{LNG} users may reflect this difference rather than a fertility impediment related to the study drug. Furthermore,

some pregnancies may have been missed as claims data may not capture all pregnancies that end with abortions.

Finally, the average length of follow-up in the ORD and similar databases is about two-to-three years and thus long-term outcomes, such as cancers, may not be identified. Furthermore, cancers that were observed within a few months after study drug initiation are unlikely to be due to the study drug as the latency period (period of development) of breast, cervical, endometrial, and ovarian cancers is typically longer.

11.3. Interpretation

In this study, current SEASONIQUE (versus current 28-day cycle COC_{LNG}) use was not associated with a statistically significant increased risk of VTE in the main analysis of naïve and new users (HR 1.40, 95% CI 0.90 to 2.19). The same was true among naïve users alone (HR 1.57, 95% CI 0.95 to 2.61), new users alone (HR 1.07, 95% CI 0.45 to 2.53), re-starters (HR 1.12, 95% CI 0.55 to 2.28), and switchers (HR 0.64, 95% CI 0.28 to 1.43). However, some sensitivity analyses suggested a statistically significant increased risk among naïve users, as did an analysis limited to confirmed VTE cases.

The main study results are similar to those of Li et al. (25) comparing extended versus 28-day cycle COC_{LNG} use in several administrative claims databases including the ORD. Li et al. concluded that these results did not provide strong evidence for a difference in risk between extended and traditional 28-day cycle COC_{LNG} users. This conclusion was based mainly on the relatively small risk difference observed as well as the potential for residual confounding in such observational studies of healthcare claims data.

Findings for the secondary outcome ATE were similar to those for VTE. Current SEASONIQUE (versus current 28-day cycle COC_{LNG}) use was not associated with risk of ATE (HR 1.21, 95% CI 0.58 to 2.53) in the main analysis of naïve and new users or among naïve users alone, new users alone, re-starters, or switchers.

SEASONIQUE discontinuers tended to have lower pregnancy rates compared to 28-day cycle COC_{LNG} discontinuers; however, it is impossible to determine if this is due to differences in fertility or differences in the proportion of women trying to conceive. Overall, women in both cohorts had expected pregnancy rates of four to five per 100 women per year. Among women who became pregnant during treatment, there was no suggestion of delayed pregnancy detection based on the date of the first prenatal care code, but naïve SEASONIQUE users tended to have a few additional days of exposure to the study drug during the first trimester using the estimated date of conception and the estimated end of treatment.

Overall, there were no consistent associations between SEASONIQUE and risk of breast cancer. Although some sensitivity analyses suggested a positive association, the study design and statistical methods used were tailored for the primary outcome, VTE, rather than non-acute outcomes such as breast cancer; future studies are needed to adequately test these associations. There were too few cervical, endometrial, and ovarian cancers to draw conclusions and no associations between SEASONIQUE versus 28-day cycle COC_{LNG} use and risk of these cancers were observed.

11.4. Generalisability

Women in the ORD are geographically diverse and representative of the non-elderly, commercially-insured US population. Therefore, while these findings are expected to be broadly generalizable to women of reproductive age; their generalizability to non-insured women may be limited. The stratification of these results by age allows for better comparison with women in other countries, such as European countries, with varying demographics.

12. Other Information

Not applicable.

13. Conclusion

In conclusion, while the main study results did not suggest a statistically significant association between SEASONIQUE, an extended LNG-containing COC, as compared with traditional 28-day cycle COCs and risk of VTE, the magnitude of the HR estimates and some sensitivity and ad hoc analyses suggested a possible positive association, particularly among naïve users. These results do not suggest an important association between SEASONIQUE as compared to traditional 28-day cycle COCs in terms of risk of ATE, fertility, or delayed pregnancy detection. Further analyses among naïve users may aid in interpreting the statistically significant increased risk of VTE and ATE observed in some sensitivity analyses.

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Appendices

Annex 1. List of Stand-alone Documents

Not applicable.

Annex 2. Tables

List of Tables

Table 1. Observed Number of Dispensings and Length of Follow-up within the Matched SEASONIQUE and Comparator Cohorts

	Matched Episodes[1]			
	SEASONIQUE (N=44,078)		Comparator (N=132,245)	
	SEASONIQUE	N=25,587	Comparator	N=76,575
Main Analysis (Naïve and New Users)	**Median**	**IQR**	**Median**	**IQR**
Total days' supply[2], current exposure	121	121-303	105	42-263
Number of dispensings of index medication[3]	1	1-3	2	1-6
Reason for censoring[3]:	**N**	**%**	**N**	**%**
Occurrence of venous thromboembolism	82	0.3	148	0.2
Cancer diagnosis or chemotherapy	331	1.3	1,006	1.3
End of study period	4,286	16.8	13,300	17.4
End of enrolment in the health plan or death4	14,977	58.5	42,869	56.0
Started a new treatment episode	5,911	23.1	17,367	22.7
Continuous use[5] (comparators only)	0	0.0	1,885	2.5
Discontinuation or switching from index medication (flag only, not censored)	18,509	72.3	55,147	72.0
Occurrence of pregnancy (flag only, not censored)	1,161	4.5	3,986	5.2
	SEASONIQUE	N=15,133	Comparator	N=52,642
Naïve Users	**Median**	**IQR**	**Median**	**IQR**
Total days' supply[2], current exposure	121	121-254	105	42-269
Number of dispensings of index medication[3]	1	1-3	2	1-6
Reason for censoring[3]:	**N**	**%**	**N**	**%**
Occurrence of venous thromboembolism	58	0.4	112	0.2
Cancer diagnosis or chemotherapy	194	1.3	732	1.4
End of study period	2,880	19.0	9,940	18.9
End of enrolment in the health plan or death4	9,072	59.9	30,025	57.0
Started a new treatment episode	2,929	19.4	10,561	20.1
Continuous use[5] (comparators only)	0	0.0	1,272	2.4
Discontinuation or switching from index medication (flag only, not censored)	11,029	72.9	37,768	71.7
Occurrence of pregnancy (flag only, not censored)	692	4.6	2,790	5.3

Abbreviations: IQR, interquartile range; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]Includes grace period.

[3]VTE analysis.

[4]Prior to end of study.

[5]Three or more consecutive early dispensings (comparators only).

Note: Seasonique episodes were matched to comparator episodes within calendar period, but not within user group (naïve, new, etc.); therefore comparisons between user groups effectively break the matching.

296 episodes had zero days of current exposure or were matched to episodes with zero days of current exposure and were excluded from the analyses.

Table 1. Observed Number of Dispensings and Length of Follow-up within the Matched SEASONIQUE and Comparator Cohorts

	Matched Episodes[1]			
	SEASONIQUE (N=44,078)		Comparator (N=132,245)	
	SEASONIQUE	N=10,454	Comparator	N=23,933
New Users	**Median**	**IQR**	**Median**	**IQR**
Total days' supply[2], current exposure	172	121-310	105	42-242
Number of dispensings of index medication[3]	2	1-3	2	1-5
Reason for censoring[3]:	**N**	**%**	**N**	**%**
Occurrence of venous thromboembolism	24	0.2	36	0.2
Cancer diagnosis or chemotherapy	137	1.3	274	1.1
End of study period	1,406	13.4	3,360	14.0
End of enrolment in the health plan or death4	5,905	56.5	12,844	53.7
Started a new treatment episode	2,982	28.5	6,806	28.4
Continuous use[5] (comparators only)	0	0.0	613	2.6
Discontinuation or switching from index medication (flag only, not censored)	7,480	71.6	17,379	72.6
Occurrence of pregnancy (flag only, not censored)	469	4.5	1,196	5.0
	SEASONIQUE	**N=8,339**	**Comparator**	**N=25,953**
Re-starters	**Median**	**IQR**	**Median**	**IQR**
Total days' supply[2], current exposure	166	121-320	105	42-277
Number of dispensings of index medication[3]	2	1-3	3	1-6
Reason for censoring[3]:	**N**	**%**	**N**	**%**
Occurrence of venous thromboembolism	27	0.3	55	0.2
Cancer diagnosis or chemotherapy	97	1.2	266	1.0
End of study period	1,249	15.0	3,561	13.7
End of enrolment in the health plan or death4	4,418	53.0	13,014	50.1
Started a new treatment episode	2,548	30.6	8,437	32.5
Continuous use[5] (comparators only)	0	0.0	620	2.4
Discontinuation or switching from index medication (flag only, not censored)	5,808	69.6	18,336	70.7
Occurrence of pregnancy (flag only, not censored)	303	3.6	1,223	4.7

Abbreviations: IQR, interquartile range; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]Includes grace period.

[3]VTE analysis.

[4]Prior to end of study.

[5]Three or more consecutive early dispensings (comparators only).

Note: Seasonique episodes were matched to comparator episodes within calendar period, but not within user group (naïve, new, etc.); therefore comparisons between user groups effectively break the matching.

296 episodes had zero days of current exposure or were matched to episodes with zero days of current exposure and were excluded from the analyses.

Table 1. Observed Number of Dispensings and Length of Follow-up within the Matched SEASONIQUE and Comparator Cohorts

	Matched Episodes[1]			
	SEASONIQUE (N=44,078)		Comparator (N=132,245)	
	SEASONIQUE	N=10,152	Comparator	N=29,717
Switchers	**Median**	**IQR**	**Median**	**IQR**
Total days' supply[2], current exposure	158	98-352	137	65-336
Number of dispensings of index medication[3]	2	1-4	3	1-8
Reason for censoring[3]:	**N**	**%**	**N**	**%**
Occurrence of venous thromboembolism	22	0.2	54	0.2
Cancer diagnosis or chemotherapy	117	1.2	322	1.1
End of study period	2,388	23.5	6,396	21.5
End of enrolment in the health plan or death [4]	5,494	54.1	16,278	54.8
Started a new treatment episode	2,131	21.0	5,210	17.5
Continuous use[5] (comparators only)	0	0.0	1,457	4.9
Discontinuation or switching from index medication (flag only, not censored)	6,771	66.7	19,002	63.9
Occurrence of pregnancy (flag only, not censored)	323	3.2	1,312	4.4

Abbreviations: IQR, interquartile range; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]Includes grace period.

[3]VTE analysis.

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Table 2a. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Naïve and New Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=28,245)		Comparator (N=150,446)		SEASONIQUE (N=25,593)		Comparator (N=76,586)		SEASONIQUE (N=2,652)		
	N	%	N	%	N	%	N	%	N	%	
Demographic											
Age (Years) [Median, IQR]	29.0	22.0-38.0	26.0	20.0-35.0	29.0	22.0-37.0	28.0	20.0-36.0	33.0	26.0-40.0	0.10
Age (Years) [Mean, SD]	30.2	9.6	28.0	9.6	29.9	9.6	28.9	9.8	33.0	9.3	0.10
Age Groups (Years)											
12 to < 15	264	0.9	2,058	1.4	260	1.0	1,021	1.3	4	0.2	0.03
≥ 15 to ≤ 35	19,218	68.0	113,959	75.7	17,681	69.1	54,889	71.7	1,537	58.0	0.06
> 35 to ≤ 50	8,443	29.9	32,434	21.6	7,360	28.8	19,794	25.8	1,083	40.8	0.07
> 50	320	1.1	1,995	1.3	292	1.1	882	1.2	28	1.1	0.00
Geographic Region											
Northeast	2,776	9.8	16,102	10.7	2,543	9.9	8,275	10.8	233	8.8	0.03
South/Southeast	15,111	53.5	55,946	37.2	13,269	51.8	34,985	45.7	1,842	69.5	0.12
Midwest	5,917	20.9	44,599	29.6	5,582	21.8	18,823	24.6	335	12.6	0.07
West	4,405	15.6	33,626	22.4	4,169	16.3	14,413	18.8	236	8.9	0.07
Other	36	0.1	173	0.1	30	0.1	90	0.1	6	0.2	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2a. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Naïve and New Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
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	N	%	N	%	N	%	N	%	N	%	
Calendar Month of Initiation											
January	2,462	8.7	16,448	10.9	2,294	9.0	7,328	9.6	168	6.3	0.02
February	2,241	7.9	13,037	8.7	2,053	8.0	6,087	7.9	188	7.1	0.00
March	2,246	8.0	13,842	9.2	2,113	8.3	6,576	8.6	133	5.0	0.01
April	2,182	7.7	12,421	8.3	2,007	7.8	6,147	8.0	175	6.6	0.01
May	2,300	8.1	12,247	8.1	2,108	8.2	6,317	8.2	192	7.2	0.00
June	2,487	8.8	13,016	8.7	2,275	8.9	6,891	9.0	212	8.0	0.00
July	2,204	7.8	12,392	8.2	2,008	7.8	6,281	8.2	196	7.4	0.01
August	2,587	9.2	13,237	8.8	2,356	9.2	6,815	8.9	231	8.7	0.01
September	2,324	8.2	11,353	7.5	2,076	8.1	5,975	7.8	248	9.4	0.01
October	2,486	8.8	11,312	7.5	2,173	8.5	6,128	8.0	313	11.8	0.02
November	2,328	8.2	10,530	7.0	2,037	8.0	5,893	7.7	291	11.0	0.01
December	2,398	8.5	10,611	7.1	2,093	8.2	6,148	8.0	305	11.5	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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	N	%	N	%	N	%	N	%	N	%	
Clinical Conditions											
VTE and Cardiovascular Risk Factors											
Cardiac dysrhythmias	412	1.5	1,663	1.1	368	1.4	1,087	1.4	44	1.7	0.00
Cerebrovascular or coronary artery disease	65	0.2	155	0.1	50	0.2	117	0.2	15	0.6	0.01
Coagulation defects	118	0.4	531	0.4	111	0.4	365	0.5	7	0.3	0.01
Chronic obstructive pulmonary disease	87	0.3	311	0.2	76	0.3	208	0.3	11	0.4	0.00
Diabetes mellitus Type 1 or 2	391	1.4	2,030	1.3	367	1.4	1,089	1.4	24	0.9	0.00
Hyperlipidemia	1,410	5.0	5,324	3.5	1,250	4.9	3,218	4.2	160	6.0	0.03
Hypertension	1,414	5.0	5,696	3.8	1,255	4.9	3,357	4.4	159	6.0	0.02
Overweight and obesity	1,228	4.3	6,359	4.2	1,156	4.5	3,553	4.6	72	2.7	0.01
Pregnancy up to 3 months before treatment initiation	1,279	4.5	8,749	5.8	1,259	4.9	4,369	5.7	20	0.8	0.04
Prior arterial thromboembolism[3]	23	0.1	58	0.0	21	0.1	38	0.0	2	0.1	0.01
Prior thromboembolic event[4]	27	0.1	109	0.1	27	0.1	65	0.1	0	0.0	0.01
Tobacco use	1,623	5.7	6,313	4.2	1,478	5.8	4,044	5.3	145	5.5	0.02
Unstable angina	5	0.0	14	0.0	4	0.0	10	0.0	1	0.0	0.00
Vascular disease[5]	114	0.4	484	0.3	102	0.4	303	0.4	12	0.5	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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	N	%	N	%	N	%	N	%	N	%	
Other Risk Factors											
Combined Charlson-Elixhauser comorbidity score (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.01
Anovulation	28	0.1	259	0.2	28	0.1	97	0.1	0	0.0	0.01
Asthma	1,883	6.7	8,488	5.6	1,699	6.6	4,949	6.5	184	6.9	0.01
Dysmenorrhea	2,907	10.3	12,179	8.1	2,671	10.4	8,190	10.7	236	8.9	0.01
Epilepsy	186	0.7	485	0.3	159	0.6	379	0.5	27	1.0	0.02
Gynaecological disorders[6]	7,530	26.7	38,077	25.3	6,948	27.1	20,876	27.3	582	21.9	0.00
Hepatitis C	12	0.0	78	0.1	12	0.0	38	0.0	0	0.0	0.00
History of abortion	126	0.4	1,032	0.7	123	0.5	410	0.5	3	0.1	0.01
HIV/AIDS	7	0.0	38	0.0	7	0.0	20	0.0	0	0.0	0.00
Liver failure	90	0.3	415	0.3	81	0.3	252	0.3	9	0.3	0.00
Migraine	2,334	8.3	6,100	4.1	1,944	7.6	4,630	6.0	390	14.7	0.06
Polycystic ovary syndrome	392	1.4	2,367	1.6	361	1.4	1,253	1.6	31	1.2	0.02
Renal failure	35	0.1	107	0.1	34	0.1	69	0.1	1	0.0	0.01
Thyroid disorder	753	2.7	3,336	2.2	696	2.7	1,936	2.5	57	2.1	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2a. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Naïve and New Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=28,245)		Comparator (N=150,446)		SEASONIQUE (N=25,593)		Comparator (N=76,586)		SEASONIQUE (N=2,652)		
	N	%	N	%	N	%	N	%	N	%	
Prior Prescription Drug Use											
Prior Contraceptive Use											
Use of other forms of contraception[7]	1,199	4.2	8,710	5.8	1,177	4.6	4,229	5.5	22	0.8	0.04
Prior days on CHCs (median, IQR)	0.0	0.0-182.0	0.0	0.0-56.0	0.0	0.0-112.0	0.0	0.0-91.0	182.0	147.0-252.0	0.19
Number of prior CHCs (median, IQR)	0.0	0.0-1.0	0.0	0.0-1.0	0.0	0.0-1.0	0.0	0.0-1.0	1.0	1.0-1.0	0.19
Other Drug Use											
Anticoagulants or alteplase	92	0.3	294	0.2	80	0.3	195	0.3	12	0.5	0.01
ACEI or ARB	631	2.2	2,409	1.6	560	2.2	1,435	1.9	71	2.7	0.02
Benzodiazepines	3,334	11.8	11,352	7.5	2,942	11.5	7,644	10.0	392	14.8	0.05
Beta-blockers	914	3.2	2,887	1.9	778	3.0	1,928	2.5	136	5.1	0.03
Calcium channel blockers	155	0.5	338	0.2	120	0.5	242	0.3	35	1.3	0.02
COX-2 inhibitors	265	0.9	609	0.4	209	0.8	464	0.6	56	2.1	0.03
Diabetes medications	601	2.1	3,055	2.0	569	2.2	1,736	2.3	32	1.2	0.00
NSAIDs other than COX-2 inhibitors	5,286	18.7	22,435	14.9	4,775	18.7	13,625	17.8	511	19.3	0.02
Spironolactone	342	1.2	1,695	1.1	311	1.2	968	1.3	31	1.2	0.00
SSRI/TCA	5,708	20.2	21,919	14.6	5,070	19.8	13,723	17.9	638	24.1	0.05
Statin/fibrate	563	2.0	1,834	1.2	481	1.9	1,185	1.5	82	3.1	0.03

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2a. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Naïve and New Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=28,245)		Comparator (N=150,446)		SEASONIQUE (N=25,593)		Comparator (N=76,586)		SEASONIQUE (N=2,652)		
	N	%	N	%	N	%	N	%	N	%	
Healthcare Utilization											
Outpatients visits (median, IQR)	5.0	2.0-8.0	4.0	2.0-6.0	5.0	2.0-8.0	4.0	2.0-7.0	5.0	3.0-9.0	0.06
Number of emergency room visits (median, IQR)	0.0	0.0-1.0	0.0	0.0-0.0	0.0	0.0-1.0	0.0	0.0-1.0	0.0	0.0-1.0	0.04
Number of hospitalizations (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2b. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Naïve Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=15,183)		Comparator (N=105,431)		SEASONIQUE (N=15,133)		Comparator (N=52,642)		SEASONIQUE (N=50)		
	N	%	N	%	N	%	N	%	N	%	
Demographic											
Age (Years) [Median, IQR]	29.0	21.0-37.0	25.0	19.0-34.0	29.0	21.0-37.0	27.0	19.0-36.0	37.0	30.0-42.0	0.12
Age (Years) [Mean, SD]	29.5	9.6	27.3	9.6	29.5	9.6	28.3	9.9	35.3	8.6	0.12
Age Groups (Years)											
12 to < 15	235	1.5	1,917	1.8	235	1.6	958	1.8	0	0.0	0.02
≥ 15 to ≤ 35	10,484	69.1	80,810	76.6	10,463	69.1	37,998	72.2	21	42.0	0.07
> 35 to ≤ 50	4,343	28.6	21,527	20.4	4,314	28.5	13,250	25.2	29	58.0	0.08
> 50	121	0.8	1,177	1.1	121	0.8	436	0.8	0	0.0	0.00
Geographic Region											
Northeast	1,418	9.3	11,102	10.5	1,417	9.4	5,598	10.6	1	2.0	0.04
South/Southeast	7,960	52.4	37,524	35.6	7,916	52.3	23,865	45.3	44	88.0	0.14
Midwest	3,282	21.6	32,496	30.8	3,277	21.7	13,058	24.8	5	10.0	0.07
West	2,503	16.5	24,197	23.0	2,503	16.5	10,067	19.1	0	0.0	0.07
Other	20	0.1	112	0.1	20	0.1	54	0.1	0	0.0	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2b. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Naïve Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=15,183)		Comparator (N=105,431)		SEASONIQUE (N=15,133)		Comparator (N=52,642)		SEASONIQUE (N=50)		
	N	%	N	%	N	%	N	%	N	%	
Calendar Month of Initiation											
January	1,318	8.7	10,980	10.4	1,316	8.7	5,016	9.5	2	4.0	0.03
February	1,169	7.7	9,159	8.7	1,169	7.7	4,243	8.1	0	0.0	0.01
March	1,239	8.2	9,825	9.3	1,239	8.2	4,518	8.6	0	0.0	0.01
April	1,210	8.0	8,896	8.4	1,207	8.0	4,282	8.1	3	6.0	0.01
May	1,236	8.1	8,573	8.1	1,232	8.1	4,277	8.1	4	8.0	0.00
June	1,362	9.0	9,182	8.7	1,359	9.0	4,762	9.0	3	6.0	0.00
July	1,209	8.0	8,597	8.2	1,204	8.0	4,207	8.0	5	10.0	0.00
August	1,367	9.0	9,426	8.9	1,363	9.0	4,741	9.0	4	8.0	0.00
September	1,264	8.3	8,037	7.6	1,258	8.3	4,084	7.8	6	12.0	0.02
October	1,294	8.5	8,043	7.6	1,289	8.5	4,257	8.1	5	10.0	0.02
November	1,225	8.1	7,405	7.0	1,213	8.0	4,099	7.8	12	24.0	0.01
December	1,290	8.5	7,308	6.9	1,284	8.5	4,156	7.9	6	12.0	0.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Table 2b. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Naïve Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=15,183)		Comparator (N=105,431)		SEASONIQUE (N=15,133)		Comparator (N=52,642)		SEASONIQUE (N=50)		
	N	%	N	%	N	%	N	%	N	%	
Clinical Conditions											
VTE and Cardiovascular Risk Factors											
Cardiac dysrhythmias	247	1.6	1,156	1.1	244	1.6	742	1.4	3	6.0	0.02
Cerebrovascular or coronary artery disease	36	0.2	104	0.1	30	0.2	80	0.2	6	12.0	0.01
Coagulation defects	75	0.5	394	0.4	75	0.5	276	0.5	0	0.0	0.00
Chronic obstructive pulmonary disease	49	0.3	203	0.2	49	0.3	132	0.3	0	0.0	0.01
Diabetes mellitus Type 1 or 2	230	1.5	1,336	1.3	229	1.5	661	1.3	1	2.0	0.02
Hyperlipidemia	664	4.4	3,354	3.2	656	4.3	1,955	3.7	8	16.0	0.03
Hypertension	735	4.8	3,778	3.6	730	4.8	2,150	4.1	5	10.0	0.04
Overweight and obesity	770	5.1	4,442	4.2	766	5.1	2,468	4.7	4	8.0	0.02
Pregnancy up to 3 months before treatment initiation	1,091	7.2	7,689	7.3	1,089	7.2	3,945	7.5	2	4.0	0.01
Prior arterial thromboembolism[3]	14	0.1	37	0.0	14	0.1	22	0.0	0	0.0	0.02
Prior thromboembolic event[4]	16	0.1	62	0.1	16	0.1	34	0.1	0	0.0	0.01
Tobacco use	889	5.9	4,208	4.0	884	5.8	2,597	4.9	5	10.0	0.04
Unstable angina	4	0.0	10	0.0	4	0.0	7	0.0	0	0.0	0.01
Vascular disease[5]	62	0.4	317	0.3	61	0.4	195	0.4	1	2.0	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2b. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Naïve Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=15,183)		Comparator (N=105,431)		SEASONIQUE (N=15,133)		Comparator (N=52,642)		SEASONIQUE (N=50)		
	N	%	N	%	N	%	N	%	N	%	
Other Risk Factors											
Combined Charlson-Elixhauser comorbidity score (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-1.0	0.02
Anovulation	15	0.1	196	0.2	15	0.1	72	0.1	0	0.0	0.01
Asthma	974	6.4	5,917	5.6	969	6.4	3,337	6.3	5	10.0	0.00
Dysmenorrhea	1,874	12.3	9,806	9.3	1,855	12.3	6,674	12.7	19	38.0	0.01
Epilepsy	111	0.7	331	0.3	107	0.7	255	0.5	4	8.0	0.03
Gynaecological disorders[6]	4,479	29.5	27,343	25.9	4,456	29.4	14,952	28.4	23	46.0	0.02
Hepatitis C	4	0.0	46	0.0	4	0.0	19	0.0	0	0.0	0.01
History of abortion	84	0.6	626	0.6	84	0.6	271	0.5	0	0.0	0.01
HIV/AIDS	4	0.0	28	0.0	4	0.0	14	0.0	0	0.0	0.00
Liver failure	53	0.3	287	0.3	53	0.4	174	0.3	0	0.0	0.00
Migraine	1,142	7.5	4,014	3.8	1,123	7.4	3,072	5.8	19	38.0	0.06
Polycystic ovary syndrome	229	1.5	1,589	1.5	228	1.5	833	1.6	1	2.0	0.01
Renal failure	23	0.2	68	0.1	23	0.2	44	0.1	0	0.0	0.02
Thyroid disorder	428	2.8	2,310	2.2	425	2.8	1,312	2.5	3	6.0	0.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Table 2b. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Naïve Users

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	SEASONIQUE (N=15,183)		Comparator (N=105,431)		SEASONIQUE (N=15,133)		Comparator (N=52,642)		SEASONIQUE (N=50)		
	N	%	N	%	N	%	N	%	N	%	
Prior Prescription Drug Use											
Prior Contraceptive Use											
Use of other forms of contraception[7]	1,023	6.7	7,602	7.2	1,022	6.8	3,667	7.0	1	2.0	0.01
Prior days on CHCs (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	NA
Number of prior CHCs (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	NA
Other Drug Use											
Anticoagulants or alteplase	55	0.4	198	0.2	54	0.4	126	0.2	1	2.0	0.02
ACEI or ARB	294	1.9	1,414	1.3	293	1.9	792	1.5	1	2.0	0.03
Benzodiazepines	1,666	11.0	6,988	6.6	1,646	10.9	4,685	8.9	20	40.0	0.07
Beta-blockers	442	2.9	1,810	1.7	437	2.9	1,178	2.2	5	10.0	0.04
Calcium channel blockers	63	0.4	217	0.2	62	0.4	158	0.3	1	2.0	0.02
COX-2 inhibitors	123	0.8	381	0.4	119	0.8	296	0.6	4	8.0	0.03
Diabetes medications	343	2.3	2,019	1.9	343	2.3	1,095	2.1	0	0.0	0.01
NSAIDs other than COX-2 inhibitors	2,961	19.5	15,685	14.9	2,938	19.4	9,580	18.2	23	46.0	0.03
Spironolactone	166	1.1	1,104	1.0	164	1.1	572	1.1	2	4.0	0.00
SSRI/TCA	2,884	19.0	14,092	13.4	2,863	18.9	8,559	16.3	21	42.0	0.07
Statin/fibrate	235	1.5	1,037	1.0	232	1.5	629	1.2	3	6.0	0.03

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2b. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Naïve Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=15,183)		Comparator (N=105,431)		SEASONIQUE (N=15,133)		Comparator (N=52,642)		SEASONIQUE (N=50)		
	N	%	N	%	N	%	N	%	N	%	
Healthcare Utilization											
Outpatients visits (median, IQR)	5.0	2.0-8.0	4.0	2.0-6.0	5.0	2.0-8.0	4.0	2.0-7.0	12.5	9.0-19.0	0.08
Number of emergency room visits (median, IQR)	0.0	0.0-1.0	0.0	0.0-0.0	0.0	0.0-1.0	0.0	0.0-1.0	1.0	0.0-2.0	0.04
Number of hospitalizations (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2c. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, New Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=13,062)		Comparator (N=45,015)		SEASONIQUE (N=10,460)		Comparator (N=23,944)		SEASONIQUE (N=2,602)		
	N	%	N	%	N	%	N	%	N	%	
Demographic											
Age (Years) [Median, IQR]	30.0	23.0-38.0	28.0	22.0-36.0	29.0	22.0-38.0	29.0	22.0-37.0	33.0	25.0-40.0	0.02
Age (Years) [Mean, SD]	30.9	9.5	29.4	9.3	30.4	9.5	30.2	9.5	33.0	9.3	0.02
Age Groups (Years)											
12 to < 15	29	0.2	141	0.3	25	0.2	63	0.3	4	0.2	0.00
≥ 15 to ≤ 35	8,734	66.9	33,149	73.6	7,218	69.0	16,891	70.5	1,516	58.3	0.03
> 35 to ≤ 50	4,100	31.4	10,907	24.2	3,046	29.1	6,544	27.3	1,054	40.5	0.04
> 50	199	1.5	818	1.8	171	1.6	446	1.9	28	1.1	0.02
Geographic Region											
Northeast	1,358	10.4	5,000	11.1	1,126	10.8	2,677	11.2	232	8.9	0.01
South/Southeast	7,151	54.7	18,422	40.9	5,353	51.2	11,120	46.4	1,798	69.1	0.09
Midwest	2,635	20.2	12,103	26.9	2,305	22.0	5,765	24.1	330	12.7	0.05
West	1,902	14.6	9,429	20.9	1,666	15.9	4,346	18.2	236	9.1	0.06
Other	16	0.1	61	0.1	10	0.1	36	0.2	6	0.2	0.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2c. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, New Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=13,062)		Comparator (N=45,015)		SEASONIQUE (N=10,460)		Comparator (N=23,944)		SEASONIQUE (N=2,602)		
	N	%	N	%	N	%	N	%	N	%	
Calendar Month of Initiation											
January	1,144	8.8	5,468	12.1	978	9.3	2,312	9.7	166	6.4	0.01
February	1,072	8.2	3,878	8.6	884	8.5	1,844	7.7	188	7.2	0.03
March	1,007	7.7	4,017	8.9	874	8.4	2,058	8.6	133	5.1	0.01
April	972	7.4	3,525	7.8	800	7.6	1,865	7.8	172	6.6	0.01
May	1,064	8.1	3,674	8.2	876	8.4	2,040	8.5	188	7.2	0.01
June	1,125	8.6	3,834	8.5	916	8.8	2,129	8.9	209	8.0	0.00
July	995	7.6	3,795	8.4	804	7.7	2,074	8.7	191	7.3	0.04
August	1,220	9.3	3,811	8.5	993	9.5	2,074	8.7	227	8.7	0.03
September	1,060	8.1	3,316	7.4	818	7.8	1,891	7.9	242	9.3	0.00
October	1,192	9.1	3,269	7.3	884	8.5	1,871	7.8	308	11.8	0.02
November	1,103	8.4	3,125	6.9	824	7.9	1,794	7.5	279	10.7	0.01
December	1,108	8.5	3,303	7.3	809	7.7	1,992	8.3	299	11.5	0.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2c. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, New Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=13,062)		Comparator (N=45,015)		SEASONIQUE (N=10,460)		Comparator (N=23,944)		SEASONIQUE (N=2,602)		
	N	%	N	%	N	%	N	%	N	%	
Clinical Conditions											
VTE and Cardiovascular Risk Factors											
Cardiac dysrhythmias	165	1.3	507	1.1	124	1.2	345	1.4	41	1.6	0.02
Cerebrovascular or coronary artery disease	29	0.2	51	0.1	20	0.2	37	0.2	9	0.3	0.01
Coagulation defects	43	0.3	137	0.3	36	0.3	89	0.4	7	0.3	0.00
Chronic obstructive pulmonary disease	38	0.3	108	0.2	27	0.3	76	0.3	11	0.4	0.01
Diabetes mellitus Type 1 or 2	161	1.2	694	1.5	138	1.3	428	1.8	23	0.9	0.04
Hyperlipidemia	746	5.7	1,970	4.4	594	5.7	1,263	5.3	152	5.8	0.02
Hypertension	679	5.2	1,918	4.3	525	5.0	1,207	5.0	154	5.9	0.00
Overweight and obesity	458	3.5	1,917	4.3	390	3.7	1,085	4.5	68	2.6	0.04
Pregnancy up to 3 months before treatment initiation	188	1.4	1,060	2.4	170	1.6	424	1.8	18	0.7	0.01
Prior arterial thromboembolism[3]	9	0.1	21	0.0	7	0.1	16	0.1	2	0.1	0.00
Prior thromboembolic event[4]	11	0.1	47	0.1	11	0.1	31	0.1	0	0.0	0.01
Tobacco use	734	5.6	2,105	4.7	594	5.7	1,447	6.0	140	5.4	0.02
Unstable angina	1	0.0	4	0.0	0	0.0	3	0.0	1	0.0	0.02
Vascular disease[5]	52	0.4	167	0.4	41	0.4	108	0.5	11	0.4	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2c. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, New Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=13,062)		Comparator (N=45,015)		SEASONIQUE (N=10,460)		Comparator (N=23,944)		SEASONIQUE (N=2,602)		
	N	%	N	%	N	%	N	%	N	%	
Other Risk Factors											
Combined Charlson-Elixhauser comorbidity score (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.02
Anovulation	13	0.1	63	0.1	13	0.1	25	0.1	0	0.0	0.01
Asthma	909	7.0	2,571	5.7	730	7.0	1,612	6.7	179	6.9	0.01
Dysmenorrhea	1,033	7.9	2,373	5.3	816	7.8	1,516	6.3	217	8.3	0.06
Epilepsy	75	0.6	154	0.3	52	0.5	124	0.5	23	0.9	0.00
Gynaecological disorders[6]	3,051	23.4	10,734	23.8	2,492	23.8	5,924	24.7	559	21.5	0.02
Hepatitis C	8	0.1	32	0.1	8	0.1	19	0.1	0	0.0	0.00
History of abortion	42	0.3	406	0.9	39	0.4	139	0.6	3	0.1	0.03
HIV/AIDS	3	0.0	10	0.0	3	0.0	6	0.0	0	0.0	0.00
Liver failure	37	0.3	128	0.3	28	0.3	78	0.3	9	0.3	0.01
Migraine	1,192	9.1	2,086	4.6	821	7.8	1,558	6.5	371	14.3	0.05
Polycystic ovary syndrome	163	1.2	778	1.7	133	1.3	420	1.8	30	1.2	0.04
Renal failure	12	0.1	39	0.1	11	0.1	25	0.1	1	0.0	0.00
Thyroid disorder	325	2.5	1,026	2.3	271	2.6	624	2.6	54	2.1	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2c. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, New Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=13,062)		Comparator (N=45,015)		SEASONIQUE (N=10,460)		Comparator (N=23,944)		SEASONIQUE (N=2,602)		
	N	%	N	%	N	%	N	%	N	%	
Prior Prescription Drug Use											
Prior Contraceptive Use											
Use of other forms of contraception[7]	176	1.3	1,108	2.5	155	1.5	562	2.3	21	0.8	0.06
Prior days on CHCs (median, IQR)	182.0	91.0-182.0	112.0	56.0-182.0	182.0	91.0-182.0	168.0	91.0-196.0	182.0	168.0-252.0	0.05
Number of prior CHCs (median, IQR)	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0	0.00
Other Drug Use											
Anticoagulants or alteplase	37	0.3	96	0.2	26	0.2	69	0.3	11	0.4	0.01
ACEI or ARB	337	2.6	995	2.2	267	2.6	643	2.7	70	2.7	0.01
Benzodiazepines	1,668	12.8	4,364	9.7	1,296	12.4	2,959	12.4	372	14.3	0.00
Beta-blockers	472	3.6	1,077	2.4	341	3.3	750	3.1	131	5.0	0.01
Calcium channel blockers	92	0.7	121	0.3	58	0.6	84	0.4	34	1.3	0.03
COX-2 inhibitors	142	1.1	228	0.5	90	0.9	168	0.7	52	2.0	0.02
Diabetes medications	258	2.0	1,036	2.3	226	2.2	641	2.7	32	1.2	0.03
NSAIDs other than COX-2 inhibitors	2,325	17.8	6,750	15.0	1,837	17.6	4,045	16.9	488	18.8	0.02
Spironolactone	176	1.3	591	1.3	147	1.4	396	1.7	29	1.1	0.02
SSRI/TCA	2,824	21.6	7,827	17.4	2,207	21.1	5,164	21.6	617	23.7	0.01
Statin/fibrate	328	2.5	797	1.8	249	2.4	556	2.3	79	3.0	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2c. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, New Users

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=13,062)		Comparator (N=45,015)		SEASONIQUE (N=10,460)		Comparator (N=23,944)		SEASONIQUE (N=2,602)		
	N	%	N	%	N	%	N	%	N	%	
Healthcare Utilization											
Outpatients visits (median, IQR)	5.0	3.0-8.0	4.0	2.0-7.0	5.0	2.0-8.0	4.0	2.0-8.0	5.0	3.0-9.0	0.03
Number of emergency room visits (median, IQR)	0.0	0.0-1.0	0.0	0.0-0.0	0.0	0.0-1.0	0.0	0.0-1.0	0.0	0.0-1.0	0.02
Number of hospitalizations (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2d. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Re-starters

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=8,720)		Comparator (N=74,932)		SEASONIQUE (N=8,340)		Comparator (N=25,961)		SEASONIQUE (N=380)		
	N	%	N	%	N	%	N	%	N	%	
Demographic											
Age (Years) [Median, IQR]	30.0	22.0-39.0	28.0	22.0-37.0	30.0	22.0-39.0	30.0	23.0-39.0	35.0	26.5-43.0	0.01
Age (Years) [Mean, SD]	31.3	9.9	29.9	9.6	31.1	9.9	31.2	9.8	34.4	9.8	0.01
Age Groups (Years)											
12 to < 15	21	0.2	266	0.4	20	0.2	58	0.2	1	0.3	0.00
≥ 15 to ≤ 35	5,648	64.8	53,683	71.6	5,452	65.4	17,110	65.9	196	51.6	0.01
> 35 to ≤ 50	2,904	33.3	19,475	26.0	2,725	32.7	8,276	31.9	179	47.1	0.02
> 50	147	1.7	1,508	2.0	143	1.7	517	2.0	4	1.1	0.02
Geographic Region											
Northeast	950	10.9	8,280	11.1	914	11.0	2,905	11.2	36	9.5	0.01
South/Southeast	4,601	52.8	30,872	41.2	4,335	52.0	13,224	50.9	266	70.0	0.02
Midwest	1,831	21.0	20,170	26.9	1,780	21.3	5,575	21.5	51	13.4	0.00
West	1,328	15.2	15,506	20.7	1,302	15.6	4,226	16.3	26	6.8	0.02
Other	10	0.1	104	0.1	9	0.1	31	0.1	1	0.3	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2d. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Re-starters

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=8,720)		Comparator (N=74,932)		SEASONIQUE (N=8,340)		Comparator (N=25,961)		SEASONIQUE (N=380)		
	N	%	N	%	N	%	N	%	N	%	
Calendar Month of Initiation											
January	802	9.2	7,608	10.2	770	9.2	2,276	8.8	32	8.4	0.02
February	673	7.7	6,218	8.3	645	7.7	2,071	8.0	28	7.4	0.01
March	747	8.6	6,637	8.9	729	8.7	2,153	8.3	18	4.7	0.02
April	679	7.8	6,086	8.1	658	7.9	2,048	7.9	21	5.5	0.00
May	721	8.3	6,430	8.6	697	8.4	2,189	8.4	24	6.3	0.00
June	764	8.8	6,594	8.8	733	8.8	2,321	8.9	31	8.2	0.01
July	687	7.9	6,178	8.2	657	7.9	2,071	8.0	30	7.9	0.00
August	686	7.9	6,131	8.2	656	7.9	2,171	8.4	30	7.9	0.02
September	683	7.8	5,731	7.6	645	7.7	2,053	7.9	38	10.0	0.01
October	740	8.5	5,937	7.9	699	8.4	2,220	8.6	41	10.8	0.01
November	695	8.0	5,550	7.4	660	7.9	2,106	8.1	35	9.2	0.01
December	843	9.7	5,832	7.8	791	9.5	2,282	8.8	52	13.7	0.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2d. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Re-starters

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=8,720)		Comparator (N=74,932)		SEASONIQUE (N=8,340)		Comparator (N=25,961)		SEASONIQUE (N=380)		
	N	%	N	%	N	%	N	%	N	%	
Clinical Conditions											
VTE and Cardiovascular Risk Factors											
Cardiac dysrhythmias	145	1.7	760	1.0	142	1.7	351	1.4	3	0.8	0.03
Cerebrovascular or coronary artery disease	18	0.2	77	0.1	16	0.2	38	0.1	2	0.5	0.01
Coagulation defects	33	0.4	224	0.3	32	0.4	100	0.4	1	0.3	0.00
Chronic obstructive pulmonary disease	33	0.4	191	0.3	30	0.4	86	0.3	3	0.8	0.00
Diabetes mellitus Type 1 or 2	121	1.4	1,138	1.5	117	1.4	507	2.0	4	1.1	0.04
Hyperlipidemia	552	6.3	3,577	4.8	511	6.1	1,617	6.2	41	10.8	0.00
Hypertension	500	5.7	3,412	4.6	476	5.7	1,556	6.0	24	6.3	0.01
Overweight and obesity	389	4.5	3,080	4.1	371	4.4	1,218	4.7	18	4.7	0.01
Pregnancy up to 3 months before treatment initiation	148	1.7	2,349	3.1	147	1.8	479	1.8	1	0.3	0.01
Prior arterial thromboembolism[3]	5	0.1	38	0.1	5	0.1	22	0.1	0	0.0	0.01
Prior thromboembolic event[4]	11	0.1	63	0.1	11	0.1	29	0.1	0	0.0	0.01
Tobacco use	539	6.2	3,440	4.6	513	6.2	1,817	7.0	26	6.8	0.03
Unstable angina	4	0.0	11	0.0	3	0.0	3	0.0	1	0.3	0.02
Vascular disease[5]	38	0.4	228	0.3	36	0.4	114	0.4	2	0.5	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

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[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2d. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Re-starters

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=8,720)		Comparator (N=74,932)		SEASONIQUE (N=8,340)		Comparator (N=25,961)		SEASONIQUE (N=380)		
	N	%	N	%	N	%	N	%	N	%	
Other Risk Factors											
Combined Charlson-Elixhauser comorbidity score (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.01
Anovulation	8	0.1	58	0.1	8	0.1	11	0.0	0	0.0	0.02
Asthma	616	7.1	4,266	5.7	583	7.0	1,930	7.4	33	8.7	0.02
Dysmenorrhea	683	7.8	3,816	5.1	651	7.8	1,523	5.9	32	8.4	0.08
Epilepsy	64	0.7	232	0.3	55	0.7	157	0.6	9	2.4	0.01
Gynaecological disorders[6]	1,906	21.9	14,818	19.8	1,823	21.9	5,227	20.1	83	21.8	0.04
Hepatitis C	2	0.0	31	0.0	2	0.0	8	0.0	0	0.0	0.00
History of abortion	29	0.3	473	0.6	29	0.3	93	0.4	0	0.0	0.00
HIV/AIDS	3	0.0	24	0.0	3	0.0	7	0.0	0	0.0	0.01
Liver failure	34	0.4	218	0.3	33	0.4	105	0.4	1	0.3	0.00
Migraine	836	9.6	3,293	4.4	774	9.3	1,820	7.0	62	16.3	0.08
Polycystic ovary syndrome	128	1.5	1,040	1.4	123	1.5	370	1.4	5	1.3	0.00
Renal failure	8	0.1	56	0.1	7	0.1	36	0.1	1	0.3	0.02
Thyroid disorder	256	2.9	1,666	2.2	248	3.0	764	2.9	8	2.1	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2d. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Re-starters

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=8,720)		Comparator (N=74,932)		SEASONIQUE (N=8,340)		Comparator (N=25,961)		SEASONIQUE (N=380)		
	N	%	N	%	N	%	N	%	N	%	
Prior Prescription Drug Use											
Prior Contraceptive Use											
Use of other forms of contraception[7]	111	1.3	1,601	2.1	110	1.3	399	1.5	1	0.3	0.02
Prior days on CHCs (median, IQR)	273.0	182.0-273.0	238.0	140.0-280.0	266.0	182.0-273.0	266.0	196.0-301.0	273.0	182.0-273.0	0.23
Number of prior CHCs (median, IQR)	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0	0.02
Other Drug Use											
Anticoagulants or alteplase	34	0.4	170	0.2	33	0.4	89	0.3	1	0.3	0.01
ACEI or ARB	258	3.0	1,788	2.4	244	2.9	874	3.4	14	3.7	0.03
Benzodiazepines	1,215	13.9	6,808	9.1	1,166	14.0	3,399	13.1	49	12.9	0.03
Beta-blockers	354	4.1	1,814	2.4	332	4.0	965	3.7	22	5.8	0.01
Calcium channel blockers	52	0.6	260	0.3	51	0.6	153	0.6	1	0.3	0.00
COX-2 inhibitors	90	1.0	369	0.5	83	1.0	217	0.8	7	1.8	0.02
Diabetes medications	198	2.3	1,642	2.2	192	2.3	742	2.9	6	1.6	0.04
NSAIDs other than COX-2 inhibitors	1,526	17.5	11,216	15.0	1,454	17.4	4,386	16.9	72	18.9	0.01
Spironolactone	132	1.5	974	1.3	128	1.5	454	1.7	4	1.1	0.02
SSRI/TCA	1,961	22.5	12,939	17.3	1,869	22.4	6,133	23.6	92	24.2	0.03
Statin/fibrate	235	2.7	1,460	1.9	215	2.6	794	3.1	20	5.3	0.03

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

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[5]Including peripheral vascular disease and varicose veins of lower extremity.

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[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2d. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Re-starters

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=8,720)		Comparator (N=74,932)		SEASONIQUE (N=8,340)		Comparator (N=25,961)		SEASONIQUE (N=380)		
	N	%	N	%	N	%	N	%	N	%	
Healthcare Utilization											
Outpatients visits (median, IQR)	5.0	3.0-8.0	4.0	2.0-6.0	5.0	3.0-8.0	4.0	2.0-8.0	5.0	3.0-9.0	0.07
Number of emergency room visits (median, IQR)	0.0	0.0-1.0	0.0	0.0-0.0	0.0	0.0-1.0	0.0	0.0-1.0	0.0	0.0-0.0	0.04
Number of hospitalizations (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

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[3]Including acute myocardial infarction and ischemic stroke.

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[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2e. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Switchers

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=10,726)		Comparator (N=51,130)		SEASONIQUE (N=10,152)		Comparator (N=29,717)		SEASONIQUE (N=574)		
	N	%	N	%	N	%	N	%	N	%	
Demographic											
Age (Years) [Median, IQR]	28.0	21.0-37.0	27.0	21.0-35.0	28.0	21.0-37.0	27.0	21.0-36.0	33.0	24.0-41.0	0.03
Age (Years) [Mean, SD]	29.6	9.8	28.8	9.1	29.4	9.8	29.1	9.3	32.9	9.9	0.03
Age Groups (Years)											
12 to < 15	67	0.6	270	0.5	65	0.6	146	0.5	2	0.3	0.02
≥ 15 to ≤ 35	7,454	69.5	38,837	76.0	7,139	70.3	21,972	73.9	315	54.9	0.08
> 35 to ≤ 50	3,070	28.6	11,426	22.3	2,819	27.8	7,282	24.5	251	43.7	0.07
> 50	135	1.3	597	1.2	129	1.3	317	1.1	6	1.0	0.02
Geographic region											
Northeast	1,344	12.5	6,007	11.7	1,288	12.7	3,543	11.9	56	9.8	0.02
South/Southeast	5,197	48.5	20,410	39.9	4,815	47.4	13,870	46.7	382	66.6	0.02
Midwest	2,427	22.6	15,187	29.7	2,344	23.1	7,443	25.0	83	14.5	0.05
West	1,745	16.3	9,467	18.5	1,695	16.7	4,829	16.2	50	8.7	0.01
Other	13	0.1	59	0.1	10	0.1	32	0.1	3	0.5	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

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[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2e. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Switchers

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=10,726)		Comparator (N=51,130)		SEASONIQUE (N=10,152)		Comparator (N=29,717)		SEASONIQUE (N=574)		
	N	%	N	%	N	%	N	%	N	%	
Calendar Month of Initiation											
January	907	8.5	4,643	9.1	878	8.6	2,599	8.7	29	5.1	0.00
February	850	7.9	4,343	8.5	809	8.0	2,463	8.3	41	7.1	0.01
March	877	8.2	4,747	9.3	830	8.2	2,667	9.0	47	8.2	0.03
April	863	8.0	4,338	8.5	829	8.2	2,481	8.3	34	5.9	0.01
May	908	8.5	4,195	8.2	860	8.5	2,449	8.2	48	8.4	0.01
June	960	9.0	4,289	8.4	911	9.0	2,632	8.9	49	8.5	0.00
July	880	8.2	4,184	8.2	830	8.2	2,355	7.9	50	8.7	0.01
August	980	9.1	4,801	9.4	933	9.2	2,744	9.2	47	8.2	0.00
September	879	8.2	4,278	8.4	831	8.2	2,424	8.2	48	8.4	0.00
October	901	8.4	4,160	8.1	851	8.4	2,503	8.4	50	8.7	0.00
November	858	8.0	3,602	7.0	799	7.9	2,160	7.3	59	10.3	0.02
December	863	8.0	3,550	6.9	791	7.8	2,240	7.5	72	12.5	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

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[3]Including acute myocardial infarction and ischemic stroke.

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[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2e. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Switchers

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=10,726)		Comparator (N=51,130)		SEASONIQUE (N=10,152)		Comparator (N=29,717)		SEASONIQUE (N=574)		
	N	%	N	%	N	%	N	%	N	%	
Clinical Conditions											
VTE and Cardiovascular Risk Factors											
Cardiac dysrhythmias	175	1.6	593	1.2	163	1.6	432	1.5	12	2.1	0.01
Cerebral vascular or coronary artery disease	20	0.2	66	0.1	19	0.2	45	0.2	1	0.2	0.01
Coagulation defects	54	0.5	156	0.3	52	0.5	101	0.3	2	0.3	0.03
Chronic obstructive pulmonary disease	29	0.3	109	0.2	26	0.3	69	0.2	3	0.5	0.00
Diabetes mellitus Type 1 or 2	154	1.4	668	1.3	143	1.4	386	1.3	11	1.9	0.01
Hyperlipidemia	600	5.6	2,294	4.5	543	5.3	1,463	4.9	57	9.9	0.02
Hypertension	504	4.7	1,995	3.9	454	4.5	1,258	4.2	50	8.7	0.01
Overweight and obesity	513	4.8	1,863	3.6	489	4.8	1,228	4.1	24	4.2	0.03
Pregnancy up to 3 months before treatment initiation	217	2.0	1,939	3.8	212	2.1	843	2.8	5	0.9	0.05
Prior arterial thromboembolism[3]	9	0.1	24	0.0	8	0.1	17	0.1	1	0.2	0.01
Prior thromboembolic event[4]	9	0.1	32	0.1	9	0.1	16	0.1	0	0.0	0.01
Tobacco use	759	7.1	2,338	4.6	719	7.1	1,654	5.6	40	7.0	0.06
Unstable angina	1	0.0	9	0.0	1	0.0	3	0.0	0	0.0	0.00
Vascular disease[5]	55	0.5	200	0.4	51	0.5	125	0.4	4	0.7	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[3]Including acute myocardial infarction and ischemic stroke.

[4]Including pulmonary embolism and deep venous thromboembolism.

[5]Including peripheral vascular disease and varicose veins of lower extremity.

[6]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2e. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Switchers

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=10,726)		Comparator (N=51,130)		SEASONIQUE (N=10,152)		Comparator (N=29,717)		SEASONIQUE (N=574)		
	N	%	N	%	N	%	N	%	N	%	
Other Risk Factors											
Combined Charlson-Elixhauser comorbidity score (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.08
Anovulation	5	0.0	40	0.1	4	0.0	17	0.1	1	0.2	0.01
Asthma	831	7.7	3,192	6.2	791	7.8	1,998	6.7	40	7.0	0.04
Dysmenorrhea	1,246	11.6	4,305	8.4	1,193	11.8	3,115	10.5	53	9.2	0.04
Epilepsy	91	0.8	161	0.3	81	0.8	130	0.4	10	1.7	0.05
Gynaecological disorders[6]	2,838	26.5	13,882	27.2	2,694	26.5	7,991	26.9	144	25.1	0.01
Hepatitis C	4	0.0	14	0.0	4	0.0	6	0.0	0	0.0	0.01
History of abortion	21	0.2	278	0.5	21	0.2	119	0.4	0	0.0	0.04
HIV/AIDS	1	0.0	9	0.0	1	0.0	5	0.0	0	0.0	0.01
Liver failure	41	0.4	128	0.3	39	0.4	79	0.3	2	0.3	0.02
Migraine	1,216	11.3	3,253	6.4	1,103	10.9	2,486	8.4	113	19.7	0.08
Polycystic ovary syndrome	196	1.8	812	1.6	191	1.9	491	1.7	5	0.9	0.02
Renal failure	8	0.1	31	0.1	8	0.1	24	0.1	0	0.0	0.00
Thyroid disorder	302	2.8	1,205	2.4	277	2.7	808	2.7	25	4.4	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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[7]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

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	SEASONIQUE (N=10,726)		Comparator (N=51,130)		SEASONIQUE (N=10,152)		Comparator (N=29,717)		SEASONIQUE (N=574)		
	N	%	N	%	N	%	N	%	N	%	
Prior Prescription Drug Use											
Prior Contraceptive Use											
Use of other forms of contraception[7]	175	1.6	1,512	3.0	173	1.7	624	2.1	2	0.3	0.03
Prior days on CHCs (median, IQR)	300.0	218.0-354.0	291.0	152.0-347.0	301.0	213.0-355.0	307.0	197.0-352.0	273.0	267.0-351.0	0.02
Number of prior CHCs (median, IQR)	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0	0.10
Other Drug Use											
Anticoagulants or alteplase	31	0.3	90	0.2	27	0.3	62	0.2	4	0.7	0.01
ACEI or ARB	258	2.4	905	1.8	236	2.3	579	1.9	22	3.8	0.03
Benzodiazepines	1,473	13.7	4,929	9.6	1,363	13.4	3,433	11.6	110	19.2	0.06
Beta-blockers	395	3.7	1,232	2.4	366	3.6	881	3.0	29	5.1	0.04
Calcium channel blockers	65	0.6	150	0.3	55	0.5	109	0.4	10	1.7	0.03
COX-2 inhibitors	108	1.0	293	0.6	98	1.0	213	0.7	10	1.7	0.03
Diabetes medications	246	2.3	1,039	2.0	233	2.3	623	2.1	13	2.3	0.01
NSAIDs other than COX-2 inhibitors	2,156	20.1	8,077	15.8	2,006	19.8	5,379	18.1	150	26.1	0.04
Spironolactone	211	2.0	784	1.5	201	2.0	503	1.7	10	1.7	0.02
SSRI/TCA	2,619	24.4	8,695	17.0	2,439	24.0	5,800	19.5	180	31.4	0.11
Statin/fibrate	265	2.5	809	1.6	237	2.3	531	1.8	28	4.9	0.04

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2e. Baseline Characteristics of SEASONIQUE and Comparator Cohorts, Switchers

Description	All Episodes				Matched Episodes[1]				Unmatched Episodes		Standardized Difference for Matched Episodes[2]
	SEASONIQUE (N=10,726)		Comparator (N=51,130)		SEASONIQUE (N=10,152)		Comparator (N=29,717)		SEASONIQUE (N=574)		
	N	%	N	%	N	%	N	%	N	%	
Healthcare Utilization											
Outpatients visits (median, IQR)	5.0	3.0-9.0	5.0	3.0-7.0	5.0	3.0-9.0	5.0	3.0-8.0	6.0	4.0-10.0	0.11
Number of emergency room visits (median, IQR)	0.0	0.0-1.0	0.0	0.0-0.0	0.0	0.0-1.0	0.0	0.0-1.0	0.0	0.0-1.0	0.01
Number of hospitalizations (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0	0.03

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]Includes all matched episodes within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks, pooled across calendar time blocks.

[2]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

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Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2f.1 Baseline Characteristics of Women Who Discontinued SEASONIQUE or Comparator for the Fertility Analysis, Naïve and New Users

Description	Naïve and New Users					Naïve Users					New Users				
	SEASONIQUE (N=11,223)		Comparator (N=19,479)		Standardized Difference[1]	SEASONIQUE (N=7,227)		Comparator (N=13,215)		Standardized Difference[1]	SEASONIQUE (N=3,996)		Comparator (N=6,264)		Standardized Difference[1]
	N	%	N	%		N	%	N	%		N	%	N	%	
Demographic															
Age (Years) [Median, IQR]	28.0	21.0-36.0	27.0	20.0-35.0	0.10	29.0	21.0-36.0	27.0	20.0-35.0	0.15	27.0	21.0-35.0	27	21.0-35.0	0.01
Age (Years) [Mean, SD]	28.7	8.5	27.8	8.5	0.10	28.8	8.7	27.5	8.8	0.15	28.5	8.2	28	8.0	0.01
Age Groups (Years)															
12 to < 15	108	1.0	242	1.2	0.03	98	1.4	227	1.7	0.03	10	0.3	15	0.2	0.00
≥ 15 to ≤ 35	8,183	72.9	14,792	75.9	0.07	5,167	71.5	9,976	75.5	0.09	3,016	75.5	4,816	76.9	0.03
> 35 to ≤ 50	2,932	26.1	4,445	22.8	0.08	1,962	27.1	3,012	22.8	0.10	970	24.3	1,433	22.9	0.03
> 50	0	0.0	0	0.0	NA	0	0.0	0	0.0	NA	0	0.0	0	0.0	NA
Geographic Region															
Northeast	1,154	10.3	2,125	10.9	0.02	692	9.6	1,401	10.6	0.03	462	11.6	724	11.6	0.00
South/Southeast	5,827	51.9	9,182	47.1	0.10	3,877	53.6	6,202	46.9	0.13	1,950	48.8	2,980	47.6	0.02
Midwest	2,439	21.7	4,536	23.3	0.04	1,499	20.7	3,075	23.3	0.06	940	23.5	1,461	23.3	0.00
West	1,792	16.0	3,611	18.5	0.07	1,151	15.9	2,524	19.1	0.08	641	16.0	1,087	17.4	0.04
Other	11	0.1	25	0.1	0.01	8	0.1	13	0.1	0.00	3	0.1	12	0.2	0.03

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2f.1 Baseline Characteristics of Women Who Discontinued SEASONIQUE or Comparator for the Fertility Analysis, Naïve and New Users

Description	Naïve and New Users					Naïve Users					New Users				
	SEASONIQUE (N=11,223)		Comparator (N=19,479)		Standardized Difference[1]	SEASONIQUE (N=7,227)		Comparator (N=13,215)		Standardized Difference[1]	SEASONIQUE (N=3,996)		Comparator (N=6,264)		Standardized Difference[1]
	N	%	N	%		N	%	N	%		N	%	N	%	
Calendar Month of Initiation															
January	1,069	9.5	1,865	9.6	0.00	665	9.2	1,273	9.6	0.01	404	10.1	592	9.5	0.02
February	912	8.1	1,573	8.1	0.00	568	7.9	1,093	8.3	0.02	344	8.6	480	7.7	0.03
March	927	8.3	1,651	8.5	0.01	581	8.0	1,133	8.6	0.02	346	8.7	518	8.3	0.01
April	876	7.8	1,523	7.8	0.00	582	8.1	1,046	7.9	0.01	294	7.4	477	7.6	0.01
May	937	8.3	1,631	8.4	0.00	606	8.4	1,091	8.3	0.00	331	8.3	540	8.6	0.01
June	938	8.4	1,702	8.7	0.01	604	8.4	1,160	8.8	0.02	334	8.4	542	8.7	0.01
July	922	8.2	1,671	8.6	0.01	592	8.2	1,115	8.4	0.01	330	8.3	556	8.9	0.02
August	1,063	9.5	1,819	9.3	0.00	663	9.2	1,220	9.2	0.00	400	10.0	599	9.6	0.02
September	900	8.0	1,526	7.8	0.01	596	8.2	1,020	7.7	0.02	304	7.6	506	8.1	0.02
October	939	8.4	1,574	8.1	0.01	634	8.8	1,094	8.3	0.02	305	7.6	480	7.7	0.00
November	851	7.6	1,467	7.5	0.00	554	7.7	1,015	7.7	0.00	297	7.4	452	7.2	0.01
December	889	7.9	1,477	7.6	0.01	582	8.1	955	7.2	0.03	307	7.7	522	8.3	0.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Description	Naïve and New Users					Naïve Users					New Users				
	SEASONIQUE (N=11,223)		Comparator (N=19,479)		Standardized Difference[1]	SEASONIQUE (N=7,227)		Comparator (N=13,215)		Standardized Difference[1]	SEASONIQUE (N=3,996)		Comparator (N=6,264)		Standardized Difference[1]
	N	%	N	%		N	%	N	%		N	%	N	%	
Clinical Conditions															
VTE and Cardiovascular Risk Factors															
Cardiac dysrhythmias	134	1.2	224	1.1	0.00	94	1.3	157	1.2	0.01	40	1.0	67	1.1	0.01
Cerebrovascular or coronary artery disease	17	0.2	21	0.1	0.01	11	0.2	16	0.1	0.01	6	0.2	5	0.1	0.02
Coagulation defects	46	0.4	72	0.4	0.01	35	0.5	52	0.4	0.01	11	0.3	20	0.3	0.01
Chronic obstructive pulmonary disease	28	0.2	48	0.2	0.00	20	0.3	35	0.3	0.00	8	0.2	13	0.2	0.00
Diabetes mellitus Type 1 or 2	167	1.5	280	1.4	0.00	110	1.5	172	1.3	0.02	57	1.4	108	1.7	0.02
Hyperlipidemia	480	4.3	734	3.8	0.03	299	4.1	472	3.6	0.03	181	4.5	262	4.2	0.02
Hypertension	479	4.3	715	3.7	0.03	325	4.5	465	3.5	0.05	154	3.9	250	4.0	0.01
Overweight and obesity	509	4.5	857	4.4	0.01	358	5.0	580	4.4	0.03	151	3.8	277	4.4	0.03
Pregnancy up to 3 months before treatment initiation	604	5.4	1,188	6.1	0.03	535	7.4	1,056	8.0	0.02	69	1.7	132	2.1	0.03
Prior arterial thromboembolism[2]	9	0.1	7	0.0	0.02	7	0.1	3	0.0	0.03	2	0.1	4	0.1	0.01
Prior thromboembolic event[3]	10	0.1	13	0.1	0.01	5	0.1	11	0.1	0.01	5	0.1	2	0.0	0.03
Tobacco use	593	5.3	993	5.1	0.01	386	5.3	615	4.7	0.03	207	5.2	378	6.0	0.04
Unstable angina	1	0.0	2	0.0	0.00	1	0.0	2	0.0	0.00	0	0.0	0	0.0	NA
Vascular disease[4]	44	0.4	66	0.3	0.01	29	0.4	44	0.3	0.01	15	0.4	22	0.4	0.00

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Table 2f.1 Baseline Characteristics of Women Who Discontinued SEASONIQUE or Comparator for the Fertility Analysis, Naïve and New Users

Description	Naïve and New Users					Naïve Users					New Users				
	SEASONIQUE (N=11,223)		Comparator (N=19,479)		Standardized Difference[1]	SEASONIQUE (N=7,227)		Comparator (N=13,215)		Standardized Difference[1]	SEASONIQUE (N=3,996)		Comparator (N=6,264)		Standardized Difference[1]
	N	%	N	%		N	%	N	%		N	%	N	%	
Other Risk Factors															
Combined Charlson-Elixhauser comorbidity score (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.01	0.0	0.0-0.0	0.0	0.0-0.0	0.02	0.0	0.0-0.0	0	0.0-0.0	0.01
Anovulation	9	0.1	31	0.2	0.02	4	0.1	20	0.2	0.03	5	0.1	11	0.2	0.01
Asthma	737	6.6	1,221	6.3	0.01	442	6.1	786	5.9	0.01	295	7.4	435	6.9	0.02
Dysmenorrhea	1,172	10.4	1,996	10.2	0.01	848	11.7	1,555	11.8	0.00	324	8.1	441	7.0	0.04
Epilepsy	49	0.4	91	0.5	0.00	41	0.6	60	0.5	0.02	8	0.2	31	0.5	0.05
Gynaecological disorders[5]	3,260	29.0	5,625	28.9	0.00	2,205	30.5	3,966	30.0	0.01	1,055	26.4	1,659	26.5	0.00
Hepatitis C	7	0.1	10	0.1	0.00	2	0.0	5	0.0	0.01	5	0.1	5	0.1	0.01
History of abortion	65	0.6	133	0.7	0.01	48	0.7	83	0.6	0.00	17	0.4	50	0.8	0.05
HIV/AIDS	4	0.0	8	0.0	0.00	3	0.0	6	0.0	0.00	1	0.0	2	0.0	0.00
Liver failure	31	0.3	60	0.3	0.01	21	0.3	42	0.3	0.00	10	0.3	18	0.3	0.01
Migraine	776	6.9	1,140	5.9	0.04	502	6.9	720	5.4	0.06	274	6.9	420	6.7	0.01
Polycystic ovary syndrome	180	1.6	340	1.7	0.01	123	1.7	212	1.6	0.01	57	1.4	128	2.0	0.05
Renal failure	17	0.2	21	0.1	0.01	12	0.2	11	0.1	0.02	5	0.1	10	0.2	0.01
Thyroid disorder	263	2.3	434	2.2	0.01	170	2.4	300	2.3	0.01	93	2.3	134	2.1	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[2]Including acute myocardial infarction and ischemic stroke.

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[5]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[6]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2f.1 Baseline Characteristics of Women Who Discontinued SEASONIQUE or Comparator for the Fertility Analysis, Naïve and New Users

Description	Naïve and New Users					Naïve Users					New Users				
	SEASONIQUE (N=11,223)		Comparator (N=19,479)		Standardized Difference[1]	SEASONIQUE (N=7,227)		Comparator (N=13,215)		Standardized Difference[1]	SEASONIQUE (N=3,996)		Comparator (N=6,264)		Standardized Difference[1]
	N	%	N	%		N	%	N	%		N	%	N	%	
Prior Prescription Drug Use															
Prior Contraceptive Use															
Use of other forms of contraception[6]	510	4.5	926	4.8	0.01	448	6.2	809	6.1	0.00	62	1.6	117	1.9	0.02
Prior days on CHCs (median, IQR)	0.0	0.0-91.0	0.0	0.0-84.0	0.05	0.0	0.0-0.0	0.0	0.0-0.0	NA	140.0	182.0	140	196.0	0.05
Number of prior CHCs (median, IQR)	0.0	0.0-1.0	0.0	0.0-1.0	0.07	0.0	0.0-0.0	0.0	0.0-0.0	NA	1.0	1.0-1.0	1	1.0-1.0	0.01
Other Drug Use															
Anticoagulants or alteplase	40	0.4	33	0.2	0.04	29	0.4	22	0.2	0.04	11	0.3	11	0.2	0.02
ACEI or ARB	188	1.7	278	1.4	0.02	116	1.6	152	1.2	0.04	72	1.8	126	2.0	0.02
Benzodiazepines	1,205	10.7	1,889	9.7	0.03	733	10.1	1,161	8.8	0.05	472	11.8	728	11.6	0.01
Beta-blockers	276	2.5	421	2.2	0.02	172	2.4	265	2.0	0.03	104	2.6	156	2.5	0.01
Calcium channel blockers	41	0.4	58	0.3	0.01	26	0.4	39	0.3	0.01	15	0.4	19	0.3	0.01
COX-2 inhibitors	89	0.8	111	0.6	0.03	58	0.8	74	0.6	0.03	31	0.8	37	0.6	0.02
Diabetes medications	264	2.4	456	2.3	0.00	174	2.4	288	2.2	0.02	90	2.3	168	2.7	0.03
NSAIDs other than COX-2 inhibitors	2,063	18.4	3,522	18.1	0.01	1,386	19.2	2,441	18.5	0.02	677	16.9	1,081	17.3	0.01
Spironolactone	127	1.1	224	1.1	0.00	76	1.1	128	1.0	0.01	51	1.3	96	1.5	0.02
SSRI/TCA	2,115	18.8	3,371	17.3	0.04	1,333	18.4	2,053	15.5	0.08	782	19.6	1,318	21.0	0.04
Statin/fibrate	150	1.3	227	1.2	0.02	90	1.2	132	1.0	0.02	60	1.5	95	1.5	0.00
Healthcare Utilization															
Outpatients visits (median, IQR)	4.0	2.0-8.0	4.0	2.0-7.0	0.05	4.0	2.0-7.0	4.0	2.0-7.0	0.06	4.0	2.0-8.0	4	2.0-8.0	0.02
Number of emergency room visits (median, IQR)	0.0	0.0-1.0	0.0	0.0-1.0	0.02	0.0	0.0-1.0	0.0	0.0-1.0	0.04	0.0	0.0-1.0	0	0.0-1.0	0.02
Number of hospitalizations (median, IQR)	0.0	0.0-0.0	0.0	0.0-0.0	0.01	0.0	0.0-0.0	0.0	0.0-0.0	0.00	0.0	0.0-0.0	0	0.0-0.0	0.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

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Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2f.2 Baseline Characteristics of Women who Discontinued SEASONIQUE or Comparator for the Fertility Analysis, Re-starters and Switchers

Description	Re-starters					Switchers				
	SEASONIQUE (N=3,496)		Comparator (N=6,363)		Standardized Difference[1]	SEASONIQUE (N=2,719)		Comparator (N=4,731)		Standardized Difference[1]
	N	%	N	%		N	%	N	%	
Demographic										
Age (Years) [Median, IQR]	29	22.0-37.0	28	22.0-36.0	0.03	27	21.0-36.0	27	21.0-34.0	0.08
Age (Years) [Mean, SD]	29	8.4	29	8.2	0.03	28	8.5	28	7.9	0.08
Age Groups (Years)										
12 to < 15	9	0.3	8	0.1	0.03	15	0.6	20	0.4	0.02
≥ 15 to ≤ 35	2,519	72.1	4,704	73.9	0.04	2,013	74.0	3,788	80.1	0.14
> 35 to ≤ 50	968	27.7	1,651	25.9	0.04	691	25.4	923	19.5	0.14
> 50	0	0.0	0	0.0	NA	0	0.0	0	0.0	NA
Geographic region										
Northeast	388	11.1	686	10.8	0.01	328	12.1	537	11.4	0.02
South/Southeast	1,796	51.4	3,361	52.8	0.03	1,339	49.2	2,287	48.3	0.02
Midwest	756	21.6	1,329	20.9	0.02	595	21.9	1,170	24.7	0.07
West	551	15.8	979	15.4	0.01	454	16.7	730	15.4	0.03
Other	5	0.1	8	0.1	0.00	3	0.1	7	0.1	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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[5]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[6]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

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Description	Re-starters					Switchers				
	SEASONIQUE (N=3,496)		Comparator (N=6,363)		Standardized Difference[1]	SEASONIQUE (N=2,719)		Comparator (N=4,731)		Standardized Difference[1]
	N	%	N	%		N	%	N	%	
Calendar Month of Initiation										
January	384	11.0	581	9.1	0.06	223	8.2	407	8.6	0.01
February	294	8.4	505	7.9	0.02	223	8.2	396	8.4	0.01
March	307	8.8	525	8.3	0.02	222	8.2	429	9.1	0.03
April	266	7.6	450	7.1	0.02	223	8.2	370	7.8	0.01
May	286	8.2	500	7.9	0.01	223	8.2	396	8.4	0.01
June	279	8.0	548	8.6	0.02	218	8.0	385	8.1	0.00
July	303	8.7	538	8.5	0.01	233	8.6	374	7.9	0.02
August	276	7.9	564	8.9	0.03	253	9.3	462	9.8	0.02
September	253	7.2	525	8.3	0.04	237	8.7	384	8.1	0.02
October	268	7.7	554	8.7	0.04	242	8.9	414	8.8	0.01
November	256	7.3	508	8.0	0.02	214	7.9	363	7.7	0.01
December	324	9.3	565	8.9	0.01	208	7.6	351	7.4	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2f.2 Baseline Characteristics of Women who Discontinued SEASONIQUE or Comparator for the Fertility Analysis, Re-starters and Switchers

Description	Re-starters					Switchers				
	SEASONIQUE (N=3,496)		Comparator (N=6,363)		Standardized Difference[1]	SEASONIQUE (N=2,719)		Comparator (N=4,731)		Standardized Difference[1]
	N	%	N	%		N	%	N	%	
Clinical Conditions										
VTE and Cardiovascular Risk Factors										
Cardiac dysrhythmias	49	1.4	66	1.0	0.03	28	1.0	71	1.5	0.04
Cerebrovascular or coronary artery disease	2	0.1	12	0.2	0.04	4	0.1	10	0.2	0.02
Coagulation defects	13	0.4	29	0.5	0.01	16	0.6	15	0.3	0.04
Chronic obstructive pulmonary disease	14	0.4	18	0.3	0.02	7	0.3	12	0.3	0.00
Diabetes mellitus Type 1 or 2	54	1.5	105	1.7	0.01	38	1.4	60	1.3	0.01
Hyperlipidemia	168	4.8	294	4.6	0.01	123	4.5	210	4.4	0.00
Hypertension	167	4.8	259	4.1	0.03	96	3.5	185	3.9	0.02
Overweight and obesity	159	4.5	279	4.4	0.01	117	4.3	199	4.2	0.00
Pregnancy up to 3 months before treatment initiation	60	1.7	144	2.3	0.04	84	3.1	178	3.8	0.04
Prior arterial thromboembolism[2]	0	0.0	6	0.1	0.04	2	0.1	2	0.0	0.01
Prior thromboembolic event[3]	4	0.1	6	0.1	0.01	2	0.1	5	0.1	0.01
Tobacco use	188	5.4	407	6.4	0.04	174	6.4	237	5.0	0.06
Unstable angina	0	0.0	0	0.0	NA	0	0.0	0	0.0	NA
Vascular disease[4]	12	0.3	26	0.4	0.01	11	0.4	11	0.2	0.03

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Table 2f.2 Baseline Characteristics of Women who Discontinued SEASONIQUE or Comparator for the Fertility Analysis, Re-starters and Switchers

Description	Re-starters					Switchers				
	SEASONIQUE (N=3,496)		Comparator (N=6,363)		Standardized Difference[1]	SEASONIQUE (N=2,719)		Comparator (N=4,731)		Standardized Difference[1]
	N	%	N	%		N	%	N	%	
Other Risk Factors										
Combined Charlson-Elixhauser comorbidity score (median, IQR)	0	0.0-0.0	0	0.0-0.0	0.02	0	0.0-0.0	0	0.0-0.0	0.06
Anovulation	4	0.1	2	0.0	0.03	1	0.0	4	0.1	0.02
Asthma	234	6.7	477	7.5	0.03	210	7.7	315	6.7	0.04
Dysmenorrhea	285	8.2	411	6.5	0.07	326	12.0	523	11.1	0.03
Epilepsy	16	0.5	41	0.6	0.03	18	0.7	29	0.6	0.01
Gynaecological disorders[5]	760	21.7	1,351	21.2	0.01	846	31.1	1,443	30.5	0.01
Hepatitis C	1	0.0	1	0.0	0.01	0	0.0	1	0.0	0.02
History of abortion	13	0.4	33	0.5	0.02	8	0.3	27	0.6	0.04
HIV/AIDS	1	0.0	1	0.0	0.01	0	0.0	0	0.0	NA
Liver failure	13	0.4	19	0.3	0.01	4	0.1	16	0.3	0.04
Migraine	251	7.2	437	6.9	0.01	263	9.7	362	7.7	0.07
Polycystic ovary syndrome	59	1.7	90	1.4	0.02	51	1.9	94	2.0	0.01
Renal failure	2	0.1	5	0.1	0.01	3	0.1	5	0.1	0.00
Thyroid disorder	86	2.5	173	2.7	0.02	72	2.6	92	1.9	0.05

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 2f.2 Baseline Characteristics of Women who Discontinued SEASONIQUE or Comparator for the Fertility Analysis, Re-starters and Switchers

Description	Re-starters					Switchers				
	SEASONIQUE (N=3,496)		Comparator (N=6,363)		Standardized Difference[1]	SEASONIQUE (N=2,719)		Comparator (N=4,731)		Standardized Difference[1]
	N	%	N	%		N	%	N	%	
Prior Prescription Drug Use										
Prior Contraceptive Use										
Use of other forms of contraception[6]	43	1.2	95	1.5	0.02	44	1.6	117	2.5	0.06
Prior days on CHCs (median, IQR)	203	182.0-273.0	252	182.0-280.0	0.24	277	168.0-342.0	280	168.0-336.0	0.01
Number of prior CHCs (median, IQR)	1	1.0-1.0	1	1.0-1.0	0.01	1	1.0-1.0	1	1.0-1.0	0.06
Other Drug Use										
Anticoagulants or alteplase	9	0.3	17	0.3	0.00	9	0.3	4	0.1	0.05
ACEI or ARB	69	2.0	141	2.2	0.02	45	1.7	63	1.3	0.03
Benzodiazepines	445	12.7	799	12.6	0.01	331	12.2	551	11.6	0.02
Beta-blockers	102	2.9	185	2.9	0.00	77	2.8	123	2.6	0.01
Calcium channel blockers	15	0.4	41	0.6	0.03	9	0.3	15	0.3	0.00
COX-2 inhibitors	26	0.7	52	0.8	0.01	23	0.8	39	0.8	0.00
Diabetes medications	100	2.9	171	2.7	0.01	62	2.3	95	2.0	0.02
NSAIDs other than COX-2 inhibitors	591	16.9	1,088	17.1	0.01	540	19.9	860	18.2	0.04
Spironolactone	55	1.6	94	1.5	0.01	50	1.8	59	1.2	0.05
SSRI/TCA	765	21.9	1,459	22.9	0.03	619	22.8	913	19.3	0.09
Statin/fibrate	57	1.6	123	1.9	0.02	55	2.0	64	1.4	0.05

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

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	N	%	N	%		N	%	N	%	
Healthcare Utilization										
Outpatients visits (median, IQR)	5	2.0-8.0	4	2.0-8.0	0.01	5	3.0-9.0	5	3.0-8.0	0.10
Number of emergency room visits (median, IQR)	0	0.0-1.0	0	0.0-1.0	0.02	0	0.0-1.0	0	0.0-1.0	0.03
Number of hospitalizations (median, IQR)	0	0.0-0.0	0	0.0-0.0	0.03	0	0.0-0.0	0	0.0-0.0	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immune deficiency syndrome; ARB, angiotensin receptor blocker; CHC, combined hormonal contraceptive; COX, cyclooxygenase; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NSAIDs, non-selective anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; VTE, venous thromboembolism.

[1]The standardized difference for the matched episodes, within each category of cohort entry (naïve users, new users, re-starters and switchers) within calendar time blocks pooled across calendar time blocks.

[2]Including acute myocardial infarction and ischemic stroke.

[3]Including pulmonary embolism and deep venous thromboembolism.

[4]Including peripheral vascular disease and varicose veins of lower extremity.

[5]Including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum, and uterine leiomyoma.

[6]Including intrauterine devices, patches, and depo injections.

Note: The C-statistic for the matched episodes, within each category of cohort entry, within calendar time blocks, pooled across calendar time blocks were 0.59 for naïve users, 0.66 for new users, 0.66 for re-starters, 0.64 for switchers, and 0.61 for naïve and new users combined.

Table 3a. Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	IR Difference	IR Difference 95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Current Exposure	**VTE (primary definition)**											
	SEASONIQUE	25,587	35	16,867.6	2.07	(1.45 - 2.89)	0.61	(-0.16 - 1.38)	1.40	(0.90 - 2.19)	1.41	(0.91 - 2.19)
	Comparator	76,575	68	46,462.3	1.46	(1.14 - 1.86)						
	VTE (sensitivity definition)											
	SEASONIQUE	25,591	30	16,873.3	1.78	(1.20 - 2.54)	0.70	(-0.00 - 1.40)	1.61	(0.98 - 2.63)	1.61	(0.98 - 2.63)
	Comparator	76,583	50	46,472.7	1.08	(0.80 - 1.42)						
	ATE											
	SEASONIQUE	25,592	13	16,876.6	0.77	(0.41 - 1.32)	0.17	(-0.31 - 0.64)	1.21	(0.58 - 2.53)	1.20	(0.58 - 2.49)
	Comparator	76,584	28	46,463.9	0.60	(0.40 - 0.87)						
	Breast cancer											
	SEASONIQUE	25,593	17	16,881.1	1.01	(0.59 - 1.61)	0.45	(-0.08 - 0.97)	1.57	(0.79 - 3.10)	1.51	(0.77 - 2.98)
	Comparator	76,586	26	46,485.8	0.56	(0.37 - 0.82)						
	Cervical cancer											
	SEASONIQUE	25,593	4	16,881.1	0.24	(0.06 - 0.61)	0.22	(-0.02 - 0.45)	12.01	(1.39 - 104.03)	11.33	(1.35 - 95.01)
	Comparator	76,586	1	46,485.8	0.02	(0.00 - 0.12)						
	Endometrial cancer											
	SEASONIQUE	25,593	0	16,881.1	0.00	(0.00 - 0.18)	-0.04	(-0.10 - 0.02)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	76,586	2	46,485.8	0.04	(0.01 - 0.16)						
	Ovarian cancer											
	SEASONIQUE	25,593	1	16,881.1	0.06	(0.00 - 0.33)	0.02	(-0.11 - 0.15)	1.52	(0.11 - 21.73)	1.54	(0.11 - 21.83)
	Comparator	76,586	2	46,485.8	0.04	(0.01 - 0.16)						

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3a. Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	IR Difference	IR Difference 95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Recent Exposure	**VTE (primary definition)**											
	SEASONIQUE	18,088	4	1,401.8	2.85	(0.78 - 7.31)	1.91	(-1.03 - 4.86)	2.94	(0.65 - 13.20)	2.92	(0.64 - 13.24)
	Comparator	55,019	4	4,242.1	0.94	(0.26 - 2.41)						
	VTE (sensitivity definition)											
	SEASONIQUE	18,095	4	1,402.3	2.85	(0.78 - 7.30)	2.15	(-0.76 - 5.05)	4.20	(0.89 - 19.88)	4.20	(0.87 - 20.37)
	Comparator	55,035	3	4,243.5	0.71	(0.15 - 2.07)						
	ATE											
	SEASONIQUE	18,113	0	1,403.9	0.00	(0.00 - 2.13)	0.00	(0.00 - 0.00)	NA	NA	NA	NA
	Comparator	55,058	0	4,245.4	0.00	(0.00 - 0.71)						
	Breast cancer											
	SEASONIQUE	18,123	6	1,404.7	4.27	(1.57 - 9.30)	3.33	(-0.21 - 6.87)	4.68	(1.31 - 16.80)	4.70	(1.28 - 17.25)
	Comparator	55,083	4	4,247.4	0.94	(0.26 - 2.41)						
	Cervical cancer											
	SEASONIQUE	18,123	0	1,404.7	0.00	(0.00 - 2.13)	-0.71	(-1.51 - 0.09)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	55,083	3	4,247.4	0.71	(0.15 - 2.06)						
	Endometrial cancer											
	SEASONIQUE	18,123	0	1,404.7	0.00	(0.00 - 2.13)	-0.47	(-1.12 - 0.18)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	55,083	2	4,247.4	0.47	(0.06 - 1.70)						
	Ovarian cancer											
	SEASONIQUE	18,123	0	1,404.7	0.00	(0.00 - 2.13)	-0.24	(-0.70 - 0.23)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	55,083	1	4,247.4	0.24	(0.01 - 1.31)						

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3a. Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	IR Difference	IR Difference 95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Intermediate Exposure	**VTE (primary definition)**											
	SEASONIQUE	16,162	2	1,262.7	1.58	(0.19 - 5.72)	1.04	(-1.28 - 3.36)	2.42	(0.39 - 15.17)	2.44	(0.40 - 14.85)
	Comparator	47,342	2	3,680.0	0.54	(0.07 - 1.96)						
	VTE (sensitivity definition)											
	SEASONIQUE	16,169	1	1,263.4	0.79	(0.02 - 4.41)	0.52	(-1.12 - 2.16)	2.50	(0.19 - 32.92)	2.64	(0.21 - 32.50)
	Comparator	47,359	1	3,681.4	0.27	(0.01 - 1.51)						
	ATE											
	SEASONIQUE	16,190	0	1,265.1	0.00	(0.00 - 2.37)	-0.27	(-0.80 - 0.26)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	47,382	1	3,683.3	0.27	(0.01 - 1.51)						
	Breast cancer											
	SEASONIQUE	16,200	1	1,265.9	0.79	(0.02 - 4.40)	-0.02	(-1.83 - 1.78)	0.94	(0.10 - 9.13)	0.95	(0.10 - 9.17)
	Comparator	47,406	3	3,685.3	0.81	(0.17 - 2.38)						
	Cervical cancer											
	SEASONIQUE	16,200	0	1,265.9	0.00	(0.00 - 2.37)	0.00	(0.00 - 0.00)	NA	NA	NA	NA
	Comparator	47,406	0	3,685.3	0.00	(0.00 - 0.81)						
	Endometrial cancer											
	SEASONIQUE	16,200	0	1,265.9	0.00	(0.00 - 2.37)	0.00	(0.00 - 0.00)	NA	NA	NA	NA
	Comparator	47,406	0	3,685.3	0.00	(0.00 - 0.81)						
	Ovarian cancer											
	SEASONIQUE	16,200	0	1,265.9	0.00	(0.00 - 2.37)	0.00	(0.00 - 0.00)	NA	NA	NA	NA
	Comparator	47,406	0	3,685.3	0.00	(0.00 - 0.81)						

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3a. Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	IR Difference	IR Difference 95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Remote Exposure	**VTE (primary definition)**											
	SEASONIQUE	14,242	41	26,482.2	1.55	(1.11 - 2.10)	0.60	(0.08 - 1.12)	1.66	(1.12 - 2.45)	1.67	(1.13 - 2.46)
	Comparator	42,548	74	78,232.9	0.95	(0.74 - 1.19)						
	VTE (sensitivity definition)											
	SEASONIQUE	14,250	34	26,505.0	1.28	(0.89 - 1.79)	0.54	(0.07 - 1.01)	1.80	(1.17 - 2.78)	1.81	(1.18 - 2.78)
	Comparator	42,566	58	78,286.0	0.74	(0.56 - 0.96)						
	ATE											
	SEASONIQUE	14,272	30	26,631.5	1.13	(0.76 - 1.61)	0.44	(-0.01 - 0.88)	1.56	(0.99 - 2.47)	1.58	(1.00 - 2.50)
	Comparator	42,589	54	78,401.1	0.69	(0.52 - 0.90)						
	Breast cancer											
	SEASONIQUE	14,282	33	26,690.6	1.24	(0.85 - 1.74)	0.37	(-0.10 - 0.84)	1.37	(0.91 - 2.08)	1.38	(0.91 - 2.09)
	Comparator	42,613	68	78,523.6	0.87	(0.67 - 1.10)						
	Cervical cancer											
	SEASONIQUE	14,282	2	26,690.6	0.07	(0.01 - 0.27)	0.05	(-0.06 - 0.16)	2.31	(0.27 - 19.73)	2.42	(0.29 - 20.52)
	Comparator	42,613	2	78,523.6	0.03	(0.00 - 0.09)						
	Endometrial cancer											
	SEASONIQUE	14,282	2	26,690.6	0.07	(0.01 - 0.27)	0.00	(-0.12 - 0.12)	1.12	(0.22 - 5.71)	1.18	(0.23 - 6.08)
	Comparator	42,613	6	78,523.6	0.08	(0.03 - 0.17)						
	Ovarian cancer											
	SEASONIQUE	14,282	0	26,690.6	0.00	(0.00 - 0.11)	-0.11	(-0.19 - (-0.04))	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	42,613	9	78,523.6	0.11	(0.05 - 0.22)						

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3b. Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Current Exposure	**VTE (primary definition)**									
	SEASONIQUE	15,133	25	9,231.1	2.71	(1.75 - 4.00)	1.57	(0.95 - 2.61)	1.57	(0.95 - 2.61)
	Comparator	52,642	51	32,627.7	1.56	(1.16 - 2.06)				
	VTE (sensitivity definition)									
	SEASONIQUE	15,133	21	9,231.8	2.27	(1.41 - 3.48)	1.84	(1.05 - 3.24)	1.84	(1.05 - 3.24)
	Comparator	52,642	36	32,632.8	1.10	(0.77 - 1.53)				
	ATE									
	SEASONIQUE	15,133	7	9,234.9	0.76	(0.30 - 1.56)	1.36	(0.55 - 3.38)	1.36	(0.55 - 3.38)
	Comparator	52,642	18	32,624.9	0.55	(0.33 - 0.87)				
	Breast cancer									
	SEASONIQUE	15,133	6	9,236.3	0.65	(0.24 - 1.41)	1.42	(0.53 - 3.80)	1.42	(0.53 - 3.80)
	Comparator	52,642	13	32,639.0	0.40	(0.21 - 0.68)				
	Cervical cancer									
	SEASONIQUE	15,133	2	9,236.3	0.22	(0.03 - 0.78)	NA	NA	NA	NA
	Comparator	52,642	0	32,639.0	0.00	(0.00 - 0.09)				
	Endometrial cancer									
	SEASONIQUE	15,133	0	9,236.3	0.00	(0.00 - 0.32)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	52,642	1	32,639.0	0.03	(0.00 - 0.17)				
	Ovarian cancer									
	SEASONIQUE	15,133	0	9,236.3	0.00	(0.00 - 0.32)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	52,642	2	32,639.0	0.06	(0.01 - 0.22)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3b. Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Recent Exposure	**VTE (primary definition)**									
	SEASONIQUE	10,756	1	837.8	1.19	(0.03 - 6.65)	0.99	(0.08 - 12.44)	0.99	(0.08 - 12.44)
	Comparator	37,679	3	2,914.3	1.03	(0.21 - 3.01)				
	VTE (sensitivity definition)									
	SEASONIQUE	10,759	1	838.0	1.19	(0.03 - 6.65)	1.79	(0.14 - 22.54)	1.79	(0.14 - 22.54)
	Comparator	37,689	2	2,915.1	0.69	(0.08 - 2.48)				
	ATE									
	SEASONIQUE	10,771	0	839.0	0.00	(0.00 - 3.57)	NA	NA	NA	NA
	Comparator	37,708	0	2,916.8	0.00	(0.00 - 1.03)				
	Breast cancer									
	SEASONIQUE	10,777	2	839.5	2.38	(0.29 - 8.61)	2.53	(0.44 - 14.69)	2.53	(0.44 - 14.69)
	Comparator	37,723	2	2,918.0	0.69	(0.08 - 2.48)				
	Cervical cancer									
	SEASONIQUE	10,777	0	839.5	0.00	(0.00 - 3.57)	NA	NA	NA	NA
	Comparator	37,723	0	2,918.0	0.00	(0.00 - 1.03)				
	Endometrial cancer									
	SEASONIQUE	10,777	0	839.5	0.00	(0.00 - 3.57)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	37,723	2	2,918.0	0.69	(0.08 - 2.48)				
	Ovarian cancer									
	SEASONIQUE	10,777	0	839.5	0.00	(0.00 - 3.57)	NA	NA	NA	NA
	Comparator	37,723	0	2,918.0	0.00	(0.00 - 1.03)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3b. Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Intermediate Exposure	**VTE (primary definition)**									
	SEASONIQUE	9,711	1	764.9	1.31	(0.03 - 7.28)	NA	NA	NA	NA
	Comparator	32,747	0	2,559.4	0.00	(0.00 - 1.17)				
	VTE (sensitivity definition)									
	SEASONIQUE	9,714	0	765.2	0.00	(0.00 - 3.91)	NA	NA	NA	NA
	Comparator	32,758	0	2,560.3	0.00	(0.00 - 1.17)				
	ATE									
	SEASONIQUE	9,726	0	766.2	0.00	(0.00 - 3.91)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	32,777	1	2,561.8	0.39	(0.01 - 2.17)				
	Breast cancer									
	SEASONIQUE	9,732	1	766.7	1.30	(0.03 - 7.27)	1.27	(0.11 - 14.83)	1.27	(0.11 - 14.83)
	Comparator	32,792	2	2,563.1	0.78	(0.09 - 2.82)				
	Cervical cancer									
	SEASONIQUE	9,732	0	766.7	0.00	(0.00 - 3.91)	NA	NA	NA	NA
	Comparator	32,792	0	2,563.1	0.00	(0.00 - 1.17)				
	Endometrial cancer									
	SEASONIQUE	9,732	0	766.7	0.00	(0.00 - 3.91)	NA	NA	NA	NA
	Comparator	32,792	0	2,563.1	0.00	(0.00 - 1.17)				
	Ovarian cancer									
	SEASONIQUE	9,732	0	766.7	0.00	(0.00 - 3.91)	NA	NA	NA	NA
	Comparator	32,792	0	2,563.1	0.00	(0.00 - 1.17)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3b. Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Remote Exposure	**VTE (primary definition)**									
	SEASONIQUE	8,788	31	16,751.5	1.85	(1.26 - 2.63)	1.74	(1.12 - 2.70)	1.74	(1.12 - 2.70)
	Comparator	29,747	58	56,787.3	1.02	(0.78 - 1.32)				
	VTE (sensitivity definition)									
	SEASONIQUE	8,792	25	16,768.9	1.49	(0.96 - 2.20)	1.85	(1.13 - 3.03)	1.85	(1.13 - 3.03)
	Comparator	29,758	45	56,820.9	0.79	(0.58 - 1.06)				
	ATE									
	SEASONIQUE	8,804	24	16,857.7	1.42	(0.91 - 2.12)	1.99	(1.20 - 3.30)	1.99	(1.20 - 3.30)
	Comparator	29,775	39	56,905.5	0.69	(0.49 - 0.94)				
	Breast cancer									
	SEASONIQUE	8,810	21	16,907.6	1.24	(0.77 - 1.90)	1.33	(0.80 - 2.21)	1.33	(0.80 - 2.21)
	Comparator	29,791	51	56,998.5	0.89	(0.67 - 1.18)				
	Cervical cancer									
	SEASONIQUE	8,810	0	16,907.6	0.00	(0.00 - 0.18)	NA	NA	NA	NA
	Comparator	29,791	0	56,998.5	0.00	(0.00 - 0.05)				
	Endometrial cancer									
	SEASONIQUE	8,810	2	16,907.6	0.12	(0.01 - 0.43)	1.34	(0.25 - 7.21)	1.34	(0.25 - 7.21)
	Comparator	29,791	5	56,998.5	0.09	(0.03 - 0.20)				
	Ovarian cancer									
	SEASONIQUE	8,810	0	16,907.6	0.00	(0.00 - 0.18)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	29,791	9	56,998.5	0.16	(0.07 - 0.30)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3c. Relative Hazard of VTE, ATE, and Cancer Outcomes, New Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Current Exposure	**VTE (primary definition)**									
	SEASONIQUE	10,454	10	7,636.5	1.31	(0.63 - 2.41)	1.07	(0.45 - 2.53)	1.03	(0.45 - 2.39)
	Comparator	23,933	17	13,834.6	1.23	(0.72 - 1.97)				
	VTE (sensitivity definition)									
	SEASONIQUE	10,458	9	7,641.5	1.18	(0.54 - 2.24)	1.17	(0.46 - 2.95)	1.13	(0.46 - 2.79)
	Comparator	23,941	14	13,839.9	1.01	(0.55 - 1.70)				
	ATE									
	SEASONIQUE	10,459	6	7,641.7	0.79	(0.29 - 1.71)	0.96	(0.30 - 3.10)	0.97	(0.30 - 3.06)
	Comparator	23,942	10	13,838.9	0.72	(0.35 - 1.33)				
	Breast cancer									
	SEASONIQUE	10,460	11	7,644.8	1.44	(0.72 - 2.57)	1.55	(0.62 - 3.87)	1.49	(0.59 - 3.74)
	Comparator	23,944	13	13,846.7	0.94	(0.50 - 1.61)				
	Cervical cancer									
	SEASONIQUE	10,460	2	7,644.8	0.26	(0.03 - 0.95)	4.49	(0.44 - 45.79)	4.14	(0.46 - 37.30)
	Comparator	23,944	1	13,846.7	0.07	(0.00 - 0.40)				
	Endometrial cancer									
	SEASONIQUE	10,460	0	7,644.8	0.00	(0.00 - 0.39)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	23,944	1	13,846.7	0.07	(0.00 - 0.40)				
	Ovarian cancer									
	SEASONIQUE	10,460	1	7,644.8	0.13	(0.00 - 0.73)	NA	NA	NA	NA
	Comparator	23,944	0	13,846.7	0.00	(0.00 - 0.22)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3c. Relative Hazard of VTE, ATE, and Cancer Outcomes, New Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Recent Exposure	**VTE (primary definition)**									
	SEASONIQUE	7,332	3	564.0	5.32	(1.10 - 15.54)	9.03	(0.84 - 97.70)	8.84	(0.76 - 102.21)
	Comparator	17,340	1	1,327.9	0.75	(0.02 - 4.20)				
	VTE (sensitivity definition)									
	SEASONIQUE	7,336	3	564.3	5.32	(1.10 - 15.54)	9.03	(0.84 - 97.70)	8.84	(0.76 - 102.24)
	Comparator	17,346	1	1,328.3	0.75	(0.02 - 4.19)				
	ATE									
	SEASONIQUE	7,342	0	564.9	0.00	(0.00 - 5.30)	NA	NA	NA	NA
	Comparator	17,350	0	1,328.7	0.00	(0.00 - 2.25)				
	Breast cancer									
	SEASONIQUE	7,346	4	565.2	7.08	(1.93 - 18.12)	7.30	(1.26 - 42.35)	7.32	(1.10 - 48.77)
	Comparator	17,360	2	1,329.4	1.50	(0.18 - 5.43)				
	Cervical cancer									
	SEASONIQUE	7,346	0	565.2	0.00	(0.00 - 5.30)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	17,360	3	1,329.4	2.26	(0.47 - 6.59)				
	Endometrial cancer									
	SEASONIQUE	7,346	0	565.2	0.00	(0.00 - 5.30)	NA	NA	NA	NA
	Comparator	17,360	0	1,329.4	0.00	(0.00 - 2.25)				
	Ovarian cancer									
	SEASONIQUE	7,346	0	565.2	0.00	(0.00 - 5.30)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	17,360	1	1,329.4	0.75	(0.02 - 4.19)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3c. Relative Hazard of VTE, ATE, and Cancer Outcomes, New Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Intermediate Exposure	**VTE (primary definition)**									
	SEASONIQUE	6,451	1	497.8	2.01	(0.05 - 11.19)	1.30	(0.14 - 12.24)	1.26	(0.13 - 12.08)
	Comparator	14,595	2	1,120.5	1.78	(0.22 - 6.45)				
	VTE (sensitivity definition)									
	SEASONIQUE	6,455	1	498.1	2.01	(0.05 - 11.18)	2.53	(0.20 - 32.79)	2.35	(0.17 - 32.23)
	Comparator	14,601	1	1,121.1	0.89	(0.02 - 4.97)				
	ATE									
	SEASONIQUE	6,464	0	498.9	0.00	(0.00 - 6.00)	NA	NA	NA	NA
	Comparator	14,605	0	1,121.5	0.00	(0.00 - 2.67)				
	Breast cancer									
	SEASONIQUE	6,468	0	499.2	0.00	(0.00 - 6.00)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	14,614	1	1,122.2	0.89	(0.02 - 4.96)				
	Cervical cancer									
	SEASONIQUE	6,468	0	499.2	0.00	(0.00 - 6.00)	NA	NA	NA	NA
	Comparator	14,614	0	1,122.2	0.00	(0.00 - 2.67)				
	Endometrial cancer									
	SEASONIQUE	6,468	0	499.2	0.00	(0.00 - 6.00)	NA	NA	NA	NA
	Comparator	14,614	0	1,122.2	0.00	(0.00 - 2.67)				
	Ovarian cancer									
	SEASONIQUE	6,468	0	499.2	0.00	(0.00 - 6.00)	NA	NA	NA	NA
	Comparator	14,614	0	1,122.2	0.00	(0.00 - 2.67)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3c. Relative Hazard of VTE, ATE, and Cancer Outcomes, New Users

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Remote Exposure	**VTE (primary definition)**									
	SEASONIQUE	5,454	10	9,730.7	1.03	(0.49 - 1.89)	1.43	(0.64 - 3.19)	1.44	(0.65 - 3.20)
	Comparator	12,801	16	21,445.6	0.75	(0.43 - 1.21)				
	VTE (sensitivity definition)									
	SEASONIQUE	5,458	9	9,736.1	0.92	(0.42 - 1.75)	1.68	(0.71 - 3.99)	1.67	(0.71 - 3.97)
	Comparator	12,808	13	21,465.0	0.61	(0.32 - 1.04)				
	ATE									
	SEASONIQUE	5,468	6	9,773.8	0.61	(0.23 - 1.34)	0.74	(0.28 - 1.96)	0.76	(0.29 - 2.03)
	Comparator	12,814	15	21,495.6	0.70	(0.39 - 1.15)				
	Breast cancer									
	SEASONIQUE	5,472	12	9,783.1	1.23	(0.63 - 2.14)	1.51	(0.73 - 3.13)	1.50	(0.72 - 3.14)
	Comparator	12,822	17	21,525.1	0.79	(0.46 - 1.26)				
	Cervical cancer									
	SEASONIQUE	5,472	2	9,783.1	0.20	(0.02 - 0.74)	2.26	(0.26 - 19.24)	2.13	(0.27 - 17.03)
	Comparator	12,822	2	21,525.1	0.09	(0.01 - 0.34)				
	Endometrial cancer									
	SEASONIQUE	5,472	0	9,783.1	0.00	(0.00 - 0.31)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	12,822	1	21,525.1	0.05	(0.00 - 0.26)				
	Ovarian cancer									
	SEASONIQUE	5,472	0	9,783.1	0.00	(0.00 - 0.31)	NA	NA	NA	NA
	Comparator	12,822	0	21,525.1	0.00	(0.00 - 0.14)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3d. Relative Hazard of VTE, ATE, and Cancer Outcomes, Re-starters

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Current Exposure	**VTE (primary definition)**									
	SEASONIQUE	8,339	14	6,325.8	2.21	(1.21 - 3.71)	1.12	(0.55 - 2.28)	1.12	(0.57 - 2.22)
	Comparator	25,953	23	16,468.0	1.40	(0.89 - 2.10)				
	VTE (sensitivity definition)									
	SEASONIQUE	8,339	11	6,328.0	1.74	(0.87 - 3.11)	1.12	(0.50 - 2.49)	1.10	(0.50 - 2.40)
	Comparator	25,958	19	16,472.1	1.15	(0.69 - 1.80)				
	ATE									
	SEASONIQUE	8,338	3	6,329.1	0.47	(0.10 - 1.39)	0.70	(0.17 - 2.82)	0.63	(0.15 - 2.53)
	Comparator	25,956	10	16,473.4	0.61	(0.29 - 1.12)				
	Breast cancer									
	SEASONIQUE	8,340	4	6,333.1	0.63	(0.17 - 1.62)	0.50	(0.19 - 1.35)	0.62	(0.22 - 1.74)
	Comparator	25,961	19	16,479.7	1.15	(0.69 - 1.80)				
	Cervical cancer									
	SEASONIQUE	8,340	0	6,333.1	0.00	(0.00 - 0.47)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	25,961	1	16,479.7	0.06	(0.00 - 0.34)				
	Endometrial cancer									
	SEASONIQUE	8,340	0	6,333.1	0.00	(0.00 - 0.47)	NA	NA	NA	NA
	Comparator	25,961	0	16,479.7	0.00	(0.00 - 0.18)				
	Ovarian cancer									
	SEASONIQUE	8,340	0	6,333.1	0.00	(0.00 - 0.47)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	25,961	1	16,479.7	0.06	(0.00 - 0.34)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3d. Relative Hazard of VTE, ATE, and Cancer Outcomes, Re-starters

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Recent Exposure	**VTE (primary definition)**									
	SEASONIQUE	5,676	0	422.1	0.00	(0.00 - 7.10)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	18,297	3	1,370.3	2.19	(0.45 - 6.40)				
	VTE (sensitivity definition)									
	SEASONIQUE	5,678	0	422.3	0.00	(0.00 - 7.09)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	18,304	2	1,370.9	1.46	(0.18 - 5.27)				
	ATE									
	SEASONIQUE	5,687	1	423.0	2.36	(0.06 - 13.17)	2.43	(0.25 - 23.50)	2.54	(0.23 - 27.83)
	Comparator	18,308	1	1,371.4	0.73	(0.02 - 4.06)				
	Breast cancer									
	SEASONIQUE	5,690	0	423.3	0.00	(0.00 - 7.08)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	18,321	1	1,372.4	0.73	(0.02 - 4.06)				
	Cervical cancer									
	SEASONIQUE	5,690	0	423.3	0.00	(0.00 - 7.08)	NA	NA	NA	NA
	Comparator	18,321	0	1,372.4	0.00	(0.00 - 2.18)				
	Endometrial cancer									
	SEASONIQUE	5,690	0	423.3	0.00	(0.00 - 7.08)	NA	NA	NA	NA
	Comparator	18,321	0	1,372.4	0.00	(0.00 - 2.18)				
	Ovarian cancer									
	SEASONIQUE	5,690	0	423.3	0.00	(0.00 - 7.08)	NA	NA	NA	NA
	Comparator	18,321	0	1,372.4	0.00	(0.00 - 2.18)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3d. Relative Hazard of VTE, ATE, and Cancer Outcomes, Re-starters

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Intermediate Exposure	**VTE (primary definition)**									
	SEASONIQUE	4,678	1	356.8	2.80	(0.07 - 15.61)	0.66	(0.06 - 7.06)	0.63	(0.06 - 6.43)
	Comparator	14,549	3	1,100.9	2.73	(0.56 - 7.96)				
	VTE (sensitivity definition)									
	SEASONIQUE	4,680	1	357.0	2.80	(0.07 - 15.61)	1.14	(0.10 - 12.86)	1.09	(0.10 - 11.35)
	Comparator	14,557	2	1,101.5	1.82	(0.22 - 6.56)				
	ATE									
	SEASONIQUE	4,688	0	357.7	0.00	(0.00 - 8.38)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	14,563	1	1,102.0	0.91	(0.02 - 5.06)				
	Breast cancer									
	SEASONIQUE	4,692	1	358.0	2.79	(0.07 - 15.56)	1.92	(0.22 - 16.68)	2.78	(0.35 - 22.12)
	Comparator	14,575	2	1,103.0	1.81	(0.22 - 6.55)				
	Cervical cancer									
	SEASONIQUE	4,692	0	358.0	0.00	(0.00 - 8.37)	NA	NA	NA	NA
	Comparator	14,575	0	1,103.0	0.00	(0.00 - 2.72)				
	Endometrial cancer									
	SEASONIQUE	4,692	0	358.0	0.00	(0.00 - 8.37)	NA	NA	NA	NA
	Comparator	14,575	0	1,103.0	0.00	(0.00 - 2.72)				
	Ovarian cancer									
	SEASONIQUE	4,692	0	358.0	0.00	(0.00 - 8.37)	NA	NA	NA	NA
	Comparator	14,575	0	1,103.0	0.00	(0.00 - 2.72)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3d. Relative Hazard of VTE, ATE, and Cancer Outcomes, Re-starters

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Remote Exposure	**VTE (primary definition)**									
	SEASONIQUE	3,946	12	6,937.4	1.73	(0.89 - 3.02)	1.20	(0.62 - 2.33)	1.13	(0.57 - 2.21)
	Comparator	12,425	26	20,243.6	1.28	(0.84 - 1.88)				
	VTE (sensitivity definition)									
	SEASONIQUE	3,948	5	6,963.5	0.72	(0.23 - 1.68)	0.61	(0.23 - 1.60)	0.57	(0.21 - 1.51)
	Comparator	12,433	22	20,255.2	1.09	(0.68 - 1.64)				
	ATE									
	SEASONIQUE	3,957	6	6,972.3	0.86	(0.32 - 1.87)	1.01	(0.37 - 2.72)	0.97	(0.36 - 2.64)
	Comparator	12,440	15	20,267.9	0.74	(0.41 - 1.22)				
	Breast cancer									
	SEASONIQUE	3,961	11	6,996.3	1.57	(0.78 - 2.81)	1.28	(0.61 - 2.66)	1.38	(0.66 - 2.86)
	Comparator	12,452	26	20,324.0	1.28	(0.84 - 1.87)				
	Cervical cancer									
	SEASONIQUE	3,961	0	6,996.3	0.00	(0.00 - 0.43)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	12,452	2	20,324.0	0.10	(0.01 - 0.36)				
	Endometrial cancer									
	SEASONIQUE	3,961	1	6,996.3	0.14	(0.00 - 0.80)	NA	NA	NA	NA
	Comparator	12,452	0	20,324.0	0.00	(0.00 - 0.15)				
	Ovarian cancer									
	SEASONIQUE	3,961	0	6,996.3	0.00	(0.00 - 0.43)	NA	NA	NA	NA
	Comparator	12,452	0	20,324.0	0.00	(0.00 - 0.15)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3e. Relative Hazard of VTE, ATE, and Cancer Outcomes, Switchers

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Current Exposure	**VTE (primary definition)**									
	SEASONIQUE	10,152	8	7,683.1	1.04	(0.45 - 2.05)	0.64	(0.28 - 1.43)	0.64	(0.28 - 1.43)
	Comparator	29,717	31	21,373.5	1.45	(0.99 - 2.06)				
	VTE (sensitivity definition)									
	SEASONIQUE	10,152	6	7,683.3	0.78	(0.29 - 1.70)	0.51	(0.20 - 1.26)	0.50	(0.20 - 1.25)
	Comparator	29,717	27	21,374.6	1.26	(0.83 - 1.84)				
	ATE									
	SEASONIQUE	10,150	5	7,681.5	0.65	(0.21 - 1.52)	1.52	(0.52 - 4.40)	1.53	(0.54 - 4.39)
	Comparator	29,716	9	21,375.4	0.42	(0.19 - 0.80)				
	Breast cancer									
	SEASONIQUE	10,152	8	7,684.6	1.04	(0.45 - 2.05)	1.81	(0.71 - 4.62)	1.83	(0.72 - 4.66)
	Comparator	29,717	11	21,379.5	0.51	(0.26 - 0.92)				
	Cervical cancer									
	SEASONIQUE	10,152	0	7,684.6	0.00	(0.00 - 0.39)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	29,717	1	21,379.5	0.05	(0.00 - 0.26)				
	Endometrial cancer									
	SEASONIQUE	10,152	0	7,684.6	0.00	(0.00 - 0.39)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	29,717	1	21,379.5	0.05	(0.00 - 0.26)				
	Ovarian cancer									
	SEASONIQUE	10,152	0	7,684.6	0.00	(0.00 - 0.39)	0.00	(0.00 - 0.00)	0.00	NA
	Comparator	29,717	1	21,379.5	0.05	(0.00 - 0.26)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3e. Relative Hazard of VTE, ATE, and Cancer Outcomes, Switchers

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Recent Exposure	**VTE (primary definition)**									
	SEASONIQUE	6,457	0	498.5	0.00	(0.00 - 6.01)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	18,860	2	1,457.4	1.37	(0.17 - 4.96)				
	VTE (sensitivity definition)									
	SEASONIQUE	6,458	0	498.6	0.00	(0.00 - 6.01)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	18,862	2	1,457.6	1.37	(0.17 - 4.96)				
	ATE									
	SEASONIQUE	6,458	0	498.7	0.00	(0.00 - 6.01)	NA	NA	NA	NA
	Comparator	18,879	0	1,459.1	0.00	(0.00 - 2.05)				
	Breast cancer									
	SEASONIQUE	6,464	0	499.1	0.00	(0.00 - 6.00)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	18,887	3	1,459.7	2.06	(0.42 - 6.01)				
	Cervical cancer									
	SEASONIQUE	6,464	0	499.1	0.00	(0.00 - 6.00)	NA	NA	NA	NA
	Comparator	18,887	0	1,459.7	0.00	(0.00 - 2.05)				
	Endometrial cancer									
	SEASONIQUE	6,464	0	499.1	0.00	(0.00 - 6.00)	NA	NA	NA	NA
	Comparator	18,887	0	1,459.7	0.00	(0.00 - 2.05)				
	Ovarian cancer									
	SEASONIQUE	6,464	0	499.1	0.00	(0.00 - 6.00)	NA	NA	NA	NA
	Comparator	18,887	0	1,459.7	0.00	(0.00 - 2.05)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3e. Relative Hazard of VTE, ATE, and Cancer Outcomes, Switchers

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Intermediate Exposure	**VTE (primary definition)**									
	SEASONIQUE	5,747	3	446.3	6.72	(1.39 - 19.64)	NA	NA	NA	NA
	Comparator	16,392	0	1,282.6	0.00	(0.00 - 2.34)				
	VTE (sensitivity definition)									
	SEASONIQUE	5,748	3	446.4	6.72	(1.39 - 19.64)	NA	NA	NA	NA
	Comparator	16,394	0	1,282.8	0.00	(0.00 - 2.34)				
	ATE									
	SEASONIQUE	5,749	0	446.7	0.00	(0.00 - 6.71)	NA	NA	NA	NA
	Comparator	16,413	0	1,284.4	0.00	(0.00 - 2.33)				
	Breast cancer									
	SEASONIQUE	5,754	0	447.1	0.00	(0.00 - 6.70)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	16,421	1	1,285.0	0.78	(0.02 - 4.34)				
	Cervical cancer									
	SEASONIQUE	5,754	0	447.1	0.00	(0.00 - 6.70)	NA	NA	NA	NA
	Comparator	16,421	0	1,285.0	0.00	(0.00 - 2.33)				
	Endometrial cancer									
	SEASONIQUE	5,754	0	447.1	0.00	(0.00 - 6.70)	NA	NA	NA	NA
	Comparator	16,421	0	1,285.0	0.00	(0.00 - 2.33)				
	Ovarian cancer									
	SEASONIQUE	5,754	0	447.1	0.00	(0.00 - 6.70)	NA	NA	NA	NA
	Comparator	16,421	0	1,285.0	0.00	(0.00 - 2.33)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3e. Relative Hazard of VTE, ATE, and Cancer Outcomes, Switchers

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS, Prior Number of CHCs, Prior CHC Days	95% CI
Remote Exposure	**VTE (primary definition)**									
	SEASONIQUE	5,044	11	8,773.8	1.25	(0.63 - 2.24)	1.39	(0.67 - 2.87)	1.37	(0.66 - 2.83)
	Comparator	14,881	21	26,134.9	0.80	(0.50 - 1.23)				
	VTE (sensitivity definition)									
	SEASONIQUE	5,045	8	8,777.2	0.91	(0.39 - 1.80)	1.29	(0.55 - 3.02)	1.28	(0.55 - 3.00)
	Comparator	14,883	16	26,145.0	0.61	(0.35 - 0.99)				
	ATE									
	SEASONIQUE	5,049	1	8,804.7	0.11	(0.00 - 0.63)	0.33	(0.04 - 2.53)	0.33	(0.04 - 2.51)
	Comparator	14,902	9	26,203.1	0.34	(0.16 - 0.65)				
	Breast cancer									
	SEASONIQUE	5,054	11	8,814.1	1.25	(0.62 - 2.23)	1.12	(0.56 - 2.24)	1.14	(0.57 - 2.29)
	Comparator	14,909	29	26,227.0	1.11	(0.74 - 1.59)				
	Cervical cancer									
	SEASONIQUE	5,054	0	8,814.1	0.00	(0.00 - 0.34)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	14,909	2	26,227.0	0.08	(0.01 - 0.28)				
	Endometrial cancer									
	SEASONIQUE	5,054	0	8,814.1	0.00	(0.00 - 0.34)	0.00	(0.00 - 0.00)	0.00	(0.00 - 0.00)
	Comparator	14,909	1	26,227.0	0.04	(0.00 - 0.21)				
	Ovarian cancer									
	SEASONIQUE	5,054	1	8,814.1	0.11	(0.00 - 0.63)	3.44	(0.21 - 56.02)	2.38	NA
	Comparator	14,909	1	26,227.0	0.04	(0.00 - 0.21)				

Abbreviations: ATE, arterial thromboembolism; CHC, combined hormonal contraceptive; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.
Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.1 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Using 60-day Gaps for SEASONIQUE and 28-day Gaps for Comparator (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Current Exposure	**VTE (primary definition)**							
	SEASONIQUE	25,522	40	19,002.0	2.11	(1.50 - 2.87)	1.53	(1.01 - 2.31)
	Comparator	76,442	75	54,642.5	1.37	(1.08 - 1.72)		
	VTE (sensitivity definition)							
	SEASONIQUE	25,526	33	19,008.5	1.74	(1.20 - 2.44)	1.67	(1.05 - 2.66)
	Comparator	76,450	56	54,653.6	1.02	(0.77 - 1.33)		
	ATE							
	SEASONIQUE	25,527	14	19,013.2	0.74	(0.40 - 1.24)	1.26	(0.62 - 2.53)
	Comparator	76,451	30	54,647.6	0.55	(0.37 - 0.78)		
	Breast cancer							
	SEASONIQUE	25,528	23	19,018.8	1.21	(0.77 - 1.81)	1.82	(1.03 - 3.22)
	Comparator	76,453	34	54,671.1	0.62	(0.43 - 0.87)		
	Cervical cancer							
	SEASONIQUE	25,528	4	19,018.8	0.21	(0.06 - 0.54)	6.09	(1.05 - 35.28)
	Comparator	76,453	2	54,671.1	0.04	(0.00 - 0.13)		
	Endometrial cancer							
	SEASONIQUE	25,528	0	19,018.8	0.00	(0.00 - 0.16)	0.00	(0.00 - 0.00)
	Comparator	76,453	2	54,671.1	0.04	(0.00 - 0.13)		
	Ovarian cancer							
	SEASONIQUE	25,528	1	19,018.8	0.05	(0.00 - 0.29)	1.49	(0.10 - 23.24)
	Comparator	76,453	2	54,671.1	0.04	(0.00 - 0.13)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.1 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Using 60-day Gaps for SEASONIQUE and 28-day Gaps for Comparator (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Recent Exposure	**VTE (primary definition)**							
	SEASONIQUE	17,099	3	1,335.2	2.25	(0.46 - 6.57)	8.34	(0.78 - 88.65)
	Comparator	51,280	1	3,828.5	0.26	(0.01 - 1.46)		
	VTE (sensitivity definition)							
	SEASONIQUE	17,108	2	1,336.0	1.50	(0.18 - 5.41)	6.13	(0.46 - 80.92)
	Comparator	51,297	1	3,829.9	0.26	(0.01 - 1.45)		
	ATE							
	SEASONIQUE	17,127	0	1,337.6	0.00	(0.00 - 2.24)	0.00	(0.00 - 0.00)
	Comparator	51,323	1	3,831.9	0.26	(0.01 - 1.45)		
	Breast cancer							
	SEASONIQUE	17,138	1	1,338.5	0.75	(0.02 - 4.16)	1.52	(0.15 - 15.24)
	Comparator	51,349	2	3,834.0	0.52	(0.06 - 1.88)		
	Cervical cancer							
	SEASONIQUE	17,138	0	1,338.5	0.00	(0.00 - 2.24)	0.00	(0.00 - 0.00)
	Comparator	51,349	2	3,834.0	0.52	(0.06 - 1.88)		
	Endometrial cancer							
	SEASONIQUE	17,138	0	1,338.5	0.00	(0.00 - 2.24)	0.00	(0.00 - 0.00)
	Comparator	51,349	2	3,834.0	0.52	(0.06 - 1.88)		
	Ovarian cancer							
	SEASONIQUE	17,138	0	1,338.5	0.00	(0.00 - 2.24)	0.00	(0.00 - 0.00)
	Comparator	51,349	1	3,834.0	0.26	(0.01 - 1.45)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.1 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Using 60-day Gaps for SEASONIQUE and 28-day Gaps for Comparator (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Intermediate Exposure	**VTE (primary definition)**							
	SEASONIQUE	15,065	1	1,164.3	0.86	(0.02 - 4.79)	0.93	(0.12 - 7.31)
	Comparator	43,007	3	3,359.5	0.89	(0.18 - 2.61)		
	VTE (sensitivity definition)							
	SEASONIQUE	15,075	1	1,165.1	0.86	(0.02 - 4.78)	1.41	(0.17 - 11.68)
	Comparator	43,024	2	3,361.0	0.60	(0.07 - 2.15)		
	ATE							
	SEASONIQUE	15,096	0	1,166.8	0.00	(0.00 - 2.57)	NA	NA
	Comparator	43,047	0	3,363.0	0.00	(0.00 - 0.89)		
	Breast cancer							
	SEASONIQUE	15,107	0	1,167.6	0.00	(0.00 - 2.57)	0.00	(0.00 - 0.00)
	Comparator	43,073	1	3,365.1	0.30	(0.01 - 1.66)		
	Cervical cancer							
	SEASONIQUE	15,107	0	1,167.6	0.00	(0.00 - 2.57)	NA	NA
	Comparator	43,073	0	3,365.1	0.00	(0.00 - 0.89)		
	Endometrial cancer							
	SEASONIQUE	15,107	0	1,167.6	0.00	(0.00 - 2.57)	NA	NA
	Comparator	43,073	0	3,365.1	0.00	(0.00 - 0.89)		
	Ovarian cancer							
	SEASONIQUE	15,107	0	1,167.6	0.00	(0.00 - 2.57)	0.00	(0.00 - 0.00)
	Comparator	43,073	1	3,365.1	0.30	(0.01 - 1.66)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.1 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Using 60-day Gaps for SEASONIQUE and 28-day Gaps for Comparator (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Remote Exposure	**VTE (primary definition)**							
	SEASONIQUE	13,566	41	26,778.4	1.53	(1.10 - 2.08)	1.63	(1.09 - 2.43)
	Comparator	38,882	69	74,208.3	0.93	(0.72 - 1.18)		
	VTE (sensitivity definition)							
	SEASONIQUE	13,574	34	26,807.7	1.27	(0.88 - 1.77)	1.80	(1.15 - 2.82)
	Comparator	38,900	53	74,260.7	0.71	(0.53 - 0.93)		
	ATE							
	SEASONIQUE	13,596	30	26,928.8	1.11	(0.75 - 1.59)	1.47	(0.93 - 2.33)
	Comparator	38,924	54	74,370.1	0.73	(0.55 - 0.95)		
	Breast cancer							
	SEASONIQUE	13,605	34	26,993.6	1.26	(0.87 - 1.76)	1.38	(0.91 - 2.10)
	Comparator	38,949	65	74,496.2	0.87	(0.67 - 1.11)		
	Cervical cancer							
	SEASONIQUE	13,605	2	26,993.6	0.07	(0.01 - 0.27)	2.17	(0.26 - 18.43)
	Comparator	38,949	2	74,496.2	0.03	(0.00 - 0.10)		
	Endometrial cancer							
	SEASONIQUE	13,605	2	26,993.6	0.07	(0.01 - 0.27)	1.06	(0.21 - 5.38)
	Comparator	38,949	6	74,496.2	0.08	(0.03 - 0.18)		
	Ovarian cancer							
	SEASONIQUE	13,605	0	26,993.6	0.00	(0.00 - 0.11)	0.00	(0.00 - 0.00)
	Comparator	38,949	8	74,496.2	0.11	(0.05 - 0.21)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.2 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Not Censoring Comparators with Continuous Use (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Current Exposure	**VTE (primary definition)**							
	SEASONIQUE	25,587	35	16,867.6	2.07	(1.45 - 2.89)	1.32	(0.84 - 2.06)
	Comparator	76,575	73	48,937.2	1.49	(1.17 - 1.88)		
	VTE (sensitivity definition)							
	SEASONIQUE	25,591	30	16,873.3	1.78	(1.20 - 2.54)	1.45	(0.89 - 2.38)
	Comparator	76,583	55	48,948.9	1.12	(0.85 - 1.46)		
	ATE							
	SEASONIQUE	25,592	13	16,876.6	0.77	(0.41 - 1.32)	1.20	(0.59 - 2.46)
	Comparator	76,584	31	48,939.9	0.63	(0.43 - 0.90)		
	Breast cancer							
	SEASONIQUE	25,593	17	16,881.1	1.01	(0.59 - 1.61)	1.55	(0.80 - 3.01)
	Comparator	76,586	29	48,965.8	0.59	(0.40 - 0.85)		
	Cervical cancer							
	SEASONIQUE	25,593	4	16,881.1	0.24	(0.06 - 0.61)	12.50	(1.47 - 106.55)
	Comparator	76,586	1	48,965.8	0.02	(0.00 - 0.11)		
	Endometrial cancer							
	SEASONIQUE	25,593	0	16,881.1	0.00	(0.00 - 0.18)	0.00	(0.00 - 0.00)
	Comparator	76,586	2	48,965.8	0.04	(0.00 - 0.15)		
	Ovarian cancer							
	SEASONIQUE	25,593	1	16,881.1	0.06	(0.00 - 0.33)	1.56	(0.11 - 22.52)
	Comparator	76,586	2	48,965.8	0.04	(0.00 - 0.15)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.2 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Not Censoring Comparators with Continuous Use (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Recent Exposure	**VTE (primary definition)**							
	SEASONIQUE	18,088	4	1,401.8	2.85	(0.78 - 7.31)	2.98	(0.66 - 13.39)
	Comparator	55,830	4	4,304.3	0.93	(0.25 - 2.38)		
	VTE (sensitivity definition)							
	SEASONIQUE	18,095	4	1,402.3	2.85	(0.78 - 7.30)	4.27	(0.90 - 20.16)
	Comparator	55,847	3	4,305.8	0.70	(0.14 - 2.04)		
	ATE							
	SEASONIQUE	18,113	0	1,403.9	0.00	(0.00 - 2.13)	NA	NA
	Comparator	55,874	0	4,308.0	0.00	(0.00 - 0.70)		
	Breast cancer							
	SEASONIQUE	18,123	6	1,404.7	4.27	(1.57 - 9.30)	4.75	(1.33 - 17.04)
	Comparator	55,900	4	4,310.1	0.93	(0.25 - 2.38)		
	Cervical cancer							
	SEASONIQUE	18,123	0	1,404.7	0.00	(0.00 - 2.13)	0.00	(0.00 - 0.00)
	Comparator	55,900	3	4,310.1	0.70	(0.14 - 2.03)		
	Endometrial cancer							
	SEASONIQUE	18,123	0	1,404.7	0.00	(0.00 - 2.13)	0.00	(0.00 - 0.00)
	Comparator	55,900	2	4,310.1	0.46	(0.06 - 1.68)		
	Ovarian cancer							
	SEASONIQUE	18,123	0	1,404.7	0.00	(0.00 - 2.13)	0.00	(0.00 - 0.00)
	Comparator	55,900	1	4,310.1	0.23	(0.01 - 1.29)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.2 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Not Censoring Comparators with Continuous Use (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Intermediate Exposure	**VTE (primary definition)**							
	SEASONIQUE	16,162	2	1,262.7	1.58	(0.19 - 5.72)	2.46	(0.39 - 15.42)
	Comparator	48,057	2	3,736.7	0.54	(0.06 - 1.93)		
	VTE (sensitivity definition)							
	SEASONIQUE	16,169	1	1,263.4	0.79	(0.02 - 4.41)	2.54	(0.19 - 33.49)
	Comparator	48,075	1	3,738.2	0.27	(0.01 - 1.49)		
	ATE							
	SEASONIQUE	16,190	0	1,265.1	0.00	(0.00 - 2.37)	0.00	(0.00 - 0.00)
	Comparator	48,102	2	3,740.4	0.53	(0.06 - 1.93)		
	Breast cancer							
	SEASONIQUE	16,200	1	1,265.9	0.79	(0.02 - 4.40)	0.96	(0.10 - 9.28)
	Comparator	48,127	3	3,742.5	0.80	(0.17 - 2.34)		
	Cervical cancer							
	SEASONIQUE	16,200	0	1,265.9	0.00	(0.00 - 2.37)	NA	NA
	Comparator	48,127	0	3,742.5	0.00	(0.00 - 0.80)		
	Endometrial cancer							
	SEASONIQUE	16,200	0	1,265.9	0.00	(0.00 - 2.37)	NA	NA
	Comparator	48,127	0	3,742.5	0.00	(0.00 - 0.80)		
	Ovarian cancer							
	SEASONIQUE	16,200	0	1,265.9	0.00	(0.00 - 2.37)	NA	NA
	Comparator	48,127	0	3,742.5	0.00	(0.00 - 0.80)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.2 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Not Censoring Comparators with Continuous Use (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Remote Exposure	**VTE (primary definition)**							
	SEASONIQUE	14,242	41	26,482.2	1.55	(1.11 - 2.10)	1.65	(1.12 - 2.42)
	Comparator	43,214	76	79,474.5	0.96	(0.75 - 1.20)		
	VTE (sensitivity definition)							
	SEASONIQUE	14,250	34	26,505.0	1.28	(0.89 - 1.79)	1.78	(1.16 - 2.73)
	Comparator	43,233	60	79,528.5	0.75	(0.58 - 0.97)		
	ATE							
	SEASONIQUE	14,272	30	26,631.5	1.13	(0.76 - 1.61)	1.59	(1.00 - 2.51)
	Comparator	43,259	54	79,654.8	0.68	(0.51 - 0.88)		
	Breast cancer							
	SEASONIQUE	14,282	33	26,690.6	1.24	(0.85 - 1.74)	1.38	(0.91 - 2.09)
	Comparator	43,285	69	79,779.5	0.86	(0.67 - 1.09)		
	Cervical cancer							
	SEASONIQUE	14,282	2	26,690.6	0.07	(0.01 - 0.27)	2.36	(0.28 - 20.07)
	Comparator	43,285	2	79,779.5	0.03	(0.00 - 0.09)		
	Endometrial cancer							
	SEASONIQUE	14,282	2	26,690.6	0.07	(0.01 - 0.27)	1.14	(0.23 - 5.79)
	Comparator	43,285	6	79,779.5	0.08	(0.03 - 0.16)		
	Ovarian cancer							
	SEASONIQUE	14,282	0	26,690.6	0.00	(0.00 - 0.11)	0.00	(0.00 - 0.00)
	Comparator	43,285	10	79,779.5	0.13	(0.06 - 0.23)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.3 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with at Least 24 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Current Exposure	**VTE (primary definition)**							
	SEASONIQUE	8,099	13	5,191.6	2.50	(1.33 - 4.28)	1.32	(0.67 - 2.60)
	Comparator	29,465	31	18,802.7	1.65	(1.12 - 2.34)		
	VTE (sensitivity definition)							
	SEASONIQUE	8,099	11	5,191.9	2.12	(1.06 - 3.79)	1.55	(0.73 - 3.26)
	Comparator	29,465	22	18,807.0	1.17	(0.73 - 1.77)		
	ATE							
	SEASONIQUE	8,099	3	5,193.7	0.58	(0.12 - 1.69)	1.24	(0.35 - 4.40)
	Comparator	29,465	9	18,797.7	0.48	(0.22 - 0.91)		
	Breast cancer							
	SEASONIQUE	8,099	6	5,194.1	1.16	(0.42 - 2.51)	3.28	(0.91 - 11.76)
	Comparator	29,465	5	18,809.2	0.27	(0.09 - 0.62)		
	Cervical cancer							
	SEASONIQUE	8,099	2	5,194.1	0.39	(0.05 - 1.39)	NA	NA
	Comparator	29,465	0	18,809.2	0.00	(0.00 - 0.16)		
	Endometrial cancer							
	SEASONIQUE	8,099	0	5,194.1	0.00	(0.00 - 0.58)	NA	NA
	Comparator	29,465	0	18,809.2	0.00	(0.00 - 0.16)		
	Ovarian cancer							
	SEASONIQUE	8,099	0	5,194.1	0.00	(0.00 - 0.58)	0.00	(0.00 - 0.00)
	Comparator	29,465	1	18,809.2	0.05	(0.00 - 0.30)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.3 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with at Least 24 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Recent Exposure	**VTE (primary definition)**							
	SEASONIQUE	6,013	0	486.5	0.00	(0.00 - 6.16)	0.00	(0.00 - 0.00)
	Comparator	21,449	1	1,731.9	0.58	(0.01 - 3.22)		
	VTE (sensitivity definition)							
	SEASONIQUE	6,014	0	486.6	0.00	(0.00 - 6.16)	0.00	(0.00 - 0.00)
	Comparator	21,454	1	1,732.3	0.58	(0.01 - 3.22)		
	ATE							
	SEASONIQUE	6,021	0	487.2	0.00	(0.00 - 6.15)	NA	NA
	Comparator	21,469	0	1,733.5	0.00	(0.00 - 1.73)		
	Breast cancer							
	SEASONIQUE	6,024	2	487.4	4.10	(0.50 - 14.82)	NA	NA
	Comparator	21,475	0	1,734.0	0.00	(0.00 - 1.73)		
	Cervical cancer							
	SEASONIQUE	6,024	0	487.4	0.00	(0.00 - 6.15)	NA	NA
	Comparator	21,475	0	1,734.0	0.00	(0.00 - 1.73)		
	Endometrial cancer							
	SEASONIQUE	6,024	0	487.4	0.00	(0.00 - 6.15)	0.00	(0.00 - 0.00)
	Comparator	21,475	1	1,734.0	0.58	(0.01 - 3.21)		
	Ovarian cancer							
	SEASONIQUE	6,024	0	487.4	0.00	(0.00 - 6.15)	NA	NA
	Comparator	21,475	0	1,734.0	0.00	(0.00 - 1.73)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.3 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with at Least 24 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Intermediate Exposure	**VTE (primary definition)**							
	SEASONIQUE	5,820	2	470.4	4.25	(0.51 - 15.36)	NA	NA
	Comparator	20,688	0	1,671.8	0.00	(0.00 - 1.79)		
	VTE (sensitivity definition)							
	SEASONIQUE	5,821	1	470.5	2.13	(0.05 - 11.84)	NA	NA
	Comparator	20,693	0	1,672.2	0.00	(0.00 - 1.79)		
	ATE							
	SEASONIQUE	5,828	0	471.1	0.00	(0.00 - 6.36)	0.00	(0.00 - 0.00)
	Comparator	20,708	1	1,673.4	0.60	(0.02 - 3.33)		
	Breast cancer							
	SEASONIQUE	5,831	0	471.4	0.00	(0.00 - 6.36)	NA	NA
	Comparator	20,714	0	1,674.0	0.00	(0.00 - 1.79)		
	Cervical cancer							
	SEASONIQUE	5,831	0	471.4	0.00	(0.00 - 6.36)	NA	NA
	Comparator	20,714	0	1,674.0	0.00	(0.00 - 1.79)		
	Endometrial cancer							
	SEASONIQUE	5,831	0	471.4	0.00	(0.00 - 6.36)	NA	NA
	Comparator	20,714	0	1,674.0	0.00	(0.00 - 1.79)		
	Ovarian cancer							
	SEASONIQUE	5,831	0	471.4	0.00	(0.00 - 6.36)	NA	NA
	Comparator	20,714	0	1,674.0	0.00	(0.00 - 1.79)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.3 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with at Least 24 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Remote Exposure	**VTE (primary definition)**							
	SEASONIQUE	5,638	25	13,710.1	1.82	(1.18 - 2.69)	1.60	(0.97 - 2.62)
	Comparator	19,996	48	47,143.3	1.02	(0.75 - 1.35)		
	VTE (sensitivity definition)							
	SEASONIQUE	5,640	21	13,718.9	1.53	(0.95 - 2.34)	1.87	(1.08 - 3.24)
	Comparator	20,001	36	47,165.2	0.76	(0.53 - 1.06)		
	ATE							
	SEASONIQUE	5,648	16	13,785.2	1.16	(0.66 - 1.88)	1.91	(1.01 - 3.63)
	Comparator	20,015	26	47,233.8	0.55	(0.36 - 0.81)		
	Breast cancer							
	SEASONIQUE	5,651	20	13,811.7	1.45	(0.88 - 2.24)	1.75	(1.02 - 3.00)
	Comparator	20,022	38	47,290.5	0.80	(0.57 - 1.10)		
	Cervical cancer							
	SEASONIQUE	5,651	0	13,811.7	0.00	(0.00 - 0.22)	NA	NA
	Comparator	20,022	0	47,290.5	0.00	(0.00 - 0.06)		
	Endometrial cancer							
	SEASONIQUE	5,651	2	13,811.7	0.14	(0.02 - 0.52)	2.07	(0.30 - 14.52)
	Comparator	20,022	3	47,290.5	0.06	(0.01 - 0.19)		
	Ovarian cancer							
	SEASONIQUE	5,651	0	13,811.7	0.00	(0.00 - 0.22)	0.00	(0.00 - 0.00)
	Comparator	20,022	8	47,290.5	0.17	(0.07 - 0.33)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.4 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with > 24 to ≤ 36 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Current Exposure	**VTE (primary definition)**							
	SEASONIQUE	2,190	2	1,288.6	1.55	(0.19 - 5.61)	0.55	(0.11 - 2.80)
	Comparator	7,794	9	4,734.2	1.90	(0.87 - 3.61)		
	VTE (sensitivity definition)							
	SEASONIQUE	2,190	2	1,288.6	1.55	(0.19 - 5.61)	0.64	(0.12 - 3.30)
	Comparator	7,794	8	4,734.2	1.69	(0.73 - 3.33)		
	ATE							
	SEASONIQUE	2,190	1	1,288.7	0.78	(0.02 - 4.32)	0.98	(0.11 - 8.65)
	Comparator	7,794	3	4,733.4	0.63	(0.13 - 1.85)		
	Breast cancer							
	SEASONIQUE	2,190	2	1,288.8	1.55	(0.19 - 5.61)	2.41	(0.28 - 20.94)
	Comparator	7,794	2	4,734.8	0.42	(0.05 - 1.53)		
	Cervical cancer							
	SEASONIQUE	2,190	1	1,288.8	0.78	(0.02 - 4.32)	NA	NA
	Comparator	7,794	0	4,734.8	0.00	(0.00 - 0.63)		
	Endometrial cancer							
	SEASONIQUE	2,190	0	1,288.8	0.00	(0.00 - 2.32)	NA	NA
	Comparator	7,794	0	4,734.8	0.00	(0.00 - 0.63)		
	Ovarian cancer							
	SEASONIQUE	2,190	0	1,288.8	0.00	(0.00 - 2.32)	NA	NA
	Comparator	7,794	0	4,734.8	0.00	(0.00 - 0.63)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.4 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with > 24 to ≤ 36 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Recent Exposure	**VTE (primary definition)**							
	SEASONIQUE	1,579	0	127.4	0.00	(0.00 - 23.52)	NA	NA
	Comparator	5,558	0	448.1	0.00	(0.00 - 6.69)		
	VTE (sensitivity definition)							
	SEASONIQUE	1,579	0	127.4	0.00	(0.00 - 23.52)	NA	NA
	Comparator	5,559	0	448.1	0.00	(0.00 - 6.68)		
	ATE							
	SEASONIQUE	1,580	0	127.4	0.00	(0.00 - 23.51)	NA	NA
	Comparator	5,565	0	448.6	0.00	(0.00 - 6.68)		
	Breast cancer							
	SEASONIQUE	1,581	0	127.5	0.00	(0.00 - 23.49)	NA	NA
	Comparator	5,567	0	448.8	0.00	(0.00 - 6.68)		
	Cervical cancer							
	SEASONIQUE	1,581	0	127.5	0.00	(0.00 - 23.49)	NA	NA
	Comparator	5,567	0	448.8	0.00	(0.00 - 6.68)		
	Endometrial cancer							
	SEASONIQUE	1,581	0	127.5	0.00	(0.00 - 23.49)	0.00	(0.00 - 0.00)
	Comparator	5,567	1	448.8	2.23	(0.06 - 12.41)		
	Ovarian cancer							
	SEASONIQUE	1,581	0	127.5	0.00	(0.00 - 23.49)	NA	NA
	Comparator	5,567	0	448.8	0.00	(0.00 - 6.68)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.4 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with > 24 to ≤ 36 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Intermediate Exposure	**VTE (primary definition)**							
	SEASONIQUE	1,524	1	122.9	8.14	(0.21 - 45.34)	NA	NA
	Comparator	5,341	0	431.3	0.00	(0.00 - 6.95)		
	VTE (sensitivity definition)							
	SEASONIQUE	1,524	0	122.9	0.00	(0.00 - 24.37)	NA	NA
	Comparator	5,342	0	431.3	0.00	(0.00 - 6.95)		
	ATE							
	SEASONIQUE	1,525	0	123.0	0.00	(0.00 - 24.35)	NA	NA
	Comparator	5,347	0	431.7	0.00	(0.00 - 6.94)		
	Breast cancer							
	SEASONIQUE	1,526	0	123.1	0.00	(0.00 - 24.33)	NA	NA
	Comparator	5,349	0	431.9	0.00	(0.00 - 6.94)		
	Cervical cancer							
	SEASONIQUE	1,526	0	123.1	0.00	(0.00 - 24.33)	NA	NA
	Comparator	5,349	0	431.9	0.00	(0.00 - 6.94)		
	Endometrial cancer							
	SEASONIQUE	1,526	0	123.1	0.00	(0.00 - 24.33)	NA	NA
	Comparator	5,349	0	431.9	0.00	(0.00 - 6.94)		
	Ovarian cancer							
	SEASONIQUE	1,526	0	123.1	0.00	(0.00 - 24.33)	NA	NA
	Comparator	5,349	0	431.9	0.00	(0.00 - 6.94)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.4 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with > 24 to ≤ 36 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Remote Exposure	**VTE (primary definition)**							
	SEASONIQUE	1,470	11	3,400.5	3.23	(1.61 - 5.79)	2.99	(1.23 - 7.24)
	Comparator	5,161	11	11,517.6	0.96	(0.48 - 1.71)		
	VTE (sensitivity definition)							
	SEASONIQUE	1,471	8	3,408.7	2.35	(1.01 - 4.62)	2.91	(1.07 - 7.89)
	Comparator	5,162	9	11,528.2	0.78	(0.36 - 1.48)		
	ATE							
	SEASONIQUE	1,472	4	3,420.8	1.17	(0.32 - 2.99)	2.09	(0.55 - 7.97)
	Comparator	5,167	6	11,552.7	0.52	(0.19 - 1.13)		
	Breast cancer							
	SEASONIQUE	1,473	6	3,429.7	1.75	(0.64 - 3.81)	2.94	(0.97 - 8.84)
	Comparator	5,169	7	11,565.1	0.61	(0.24 - 1.25)		
	Cervical cancer							
	SEASONIQUE	1,473	0	3,429.7	0.00	(0.00 - 0.87)	NA	NA
	Comparator	5,169	0	11,565.1	0.00	(0.00 - 0.26)		
	Endometrial cancer							
	SEASONIQUE	1,473	0	3,429.7	0.00	(0.00 - 0.87)	NA	NA
	Comparator	5,169	0	11,565.1	0.00	(0.00 - 0.26)		
	Ovarian cancer							
	SEASONIQUE	1,473	0	3,429.7	0.00	(0.00 - 0.87)	0.00	(0.00 - 0.00)
	Comparator	5,169	3	11,565.1	0.26	(0.05 - 0.76)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.5 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with a Minimum of 36 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Current Exposure	**VTE (primary definition)**							
	SEASONIQUE	4,952	10	3,273.9	3.05	(1.46 - 5.62)	2.35	(1.05 - 5.24)
	Comparator	18,870	16	12,402.6	1.29	(0.74 - 2.09)		
	VTE (sensitivity definition)							
	SEASONIQUE	4,952	8	3,274.2	2.44	(1.05 - 4.81)	2.67	(1.07 - 6.64)
	Comparator	18,870	11	12,405.1	0.89	(0.44 - 1.59)		
	ATE							
	SEASONIQUE	4,952	2	3,275.7	0.61	(0.07 - 2.21)	1.41	(0.30 - 6.74)
	Comparator	18,870	6	12,396.1	0.48	(0.18 - 1.05)		
	Breast cancer							
	SEASONIQUE	4,952	4	3,276.0	1.22	(0.33 - 3.13)	4.16	(0.86 - 20.16)
	Comparator	18,870	3	12,406.3	0.24	(0.05 - 0.71)		
	Cervical cancer							
	SEASONIQUE	4,952	0	3,276.0	0.00	(0.00 - 0.91)	NA	NA
	Comparator	18,870	0	12,406.3	0.00	(0.00 - 0.24)		
	Endometrial cancer							
	SEASONIQUE	4,952	0	3,276.0	0.00	(0.00 - 0.91)	NA	NA
	Comparator	18,870	0	12,406.3	0.00	(0.00 - 0.24)		
	Ovarian cancer							
	SEASONIQUE	4,952	0	3,276.0	0.00	(0.00 - 0.91)	NA	NA
	Comparator	18,870	0	12,406.3	0.00	(0.00 - 0.24)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.5 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with a Minimum of 36 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Recent Exposure	**VTE (primary definition)**							
	SEASONIQUE	3,722	0	301.3	0.00	(0.00 - 9.94)	NA	NA
	Comparator	13,831	0	1,117.7	0.00	(0.00 - 2.68)		
	VTE (sensitivity definition)							
	SEASONIQUE	3,723	0	301.4	0.00	(0.00 - 9.94)	NA	NA
	Comparator	13,833	0	1,117.9	0.00	(0.00 - 2.68)		
	ATE							
	SEASONIQUE	3,728	0	301.8	0.00	(0.00 - 9.93)	NA	NA
	Comparator	13,839	0	1,118.4	0.00	(0.00 - 2.68)		
	Breast cancer							
	SEASONIQUE	3,730	0	302.0	0.00	(0.00 - 9.92)	NA	NA
	Comparator	13,843	0	1,118.7	0.00	(0.00 - 2.68)		
	Cervical cancer							
	SEASONIQUE	3,730	0	302.0	0.00	(0.00 - 9.92)	NA	NA
	Comparator	13,843	0	1,118.7	0.00	(0.00 - 2.68)		
	Endometrial cancer							
	SEASONIQUE	3,730	0	302.0	0.00	(0.00 - 9.92)	NA	NA
	Comparator	13,843	0	1,118.7	0.00	(0.00 - 2.68)		
	Ovarian cancer							
	SEASONIQUE	3,730	0	302.0	0.00	(0.00 - 9.92)	NA	NA
	Comparator	13,843	0	1,118.7	0.00	(0.00 - 2.68)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.5 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with a Minimum of 36 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Intermediate Exposure	**VTE (primary definition)**							
	SEASONIQUE	3,602	1	291.6	3.43	(0.09 - 19.10)	NA	NA
	Comparator	13,358	0	1,080.5	0.00	(0.00 - 2.77)		
	VTE (sensitivity definition)							
	SEASONIQUE	3,603	1	291.7	3.43	(0.09 - 19.10)	NA	NA
	Comparator	13,360	0	1,080.7	0.00	(0.00 - 2.77)		
	ATE							
	SEASONIQUE	3,608	0	292.2	0.00	(0.00 - 10.25)	NA	NA
	Comparator	13,366	0	1,081.2	0.00	(0.00 - 2.77)		
	Breast cancer							
	SEASONIQUE	3,610	0	292.4	0.00	(0.00 - 10.25)	NA	NA
	Comparator	13,370	0	1,081.5	0.00	(0.00 - 2.77)		
	Cervical cancer							
	SEASONIQUE	3,610	0	292.4	0.00	(0.00 - 10.25)	NA	NA
	Comparator	13,370	0	1,081.5	0.00	(0.00 - 2.77)		
	Endometrial cancer							
	SEASONIQUE	3,610	0	292.4	0.00	(0.00 - 10.25)	NA	NA
	Comparator	13,370	0	1,081.5	0.00	(0.00 - 2.77)		
	Ovarian cancer							
	SEASONIQUE	3,610	0	292.4	0.00	(0.00 - 10.25)	NA	NA
	Comparator	13,370	0	1,081.5	0.00	(0.00 - 2.77)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.5 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve Users, Restricted to Those with a Minimum of 36 Months of Prior Continuous Enrolment and No Combined Hormonal Contraceptive Use During this Time (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Remote Exposure	**VTE (primary definition)**							
	SEASONIQUE	3,498	10	8,757.0	1.14	(0.55 - 2.10)	0.94	(0.46 - 1.93)
	Comparator	12,926	34	31,105.9	1.09	(0.76 - 1.53)		
	VTE (sensitivity definition)							
	SEASONIQUE	3,499	9	8,757.6	1.03	(0.47 - 1.95)	1.17	(0.54 - 2.54)
	Comparator	12,928	25	31,113.5	0.80	(0.52 - 1.19)		
	ATE							
	SEASONIQUE	3,505	10	8,798.2	1.14	(0.55 - 2.09)	1.97	(0.90 - 4.34)
	Comparator	12,934	17	31,146.5	0.55	(0.32 - 0.87)		
	Breast cancer							
	SEASONIQUE	3,507	11	8,814.1	1.25	(0.62 - 2.23)	1.39	(0.70 - 2.77)
	Comparator	12,938	27	31,183.3	0.87	(0.57 - 1.26)		
	Cervical cancer							
	SEASONIQUE	3,507	0	8,814.1	0.00	(0.00 - 0.34)	NA	NA
	Comparator	12,938	0	31,183.3	0.00	(0.00 - 0.10)		
	Endometrial cancer							
	SEASONIQUE	3,507	2	8,814.1	0.23	(0.03 - 0.82)	3.56	(0.47 - 26.76)
	Comparator	12,938	2	31,183.3	0.06	(0.01 - 0.23)		
	Ovarian cancer							
	SEASONIQUE	3,507	0	8,814.1	0.00	(0.00 - 0.34)	0.00	(0.00 - 0.00)
	Comparator	12,938	4	31,183.3	0.13	(0.03 - 0.33)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.6 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Requiring 6 Months Instead of 12 Months of Prior Continuous Enrolment (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Current Exposure	**VTE (primary definition)**							
	SEASONIQUE	30,180	41	19,291.6	2.13	(1.53 - 2.88)	1.53	(1.03 - 2.28)
	Comparator	177,990	147	104,963.0	1.40	(1.18 - 1.65)		
	VTE (sensitivity definition)							
	SEASONIQUE	30,180	36	19,293.6	1.87	(1.31 - 2.58)	1.68	(1.10 - 2.58)
	Comparator	177,995	115	104,975.3	1.10	(0.90 - 1.31)		
	ATE							
	SEASONIQUE	30,180	12	19,299.6	0.62	(0.32 - 1.09)	1.57	(0.67 - 3.64)
	Comparator	177,993	37	104,978.8	0.35	(0.25 - 0.49)		
	Breast cancer							
	SEASONIQUE	30,180	16	19,301.7	0.83	(0.47 - 1.35)	1.05	(0.55 - 2.01)
	Comparator	177,996	59	105,000.8	0.56	(0.43 - 0.72)		
	Cervical cancer							
	SEASONIQUE	30,180	3	19,301.7	0.16	(0.03 - 0.45)	3.53	(0.84 - 14.81)
	Comparator	177,996	5	105,000.8	0.05	(0.02 - 0.11)		
	Endometrial cancer							
	SEASONIQUE	30,180	0	19,301.7	0.00	(0.00 - 0.16)	0.00	(0.00 - 0.00)
	Comparator	177,996	5	105,000.8	0.05	(0.02 - 0.11)		
	Ovarian cancer							
	SEASONIQUE	30,180	1	19,301.7	0.05	(0.00 - 0.29)	0.40	(0.02 - 7.15)
	Comparator	177,996	9	105,000.8	0.09	(0.04 - 0.16)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.6 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Requiring 6 Months Instead of 12 Months of Prior Continuous Enrolment (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Recent Exposure	**VTE (primary definition)**							
	SEASONIQUE	20,931	3	1,626.5	1.84	(0.38 - 5.39)	1.15	(0.24 - 5.59)
	Comparator	122,364	9	9,395.8	0.96	(0.44 - 1.82)		
	VTE (sensitivity definition)							
	SEASONIQUE	20,935	3	1,626.8	1.84	(0.38 - 5.39)	1.33	(0.27 - 6.45)
	Comparator	122,385	8	9,397.6	0.85	(0.37 - 1.68)		
	ATE							
	SEASONIQUE	20,956	0	1,628.5	0.00	(0.00 - 1.84)	0.00	(0.00 - 0.00)
	Comparator	122,462	3	9,403.9	0.32	(0.07 - 0.93)		
	Breast cancer							
	SEASONIQUE	20,966	3	1,629.4	1.84	(0.38 - 5.38)	3.53	(0.89 - 13.94)
	Comparator	122,493	5	9,406.6	0.53	(0.17 - 1.24)		
	Cervical cancer							
	SEASONIQUE	20,966	0	1,629.4	0.00	(0.00 - 1.84)	0.00	(0.00 - 0.00)
	Comparator	122,493	4	9,406.6	0.43	(0.12 - 1.09)		
	Endometrial cancer							
	SEASONIQUE	20,966	0	1,629.4	0.00	(0.00 - 1.84)	0.00	(0.00 - 0.00)
	Comparator	122,493	2	9,406.6	0.21	(0.03 - 0.77)		
	Ovarian cancer							
	SEASONIQUE	20,966	0	1,629.4	0.00	(0.00 - 1.84)	0.00	(0.00 - 0.00)
	Comparator	122,493	1	9,406.6	0.11	(0.00 - 0.59)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.6 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Requiring 6 Months Instead of 12 Months of Prior Continuous Enrolment (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Intermediate Exposure	**VTE (primary definition)**							
	SEASONIQUE	18,809	2	1,476.6	1.35	(0.16 - 4.89)	3.38	(0.33 - 34.85)
	Comparator	104,543	2	8,112.2	0.25	(0.03 - 0.89)		
	VTE (sensitivity definition)							
	SEASONIQUE	18,813	1	1,477.0	0.68	(0.02 - 3.77)	2.46	(0.04 - 156.15)
	Comparator	104,564	1	8,113.9	0.12	(0.00 - 0.69)		
	ATE							
	SEASONIQUE	18,836	0	1,478.9	0.00	(0.00 - 2.03)	0.00	(0.00 - 0.00)
	Comparator	104,639	3	8,119.8	0.37	(0.08 - 1.08)		
	Breast cancer							
	SEASONIQUE	18,846	2	1,479.7	1.35	(0.16 - 4.88)	2.23	(0.40 - 12.31)
	Comparator	104,673	4	8,122.7	0.49	(0.13 - 1.26)		
	Cervical cancer							
	SEASONIQUE	18,846	0	1,479.7	0.00	(0.00 - 2.02)	NA	NA
	Comparator	104,673	0	8,122.7	0.00	(0.00 - 0.37)		
	Endometrial cancer							
	SEASONIQUE	18,846	0	1,479.7	0.00	(0.00 - 2.02)	NA	NA
	Comparator	104,673	0	8,122.7	0.00	(0.00 - 0.37)		
	Ovarian cancer							
	SEASONIQUE	18,846	0	1,479.7	0.00	(0.00 - 2.02)	NA	NA
	Comparator	104,673	0	8,122.7	0.00	(0.00 - 0.37)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.6 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Requiring 6 Months Instead of 12 Months of Prior Continuous Enrolment (Sensitivity Analysis)

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Remote Exposure	**VTE (primary definition)**							
	SEASONIQUE	16,860	53	35,557.6	1.49	(1.12 - 1.95)	1.50	(1.04 - 2.16)
	Comparator	93,474	138	168,959.5	0.82	(0.69 - 0.96)		
	VTE (sensitivity definition)							
	SEASONIQUE	16,865	44	35,585.0	1.24	(0.90 - 1.66)	1.67	(1.12 - 2.50)
	Comparator	93,494	108	169,045.1	0.64	(0.52 - 0.77)		
	ATE							
	SEASONIQUE	16,890	37	35,724.5	1.04	(0.73 - 1.43)	1.64	(1.07 - 2.52)
	Comparator	93,563	104	169,268.2	0.61	(0.50 - 0.74)		
	Breast cancer							
	SEASONIQUE	16,899	42	35,796.3	1.17	(0.85 - 1.59)	1.26	(0.86 - 1.85)
	Comparator	93,599	132	169,518.9	0.78	(0.65 - 0.92)		
	Cervical cancer							
	SEASONIQUE	16,899	2	35,796.3	0.06	(0.01 - 0.20)	0.90	(0.19 - 4.39)
	Comparator	93,599	9	169,518.9	0.05	(0.02 - 0.10)		
	Endometrial cancer							
	SEASONIQUE	16,899	2	35,796.3	0.06	(0.01 - 0.20)	1.05	(0.19 - 5.85)
	Comparator	93,599	9	169,518.9	0.05	(0.02 - 0.10)		
	Ovarian cancer							
	SEASONIQUE	16,899	0	35,796.3	0.00	(0.00 - 0.08)	0.00	(0.00 - 0.00)
	Comparator	93,599	12	169,518.9	0.07	(0.04 - 0.12)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Age 12 to < 15	**VTE (primary definition)**							
	SEASONIQUE	260	1	195.0	5.13	(0.13 - 28.57)	NA	NA
	Comparator	1,021	0	565.1	0.00	(0.00 - 5.30)		
	VTE (sensitivity definition)							
	SEASONIQUE	260	0	196.3	0.00	(0.00 - 15.26)	NA	NA
	Comparator	1,021	0	565.1	0.00	(0.00 - 5.30)		
	ATE							
	SEASONIQUE	260	0	196.3	0.00	(0.00 - 15.26)	NA	NA
	Comparator	1,021	0	565.1	0.00	(0.00 - 5.30)		
	Breast cancer							
	SEASONIQUE	260	0	196.3	0.00	(0.00 - 15.26)	NA	NA
	Comparator	1,021	0	565.1	0.00	(0.00 - 5.30)		
	Cervical cancer							
	SEASONIQUE	260	0	196.3	0.00	(0.00 - 15.26)	NA	NA
	Comparator	1,021	0	565.1	0.00	(0.00 - 5.30)		
	Endometrial cancer							
	SEASONIQUE	260	0	196.3	0.00	(0.00 - 15.26)	NA	NA
	Comparator	1,021	0	565.1	0.00	(0.00 - 5.30)		
	Ovarian cancer							
	SEASONIQUE	260	0	196.3	0.00	(0.00 - 15.26)	NA	NA
	Comparator	1,021	0	565.1	0.00	(0.00 - 5.30)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Age ≥ 15 to ≤ 35	**VTE (primary definition)**							
	SEASONIQUE	17,677	15	11,341.2	1.32	(0.74 - 2.18)	2.05	(1.00 - 4.22)
	Comparator	54,887	23	32,501.4	0.71	(0.45 - 1.06)		
	VTE (sensitivity definition)							
	SEASONIQUE	17,681	14	11,344.9	1.23	(0.67 - 2.07)	3.04	(1.38 - 6.69)
	Comparator	54,888	15	32,504.0	0.46	(0.26 - 0.76)		
	ATE							
	SEASONIQUE	17,680	5	11,346.7	0.44	(0.14 - 1.03)	1.09	(0.35 - 3.37)
	Comparator	54,888	12	32,504.0	0.37	(0.19 - 0.64)		
	Breast cancer							
	SEASONIQUE	17,681	4	11,348.1	0.35	(0.10 - 0.90)	1.01	(0.23 - 4.38)
	Comparator	54,889	6	32,508.5	0.18	(0.07 - 0.40)		
	Cervical cancer							
	SEASONIQUE	17,681	2	11,348.1	0.18	(0.02 - 0.64)	NA	NA
	Comparator	54,889	0	32,508.5	0.00	(0.00 - 0.09)		
	Endometrial cancer							
	SEASONIQUE	17,681	0	11,348.1	0.00	(0.00 - 0.26)	NA	NA
	Comparator	54,889	0	32,508.5	0.00	(0.00 - 0.09)		
	Ovarian cancer							
	SEASONIQUE	17,681	1	11,348.1	0.09	(0.00 - 0.49)	NA	NA
	Comparator	54,889	0	32,508.5	0.00	(0.00 - 0.09)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Age > 35 to ≤ 50	**VTE (primary definition)**							
	SEASONIQUE	7,359	16	5,131.8	3.12	(1.78 - 5.06)	0.95	(0.52 - 1.75)
	Comparator	19,788	43	12,873.5	3.34	(2.42 - 4.50)		
	VTE (sensitivity definition)							
	SEASONIQUE	7,359	14	5,132.1	2.73	(1.49 - 4.58)	1.02	(0.53 - 1.99)
	Comparator	19,792	33	12,879.4	2.56	(1.76 - 3.60)		
	ATE							
	SEASONIQUE	7,360	7	5,133.0	1.36	(0.55 - 2.81)	1.30	(0.46 - 3.64)
	Comparator	19,794	14	12,871.1	1.09	(0.59 - 1.82)		
	Breast cancer							
	SEASONIQUE	7,360	11	5,136.0	2.14	(1.07 - 3.83)	1.68	(0.74 - 3.81)
	Comparator	19,794	18	12,887.7	1.40	(0.83 - 2.21)		
	Cervical cancer							
	SEASONIQUE	7,360	2	5,136.0	0.39	(0.05 - 1.41)	6.92	(0.63 - 75.73)
	Comparator	19,794	1	12,887.7	0.08	(0.00 - 0.43)		
	Endometrial cancer							
	SEASONIQUE	7,360	0	5,136.0	0.00	(0.00 - 0.58)	0.00	(0.00 - 0.00)
	Comparator	19,794	2	12,887.7	0.16	(0.02 - 0.56)		
	Ovarian cancer							
	SEASONIQUE	7,360	0	5,136.0	0.00	(0.00 - 0.58)	0.00	(0.00 - 0.00)
	Comparator	19,794	2	12,887.7	0.16	(0.02 - 0.56)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Age > 50	**VTE (primary definition)**							
	SEASONIQUE	291	3	199.7	15.02	(3.10 - 43.90)	3.39	(0.58 - 19.95)
	Comparator	879	2	522.2	3.83	(0.46 - 13.84)		
	VTE (sensitivity definition)							
	SEASONIQUE	291	2	199.9	10.00	(1.21 - 36.14)	2.03	(0.32 - 12.84)
	Comparator	882	2	524.3	3.81	(0.46 - 13.78)		
	ATE							
	SEASONIQUE	292	1	200.6	4.99	(0.13 - 27.78)	1.34	(0.10 - 17.56)
	Comparator	881	2	523.6	3.82	(0.46 - 13.80)		
	Breast cancer							
	SEASONIQUE	292	2	200.6	9.97	(1.21 - 36.01)	2.55	(0.44 - 14.74)
	Comparator	882	2	524.5	3.81	(0.46 - 13.78)		
	Cervical cancer							
	SEASONIQUE	292	0	200.6	0.00	(0.00 - 14.93)	NA	NA
	Comparator	882	0	524.5	0.00	(0.00 - 5.71)		
	Endometrial cancer							
	SEASONIQUE	292	0	200.6	0.00	(0.00 - 14.93)	NA	NA
	Comparator	882	0	524.5	0.00	(0.00 - 5.71)		
	Ovarian cancer							
	SEASONIQUE	292	0	200.6	0.00	(0.00 - 14.93)	NA	NA
	Comparator	882	0	524.5	0.00	(0.00 - 5.71)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Codes for Overweight/Obesity	**VTE (primary definition)**							
	SEASONIQUE	1,154	4	643.5	6.22	(1.69 - 15.91)	1.63	(0.43 - 6.12)
	Comparator	3,550	7	1,780.0	3.93	(1.58 - 8.10)		
	VTE (sensitivity definition)							
	SEASONIQUE	1,154	4	643.5	6.22	(1.69 - 15.91)	3.24	(0.78 - 13.37)
	Comparator	3,552	4	1,780.4	2.25	(0.61 - 5.75)		
	ATE							
	SEASONIQUE	1,155	1	644.7	1.55	(0.04 - 8.64)	NA	NA
	Comparator	3,552	0	1,781.4	0.00	(0.00 - 1.68)		
	Breast cancer							
	SEASONIQUE	1,156	1	645.3	1.55	(0.04 - 8.63)	NA	NA
	Comparator	3,553	0	1,781.6	0.00	(0.00 - 1.68)		
	Cervical cancer							
	SEASONIQUE	1,156	0	645.3	0.00	(0.00 - 4.64)	NA	NA
	Comparator	3,553	0	1,781.6	0.00	(0.00 - 1.68)		
	Endometrial cancer							
	SEASONIQUE	1,156	0	645.3	0.00	(0.00 - 4.64)	NA	NA
	Comparator	3,553	0	1,781.6	0.00	(0.00 - 1.68)		
	Ovarian cancer							
	SEASONIQUE	1,156	0	645.3	0.00	(0.00 - 4.64)	NA	NA
	Comparator	3,553	0	1,781.6	0.00	(0.00 - 1.68)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
No Codes for Overweight/Obesity	**VTE (primary definition)**							
	SEASONIQUE	24,433	31	16,224.1	1.91	(1.30 - 2.71)	1.38	(0.86 - 2.21)
	Comparator	73,025	61	44,682.3	1.37	(1.04 - 1.75)		
	VTE (sensitivity definition)							
	SEASONIQUE	24,437	26	16,229.8	1.60	(1.05 - 2.35)	1.48	(0.87 - 2.51)
	Comparator	73,031	46	44,692.4	1.03	(0.75 - 1.37)		
	ATE							
	SEASONIQUE	24,437	12	16,231.8	0.74	(0.38 - 1.29)	1.09	(0.52 - 2.31)
	Comparator	73,032	28	44,682.5	0.63	(0.42 - 0.91)		
	Breast cancer							
	SEASONIQUE	24,437	16	16,235.8	0.99	(0.56 - 1.60)	1.46	(0.73 - 2.93)
	Comparator	73,033	26	44,704.2	0.58	(0.38 - 0.85)		
	Cervical cancer							
	SEASONIQUE	24,437	4	16,235.8	0.25	(0.07 - 0.63)	11.99	(1.38 - 103.85)
	Comparator	73,033	1	44,704.2	0.02	(0.00 - 0.12)		
	Endometrial cancer							
	SEASONIQUE	24,437	0	16,235.8	0.00	(0.00 - 0.18)	0.00	(0.00 - 0.00)
	Comparator	73,033	2	44,704.2	0.04	(0.01 - 0.16)		
	Ovarian cancer							
	SEASONIQUE	24,437	1	16,235.8	0.06	(0.00 - 0.34)	1.52	(0.11 - 21.67)
	Comparator	73,033	2	44,704.2	0.04	(0.01 - 0.16)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Codes for Tobacco Use	**VTE (primary definition)**							
	SEASONIQUE	1,475	1	898.8	1.11	(0.03 - 6.20)	0.86	(0.06 - 12.99)
	Comparator	4,041	2	1,884.1	1.06	(0.13 - 3.83)		
	VTE (sensitivity definition)							
	SEASONIQUE	1,478	1	902.1	1.11	(0.03 - 6.18)	0.86	(0.06 - 13.04)
	Comparator	4,044	2	1,886.2	1.06	(0.13 - 3.83)		
	ATE							
	SEASONIQUE	1,478	2	900.3	2.22	(0.27 - 8.02)	NA	NA
	Comparator	4,043	0	1,886.6	0.00	(0.00 - 1.59)		
	Breast cancer							
	SEASONIQUE	1,478	0	902.3	0.00	(0.00 - 3.32)	0.00	(0.00 - 0.00)
	Comparator	4,044	2	1,886.8	1.06	(0.13 - 3.83)		
	Cervical cancer							
	SEASONIQUE	1,478	1	902.3	1.11	(0.03 - 6.17)	NA	NA
	Comparator	4,044	0	1,886.8	0.00	(0.00 - 1.59)		
	Endometrial cancer							
	SEASONIQUE	1,478	0	902.3	0.00	(0.00 - 3.32)	NA	NA
	Comparator	4,044	0	1,886.8	0.00	(0.00 - 1.59)		
	Ovarian cancer							
	SEASONIQUE	1,478	0	902.3	0.00	(0.00 - 3.32)	NA	NA
	Comparator	4,044	0	1,886.8	0.00	(0.00 - 1.59)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
No Codes for Tobacco Use	**VTE (primary definition)**							
	SEASONIQUE	24,112	34	15,968.9	2.13	(1.47 - 2.98)	1.43	(0.91 - 2.24)
	Comparator	72,534	66	44,578.1	1.48	(1.15 - 1.88)		
	VTE (sensitivity definition)							
	SEASONIQUE	24,113	29	15,971.2	1.82	(1.22 - 2.61)	1.65	(1.00 - 2.72)
	Comparator	72,539	48	44,586.5	1.08	(0.79 - 1.43)		
	ATE							
	SEASONIQUE	24,114	11	15,976.3	0.69	(0.34 - 1.23)	1.07	(0.48 - 2.36)
	Comparator	72,541	28	44,577.3	0.63	(0.42 - 0.91)		
	Breast cancer							
	SEASONIQUE	24,115	17	15,978.8	1.06	(0.62 - 1.70)	1.83	(0.93 - 3.59)
	Comparator	72,542	24	44,599.0	0.54	(0.34 - 0.80)		
	Cervical cancer							
	SEASONIQUE	24,115	3	15,978.8	0.19	(0.04 - 0.55)	10.43	(1.12 - 97.37)
	Comparator	72,542	1	44,599.0	0.02	(0.00 - 0.12)		
	Endometrial cancer							
	SEASONIQUE	24,115	0	15,978.8	0.00	(0.00 - 0.19)	0.00	(0.00 - 0.00)
	Comparator	72,542	2	44,599.0	0.04	(0.01 - 0.16)		
	Ovarian cancer							
	SEASONIQUE	24,115	1	15,978.8	0.06	(0.00 - 0.35)	1.53	(0.11 - 22.01)
	Comparator	72,542	2	44,599.0	0.04	(0.01 - 0.16)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Tobacco Users, Age > 35 years	**VTE (primary definition)**							
	SEASONIQUE	453	0	300.5	0.00	(0.00 - 9.97)	0.00	(0.00 - 0.00)
	Comparator	1,228	1	609.3	1.64	(0.04 - 9.14)		
	VTE (sensitivity definition)							
	SEASONIQUE	453	0	300.5	0.00	(0.00 - 9.97)	0.00	(0.00 - 0.00)
	Comparator	1,231	1	611.4	1.64	(0.04 - 9.11)		
	ATE							
	SEASONIQUE	453	2	298.5	6.70	(0.81 - 24.20)	NA	NA
	Comparator	1,231	0	611.6	0.00	(0.00 - 4.90)		
	Breast cancer							
	SEASONIQUE	453	0	300.5	0.00	(0.00 - 9.97)	0.00	(0.00 - 0.00)
	Comparator	1,231	1	611.6	1.64	(0.04 - 9.11)		
	Cervical cancer							
	SEASONIQUE	453	0	300.5	0.00	(0.00 - 9.97)	NA	NA
	Comparator	1,231	0	611.6	0.00	(0.00 - 4.90)		
	Endometrial cancer							
	SEASONIQUE	453	0	300.5	0.00	(0.00 - 9.97)	NA	NA
	Comparator	1,231	0	611.6	0.00	(0.00 - 4.90)		
	Ovarian cancer							
	SEASONIQUE	453	0	300.5	0.00	(0.00 - 9.97)	NA	NA
	Comparator	1,231	0	611.6	0.00	(0.00 - 4.90)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Tobacco Non-users, Age > 35 years	**VTE (primary definition)**							
	SEASONIQUE	7,197	19	5,030.9	3.78	(2.27 - 5.90)	1.11	(0.63 - 1.96)
	Comparator	19,439	44	12,786.4	3.44	(2.50 - 4.62)		
	VTE (sensitivity definition)							
	SEASONIQUE	7,197	16	5,031.5	3.18	(1.82 - 5.16)	1.13	(0.61 - 2.11)
	Comparator	19,443	34	12,792.2	2.66	(1.84 - 3.71)		
	ATE							
	SEASONIQUE	7,199	6	5,035.0	1.19	(0.44 - 2.59)	1.04	(0.35 - 3.12)
	Comparator	19,444	16	12,783.1	1.25	(0.72 - 2.03)		
	Breast cancer							
	SEASONIQUE	7,199	13	5,036.1	2.58	(1.37 - 4.41)	2.05	(0.97 - 4.30)
	Comparator	19,445	19	12,800.5	1.48	(0.89 - 2.32)		
	Cervical cancer							
	SEASONIQUE	7,199	2	5,036.1	0.40	(0.05 - 1.43)	6.98	(0.64 - 75.91)
	Comparator	19,445	1	12,800.5	0.08	(0.00 - 0.44)		
	Endometrial cancer							
	SEASONIQUE	7,199	0	5,036.1	0.00	(0.00 - 0.59)	0.00	(0.00 - 0.00)
	Comparator	19,445	2	12,800.5	0.16	(0.02 - 0.56)		
	Ovarian cancer							
	SEASONIQUE	7,199	0	5,036.1	0.00	(0.00 - 0.59)	0.00	(0.00 - 0.00)
	Comparator	19,445	2	12,800.5	0.16	(0.02 - 0.56)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Tobacco Users, 12 ≤ Age ≤ 35 years	**VTE (primary definition)**							
	SEASONIQUE	1,022	1	598.2	1.67	(0.04 - 9.31)	1.95	(0.09 - 41.49)
	Comparator	2,813	1	1,274.8	0.78	(0.02 - 4.37)		
	VTE (sensitivity definition)							
	SEASONIQUE	1,025	1	601.6	1.66	(0.04 - 9.26)	1.94	(0.09 - 41.72)
	Comparator	2,813	1	1,274.8	0.78	(0.02 - 4.37)		
	ATE							
	SEASONIQUE	1,025	0	601.8	0.00	(0.00 - 4.98)	NA	NA
	Comparator	2,812	0	1,275.0	0.00	(0.00 - 2.35)		
	Breast cancer							
	SEASONIQUE	1,025	0	601.8	0.00	(0.00 - 4.98)	0.00	(0.00 - 0.00)
	Comparator	2,813	1	1,275.2	0.78	(0.02 - 4.37)		
	Cervical cancer							
	SEASONIQUE	1,025	1	601.8	1.66	(0.04 - 9.26)	NA	NA
	Comparator	2,813	0	1,275.2	0.00	(0.00 - 2.35)		
	Endometrial cancer							
	SEASONIQUE	1,025	0	601.8	0.00	(0.00 - 4.98)	NA	NA
	Comparator	2,813	0	1,275.2	0.00	(0.00 - 2.35)		
	Ovarian cancer							
	SEASONIQUE	1,025	0	601.8	0.00	(0.00 - 4.98)	NA	NA
	Comparator	2,813	0	1,275.2	0.00	(0.00 - 2.35)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Tobacco Non-users, 12 ≤ Age ≤ 35 years	**VTE (primary definition)**							
	SEASONIQUE	16,915	15	10,937.9	1.37	(0.77 - 2.26)	2.17	(1.06 - 4.46)
	Comparator	53,095	22	31,791.8	0.69	(0.43 - 1.05)		
	VTE (sensitivity definition)							
	SEASONIQUE	16,916	13	10,939.7	1.19	(0.63 - 2.03)	3.10	(1.37 - 6.97)
	Comparator	53,096	14	31,794.3	0.44	(0.24 - 0.74)		
	ATE							
	SEASONIQUE	16,915	5	10,941.3	0.46	(0.15 - 1.07)	1.09	(0.35 - 3.38)
	Comparator	53,097	12	31,794.2	0.38	(0.20 - 0.66)		
	Breast cancer							
	SEASONIQUE	16,916	4	10,942.7	0.37	(0.10 - 0.94)	1.27	(0.27 - 5.93)
	Comparator	53,097	5	31,798.4	0.16	(0.05 - 0.37)		
	Cervical cancer							
	SEASONIQUE	16,916	1	10,942.7	0.09	(0.00 - 0.51)	NA	NA
	Comparator	53,097	0	31,798.4	0.00	(0.00 - 0.09)		
	Endometrial cancer							
	SEASONIQUE	16,916	0	10,942.7	0.00	(0.00 - 0.27)	NA	NA
	Comparator	53,097	0	31,798.4	0.00	(0.00 - 0.09)		
	Ovarian cancer							
	SEASONIQUE	16,916	1	10,942.7	0.09	(0.00 - 0.51)	NA	NA
	Comparator	53,097	0	31,798.4	0.00	(0.00 - 0.09)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Codes for Prior VTE or Anticoagulant Use	**VTE (primary definition)**							
	SEASONIQUE	96	1	55.5	18.02	(0.46 - 100.40)	1.09	(0.08 - 15.09)
	Comparator	237	2	104.4	19.16	(2.32 - 69.22)		
	VTE (sensitivity definition)							
	SEASONIQUE	98	1	58.2	17.18	(0.44 - 95.73)	1.08	(0.07 - 15.50)
	Comparator	242	2	106.7	18.75	(2.27 - 67.72)		
	ATE							
	SEASONIQUE	100	0	59.5	0.00	(0.00 - 50.36)	0.00	(0.00 - 0.00)
	Comparator	245	1	111.4	8.97	(0.23 - 50.00)		
	Breast cancer							
	SEASONIQUE	100	0	59.5	0.00	(0.00 - 50.36)	NA	NA
	Comparator	245	0	111.6	0.00	(0.00 - 26.85)		
	Cervical cancer							
	SEASONIQUE	100	0	59.5	0.00	(0.00 - 50.36)	NA	NA
	Comparator	245	0	111.6	0.00	(0.00 - 26.85)		
	Endometrial cancer							
	SEASONIQUE	100	0	59.5	0.00	(0.00 - 50.36)	NA	NA
	Comparator	245	0	111.6	0.00	(0.00 - 26.85)		
	Ovarian cancer							
	SEASONIQUE	100	0	59.5	0.00	(0.00 - 50.36)	NA	NA
	Comparator	245	0	111.6	0.00	(0.00 - 26.85)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
No Codes for Prior VTE or Anticoagulant Use	**VTE (primary definition)**							
	SEASONIQUE	25,491	34	16,812.2	2.02	(1.40 - 2.83)	1.41	(0.90 - 2.22)
	Comparator	76,338	66	46,357.9	1.42	(1.10 - 1.81)		
	VTE (sensitivity definition)							
	SEASONIQUE	25,493	29	16,815.1	1.72	(1.16 - 2.48)	1.63	(0.98 - 2.68)
	Comparator	76,341	48	46,366.1	1.04	(0.76 - 1.37)		
	ATE							
	SEASONIQUE	25,492	13	16,817.1	0.77	(0.41 - 1.32)	1.25	(0.59 - 2.63)
	Comparator	76,339	27	46,352.4	0.58	(0.38 - 0.85)		
	Breast cancer							
	SEASONIQUE	25,493	17	16,821.6	1.01	(0.59 - 1.62)	1.57	(0.79 - 3.10)
	Comparator	76,341	26	46,374.2	0.56	(0.37 - 0.82)		
	Cervical cancer							
	SEASONIQUE	25,493	4	16,821.6	0.24	(0.06 - 0.61)	12.02	(1.39 - 104.19)
	Comparator	76,341	1	46,374.2	0.02	(0.00 - 0.12)		
	Endometrial cancer							
	SEASONIQUE	25,493	0	16,821.6	0.00	(0.00 - 0.18)	0.00	(0.00 - 0.00)
	Comparator	76,341	2	46,374.2	0.04	(0.01 - 0.16)		
	Ovarian cancer							
	SEASONIQUE	25,493	1	16,821.6	0.06	(0.00 - 0.33)	1.52	(0.11 - 21.78)
	Comparator	76,341	2	46,374.2	0.04	(0.01 - 0.16)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Codes for Surgery/Injury During Follow-up	**VTE (primary definition)**							
	SEASONIQUE	868	1	545.1	1.83	(0.05 - 10.22)	0.53	(0.06 - 4.37)
	Comparator	2,391	6	1,497.8	4.01	(1.47 - 8.72)		
	VTE (sensitivity definition)							
	SEASONIQUE	869	1	545.4	1.83	(0.05 - 10.22)	0.79	(0.10 - 6.49)
	Comparator	2,394	4	1,500.7	2.67	(0.73 - 6.82)		
	ATE							
	SEASONIQUE	871	2	546.2	3.66	(0.44 - 13.23)	1.72	(0.32 - 9.06)
	Comparator	2,387	4	1,481.6	2.70	(0.74 - 6.91)		
	Breast cancer							
	SEASONIQUE	879	1	551.8	1.81	(0.05 - 10.10)	0.75	(0.09 - 6.30)
	Comparator	2,403	3	1,505.0	1.99	(0.41 - 5.83)		
	Cervical cancer							
	SEASONIQUE	879	1	551.8	1.81	(0.05 - 10.10)	2.38	(0.22 - 25.87)
	Comparator	2,403	1	1,505.0	0.66	(0.02 - 3.70)		
	Endometrial cancer							
	SEASONIQUE	879	0	551.8	0.00	(0.00 - 5.43)	0.00	(0.00 - 0.00)
	Comparator	2,403	2	1,505.0	1.33	(0.16 - 4.80)		
	Ovarian cancer							
	SEASONIQUE	879	1	551.8	1.81	(0.05 - 10.10)	NA	NA
	Comparator	2,403	0	1,505.0	0.00	(0.00 - 1.99)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3f.7 Relative Hazard of VTE, ATE, and Cancer Outcomes, Naïve and New Users, Current Use, by Subgroup

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
No Codes for Surgery/Injury During Follow-up	**VTE (primary definition)**							
	SEASONIQUE	24,719	34	16,322.6	2.08	(1.44 - 2.91)	1.49	(0.94 - 2.35)
	Comparator	74,184	62	44,964.5	1.38	(1.06 - 1.77)		
	VTE (sensitivity definition)							
	SEASONIQUE	24,722	29	16,327.9	1.78	(1.19 - 2.55)	1.68	(1.01 - 2.79)
	Comparator	74,189	46	44,972.1	1.02	(0.75 - 1.36)		
	ATE							
	SEASONIQUE	24,721	11	16,330.4	0.67	(0.34 - 1.21)	1.13	(0.50 - 2.53)
	Comparator	74,197	24	44,982.3	0.53	(0.34 - 0.79)		
	Breast cancer							
	SEASONIQUE	24,714	16	16,329.2	0.98	(0.56 - 1.59)	1.70	(0.83 - 3.48)
	Comparator	74,183	23	44,980.8	0.51	(0.32 - 0.77)		
	Cervical cancer							
	SEASONIQUE	24,714	3	16,329.2	0.18	(0.04 - 0.54)	NA	NA
	Comparator	74,183	0	44,980.8	0.00	(0.00 - 0.07)		
	Endometrial cancer							
	SEASONIQUE	24,714	0	16,329.2	0.00	(0.00 - 0.18)	NA	NA
	Comparator	74,183	0	44,980.8	0.00	(0.00 - 0.07)		
	Ovarian cancer							
	SEASONIQUE	24,714	0	16,329.2	0.00	(0.00 - 0.18)	0.00	(0.00 - 0.00)
	Comparator	74,183	2	44,980.8	0.04	(0.01 - 0.16)		

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable; PS, propensity score; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching; therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 3g. Relative Hazard of VTE, Naïve and New Users, Restricted to Those Without a History of Any Cancer in Baseline

		N	No. of Cases	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator	95% CI
Current Exposure	**VTE (primary definition)**							
	SEASONIQUE	25,424	35	16,768.3	2.09	(1.45 - 2.90)	1.46	(0.93 - 2.30)
	Comparator	76,110	65	46,240.7	1.41	(1.08 - 1.79)		
Recent Exposure	**VTE (primary definition)**							
	SEASONIQUE	17,980	4	1,393.4	2.87	(0.78 - 7.35)	3.78	(0.71 - 19.99)
	Comparator	54,709	3	4,218.0	0.71	(0.15 - 2.08)		
Intermediate Exposure	**VTE (primary definition)**							
	SEASONIQUE	16,064	2	1,255.0	1.59	(0.19 - 5.76)	2.42	(0.39 - 15.16)
	Comparator	47,068	2	3,658.9	0.55	(0.07 - 1.97)		
Remote Exposure	**VTE (primary definition)**							
	SEASONIQUE	14,155	41	26,320.7	1.56	(1.12 - 2.11)	1.66	(1.12 - 2.45)
	Comparator	42,303	74	77,820.8	0.95	(0.75 - 1.19)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 4. Counts of Algorithm-identified and Adjudicated VTE Cases Within the Matched Cohorts

Current Exposure	Algorithm-identified (N)	Chart Received with Sufficient Information N (%)	Adjudicated (N)	Positive Predictive Value* (95% CI)
VTE	123	89 (72.4%)	68	76.4% (66.2% - 84.8%)
SEASONIQUE	43	33 (76.7%)	28	84.8% (68.1% - 94.9%)
Comparator	80	56 (70.0%)	40	71.4% (57.8% - 82.7%)
Anticoagulant Dispensing	25	15 (60.0%)	6	40.0% (16.3% - 67.7%)
SEASONIQUE	5	3 (60.0%)	0	00.0% (00.0% - 00.0%)
Comparator	20	12 (60.0%)	6	50.0% (21.1% - 78.9%)

Abbreviations: CI, confidence interval; VTE, venous thromboembolism.

*The number of adjudicated cases divided by the number of charts received with sufficient information.

Table 5a. Comparison of Fertility Rates in Discontinuers

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Naïve and New Users	SEASONIQUE	11,223	484	8,828.7	54.82	(50.05 - 59.93)	0.77	(0.69 - 0.85)
	Comparator	19,479	959	13,839.3	69.30	(64.98 - 73.82)		
Naïve Users	SEASONIQUE	7,227	320	6,382.3	50.14	(44.80 - 55.94)	0.74	(0.64 - 0.84)
	Comparator	13,215	687	10,270.7	66.89	(61.98 - 72.08)		
New Users	SEASONIQUE	3,996	164	2,446.4	67.04	(57.17 - 78.12)	0.84	(0.69 - 1.03)
	Comparator	6,264	272	3,568.5	76.22	(67.43 - 85.84)		
Re-starters	SEASONIQUE	3,496	139	1,865.8	74.50	(62.63 - 87.97)	0.76	(0.61 - 0.93)
	Comparator	6,363	279	2,894.3	96.40	(85.42 - 108.40)		
Switchers	SEASONIQUE	2,719	105	1,546.2	67.91	(55.54 - 82.21)	0.63	(0.50 - 0.79)
	Comparator	4,731	248	2,344.3	105.79	(93.03 - 119.81)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 5b. Comparison of Fertility Rates in Discontinuers, Sensitivity Analyses

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Using 60-day Gaps for Seasonique and 28-day Gaps for Comparators								
Naïve and New Users	SEASONIQUE	9,658	451	8,186.3	55.09	(50.12 - 60.42)	0.77	(0.69 - 0.86)
	Comparator	16,233	974	13,921.7	69.96	(65.64 - 74.50)		
Naïve Users	SEASONIQUE	6,331	297	5,994.0	49.55	(44.07 - 55.52)	0.74	(0.65 - 0.85)
	Comparator	10,967	683	10,388.2	65.75	(60.91 - 70.87)		
New Users	SEASONIQUE	3,327	154	2,192.2	70.25	(59.59 - 82.26)	0.83	(0.69 - 1.02)
	Comparator	5,266	291	3,533.5	82.35	(73.16 - 92.38)		
Re-starters	SEASONIQUE	1,674	82	1,098.8	74.62	(59.35 - 92.63)	0.79	(0.62 - 1.02)
	Comparator	4,221	241	2,466.7	97.70	(85.76 - 110.85)		
Switchers	SEASONIQUE	2,175	92	1,401.5	65.64	(52.92 - 80.51)	0.59	(0.47 - 0.75)
	Comparator	3,594	260	2,367.5	109.82	(96.88 - 124.01)		
Not Censoring Comparators with Continuous Use								
Naïve and New Users	SEASONIQUE	11,239	484	8,836.9	54.77	(50.00 - 59.87)	0.76	(0.68 - 0.85)
	Comparator	19,674	974	13,993.7	69.60	(65.30 - 74.11)		
Naïve Users	SEASONIQUE	7,228	320	6,383.7	50.13	(44.79 - 55.93)	0.73	(0.64 - 0.83)
	Comparator	13,353	699	10,389.1	67.28	(62.39 - 72.46)		
New Users	SEASONIQUE	4,011	164	2,453.2	66.85	(57.01 - 77.90)	0.84	(0.69 - 1.03)
	Comparator	6,321	275	3,604.6	76.29	(67.54 - 85.86)		
Re-starters	SEASONIQUE	3,504	139	1,868.1	74.41	(62.55 - 87.86)	0.76	(0.62 - 0.94)
	Comparator	6,408	280	2,940.2	95.23	(84.40 - 107.07)		
Switchers	SEASONIQUE	2,728	105	1,549.3	67.77	(55.43 - 82.04)	0.64	(0.51 - 0.80)
	Comparator	4,810	251	2,414.4	103.96	(91.50 - 117.65)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 5b. Comparison of Fertility Rates in Discontinuers, Sensitivity Analyses

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Restricted to Those with at Least 24 Months of Prior Continuous Enrolment								
Naïve Users	SEASONIQUE	4,001	156	3,808.7	40.96	(34.78 - 47.91)	0.75	(0.63 - 0.89)
	Comparator	14,151	619	11,290.2	54.83	(50.59 - 59.32)		
Restricted to Those with > 24 to ≤ 36 Months of Prior Continuous Enrolment								
Naïve Users	SEASONIQUE	1,074	48	944.6	50.81	(37.47 - 67.37)	0.74	(0.54 - 1.02)
	Comparator	4,130	205	3,112.7	65.86	(57.15 - 75.52)		
Restricted to Those with a Minimum of 36 Months of Prior Continuous Enrolment								
Naïve Users	SEASONIQUE	2,449	76	2,473.5	30.73	(24.21 - 38.46)	0.74	(0.58 - 0.96)
	Comparator	9,477	326	7,751.8	42.05	(37.61 - 46.88)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 5c. Comparison of Fertility Rates in Discontinuers, Subgroup Analyses

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Age 12 to < 15								
Naïve and New Users	SEASONIQUE	108	1	100.2	9.98	(0.25 - 55.62)	0.97	(0.10 - 9.91)
	Comparator	242	2	177.6	11.26	(1.36 - 40.68)		
Naïve Users	SEASONIQUE	98	0	91.5	0.00	(0.00 - 32.75)	0.00	NA
	Comparator	227	2	170.2	11.75	(1.42 - 42.45)		
New Users	SEASONIQUE	10	1	8.7	115.04	(2.91 - 640.96)	NA	NA
	Comparator	15	0	7.4	0.00	(0.00 - 402.72)		
Re-starters	SEASONIQUE	9	0	6.2	0.00	(0.00 - 482.23)	NA	NA
	Comparator	8	0	1.7	0.00	(0.00 - 1790.82)		
Switchers	SEASONIQUE	15	0	6.9	0.00	(0.00 - 435.76)	NA	NA
	Comparator	20	0	15.2	0.00	(0.00 - 196.73)		
Age ≥ 15 to ≤ 35								
Naïve and New Users	SEASONIQUE	8,183	427	5,755.2	74.19	(67.32 - 81.58)	0.78	(0.70 - 0.88)
	Comparator	14,792	853	9,443.0	90.33	(84.37 - 96.60)		
Naïve Users	SEASONIQUE	5,167	285	3,960.2	71.97	(63.85 - 80.82)	0.78	(0.68 - 0.90)
	Comparator	9,976	609	6,907.6	88.16	(81.30 - 95.45)		
New Users	SEASONIQUE	3,016	142	1,794.9	79.11	(66.63 - 93.25)	0.80	(0.65 - 0.98)
	Comparator	4,816	244	2,535.4	96.24	(84.54 - 109.10)		
Re-starters	SEASONIQUE	2,519	133	1,275.1	104.30	(87.33 - 123.61)	0.83	(0.67 - 1.02)
	Comparator	4,704	244	2,000.6	121.96	(107.14 - 138.26)		
Switchers	SEASONIQUE	2,013	96	985.3	97.43	(78.92 - 118.98)	0.67	(0.53 - 0.85)
	Comparator	3,788	229	1,656.2	138.27	(120.94 - 157.39)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 5c. Comparison of Fertility Rates in Discontinuers, Subgroup Analyses

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Age > 35 to < 46								
Naïve and New Users	SEASONIQUE	2,932	56	2,973.4	18.83	(14.23 - 24.46)	0.74	(0.54 - 1.03)
	Comparator	4,445	104	4,218.6	24.65	(20.14 - 29.87)		
Naïve Users	SEASONIQUE	1,962	35	2,330.6	15.02	(10.46 - 20.89)	0.64	(0.43 - 0.95)
	Comparator	3,012	76	3,192.9	23.80	(18.75 - 29.79)		
New Users	SEASONIQUE	970	21	642.8	32.67	(20.22 - 49.94)	1.10	(0.61 - 1.97)
	Comparator	1,433	28	1,025.7	27.30	(18.14 - 39.45)		
Re-starters	SEASONIQUE	968	6	584.4	10.27	(3.77 - 22.35)	0.25	(0.11 - 0.58)
	Comparator	1,651	35	892.0	39.24	(27.33 - 54.57)		
Switchers	SEASONIQUE	691	9	553.9	16.25	(7.43 - 30.84)	0.57	(0.26 - 1.25)
	Comparator	923	19	672.8	28.24	(17.00 - 44.10)		
Codes for Overweight/Obesity								
Naïve and New Users	SEASONIQUE	509	27	419.3	64.39	(42.43 - 93.68)	1.21	(0.72 - 2.02)
	Comparator	857	32	607.8	52.65	(36.01 - 74.33)		
Naïve Users	SEASONIQUE	358	21	324.5	64.72	(40.06 - 98.94)	1.16	(0.65 - 2.07)
	Comparator	580	25	440.7	56.73	(36.71 - 83.74)		
New Users	SEASONIQUE	151	6	94.9	63.25	(23.21 - 137.66)	1.13	(0.36 - 3.50)
	Comparator	277	7	167.1	41.90	(16.84 - 86.32)		
Re-starters	SEASONIQUE	159	2	82.0	24.39	(2.95 - 88.12)	0.35	(0.08 - 1.61)
	Comparator	279	9	136.5	65.94	(30.15 - 125.18)		
Switchers	SEASONIQUE	117	2	65.0	30.78	(3.73 - 111.20)	0.25	(0.05 - 1.12)
	Comparator	199	11	97.0	113.35	(56.59 - 202.82)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 5c. Comparison of Fertility Rates in Discontinuers, Subgroup Analyses

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
No Codes for Overweight/Obesity								
Naïve and New Users	SEASONIQUE	10,714	457	8,409.4	54.34	(49.48 - 59.56)	0.75	(0.67 - 0.84)
	Comparator	18,622	927	13,231.5	70.06	(65.62 - 74.72)		
Naïve Users	SEASONIQUE	6,869	299	6,057.8	49.36	(43.92 - 55.28)	0.72	(0.63 - 0.82)
	Comparator	12,635	662	9,830.0	67.34	(62.31 - 72.68)		
New Users	SEASONIQUE	3,845	158	2,351.5	67.19	(57.12 - 78.52)	0.83	(0.68 - 1.02)
	Comparator	5,987	265	3,401.5	77.91	(68.81 - 87.87)		
Re-starters	SEASONIQUE	3,337	137	1,783.8	76.80	(64.48 - 90.79)	0.77	(0.62 - 0.95)
	Comparator	6,084	270	2,757.8	97.90	(86.57 - 110.31)		
Switchers	SEASONIQUE	2,602	103	1,481.2	69.54	(56.76 - 84.34)	0.65	(0.51 - 0.81)
	Comparator	4,532	237	2,247.2	105.46	(92.46 - 119.78)		
Codes for Tobacco Use								
Naïve and New Users	SEASONIQUE	593	25	434.0	57.60	(37.28 - 85.03)	0.91	(0.56 - 1.49)
	Comparator	993	41	655.7	62.53	(44.87 - 84.82)		
Naïve Users	SEASONIQUE	386	14	306.3	45.70	(24.98 - 76.68)	0.81	(0.43 - 1.54)
	Comparator	615	26	464.0	56.04	(36.61 - 82.11)		
New Users	SEASONIQUE	207	11	127.7	86.15	(43.00 - 154.14)	1.08	(0.48 - 2.44)
	Comparator	378	15	191.8	78.22	(43.78 - 129.02)		
Re-starters	SEASONIQUE	188	6	80.3	74.69	(27.41 - 162.56)	0.66	(0.26 - 1.70)
	Comparator	407	16	164.2	97.45	(55.70 - 158.26)		
Switchers	SEASONIQUE	174	3	101.2	29.63	(6.11 - 86.60)	0.79	(0.19 - 3.39)
	Comparator	237	4	101.2	39.53	(10.77 - 101.21)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 5c. Comparison of Fertility Rates in Discontinuers, Subgroup Analyses

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
No Codes for Tobacco Use								
Naïve and New Users	SEASONIQUE	10,630	459	8,394.7	54.68	(49.79 - 59.92)	0.76	(0.68 - 0.85)
	Comparator	18,486	918	13,183.5	69.63	(65.20 - 74.29)		
Naïve Users	SEASONIQUE	6,841	306	6,076.0	50.36	(44.88 - 56.33)	0.73	(0.64 - 0.84)
	Comparator	12,600	661	9,806.8	67.40	(62.36 - 72.74)		
New Users	SEASONIQUE	3,789	153	2,318.7	65.99	(55.94 - 77.31)	0.83	(0.68 - 1.02)
	Comparator	5,886	257	3,376.8	76.11	(67.09 - 86.00)		
Re-starters	SEASONIQUE	3,308	133	1,785.4	74.49	(62.37 - 88.28)	0.76	(0.61 - 0.94)
	Comparator	5,956	263	2,730.1	96.33	(85.04 - 108.71)		
Switchers	SEASONIQUE	2,545	102	1,444.9	70.59	(57.56 - 85.69)	0.63	(0.50 - 0.80)
	Comparator	4,494	244	2,243.1	108.78	(95.56 - 123.32)		
Tobacco Users, Age > 35 years								
Naïve and New Users	SEASONIQUE	165	3	165.6	18.11	(3.74 - 52.93)	0.89	(0.21 - 3.76)
	Comparator	234	4	185.2	21.60	(5.88 - 55.30)		
Naïve Users	SEASONIQUE	118	3	135.7	22.11	(4.56 - 64.61)	NA	NA
	Comparator	153	0	145.4	0.00	(0.00 - 20.60)		
New Users	SEASONIQUE	47	0	29.9	0.00	(0.00 - 100.05)	0.00	NA
	Comparator	81	4	39.8	100.52	(27.39 - 257.36)		
Re-starters	SEASONIQUE	57	1	24.8	40.27	(1.02 - 224.40)	0.65	(0.07 - 5.71)
	Comparator	89	2	44.7	44.71	(5.41 - 161.49)		
Switchers	SEASONIQUE	53	1	37.0	27.06	(0.69 - 150.76)	1.66	(0.06 - 42.80)
	Comparator	46	1	34.1	29.35	(0.74 - 163.54)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 5c. Comparison of Fertility Rates in Discontinuers, Subgroup Analyses

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Tobacco Non-users, Age > 35 years								
Naïve and New Users	SEASONIQUE	2,767	53	2,807.7	18.88	(14.14 - 24.69)	0.74	(0.53 - 1.03)
	Comparator	4,211	100	4,033.4	24.79	(20.17 - 30.15)		
Naïve Users	SEASONIQUE	1,844	32	2,194.9	14.58	(9.97 - 20.58)	0.59	(0.39 - 0.90)
	Comparator	2,859	76	3,047.5	24.94	(19.65 - 31.21)		
New Users	SEASONIQUE	923	21	612.8	34.27	(21.21 - 52.38)	1.30	(0.71 - 2.37)
	Comparator	1,352	24	985.9	24.34	(15.60 - 36.22)		
Re-starters	SEASONIQUE	911	5	559.6	8.93	(2.90 - 20.85)	0.22	(0.09 - 0.56)
	Comparator	1,562	33	847.3	38.95	(26.81 - 54.70)		
Switchers	SEASONIQUE	638	8	517.0	15.47	(6.68 - 30.49)	0.55	(0.24 - 1.25)
	Comparator	877	18	638.8	28.18	(16.70 - 44.54)		
Tobacco Users, 12 ≤ Age ≤ 35 years								
Naïve and New Users	SEASONIQUE	428	22	268.4	81.97	(51.37 - 124.10)	1.01	(0.60 - 1.70)
	Comparator	759	37	470.5	78.64	(55.37 - 108.39)		
Naïve Users	SEASONIQUE	268	11	170.7	64.46	(32.18 - 115.34)	0.76	(0.38 - 1.55)
	Comparator	462	26	318.6	81.62	(53.32 - 119.59)		
New Users	SEASONIQUE	160	11	97.7	112.54	(56.18 - 201.36)	1.51	(0.65 - 3.51)
	Comparator	297	11	152.0	72.39	(36.13 - 129.52)		
Re-starters	SEASONIQUE	131	5	55.5	90.08	(29.25 - 210.22)	0.70	(0.25 - 1.98)
	Comparator	318	14	119.4	117.21	(64.08 - 196.65)		
Switchers	SEASONIQUE	121	2	64.3	31.11	(3.77 - 112.40)	0.77	(0.14 - 4.29)
	Comparator	191	3	67.1	44.69	(9.22 - 130.61)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 5c. Comparison of Fertility Rates in Discontinuers, Subgroup Analyses

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
Tobacco Non-users, 12 ≤ Age ≤ 35 years								
Naïve and New Users	SEASONIQUE	7,863	406	5,586.9	72.67	(65.77 - 80.09)	0.77	(0.69 - 0.87)
	Comparator	14,275	818	9,150.1	89.40	(83.38 - 95.74)		
Naïve Users	SEASONIQUE	4,997	274	3,881.0	70.60	(62.49 - 79.47)	0.78	(0.67 - 0.90)
	Comparator	9,741	585	6,759.2	86.55	(79.68 - 93.85)		
New Users	SEASONIQUE	2,866	132	1,705.9	77.38	(64.74 - 91.76)	0.77	(0.62 - 0.95)
	Comparator	4,534	233	2,390.9	97.45	(85.34 - 110.80)		
Re-starters	SEASONIQUE	2,397	128	1,225.8	104.42	(87.11 - 124.16)	0.83	(0.67 - 1.03)
	Comparator	4,394	230	1,882.8	122.16	(106.88 - 139.00)		
Switchers	SEASONIQUE	1,907	94	927.9	101.30	(81.86 - 123.97)	0.68	(0.54 - 0.87)
	Comparator	3,617	226	1,604.3	140.87	(123.10 - 160.48)		
Codes for Prior VTE or Anticoagulant Use								
Naïve and New Users	SEASONIQUE	46	2	30.9	64.65	(7.83 - 233.54)	1.22	(0.16 - 9.29)
	Comparator	43	3	32.3	92.91	(19.16 - 271.51)		
Naïve Users	SEASONIQUE	33	2	23.1	86.49	(10.47 - 312.43)	2.52	(0.33 - 19.13)
	Comparator	31	2	29.6	67.56	(8.18 - 244.06)		
New Users	SEASONIQUE	13	0	7.8	0.00	(0.00 - 383.52)	0.00	NA
	Comparator	12	1	2.7	371.95	(9.42 - 2072.34)		
Re-starters	SEASONIQUE	12	1	9.3	107.68	(2.73 - 599.95)	NA	NA
	Comparator	22	0	5.7	0.00	(0.00 - 521.54)		
Switchers	SEASONIQUE	10	0	7.8	0.00	(0.00 - 385.28)	NA	NA
	Comparator	9	0	1.0	0.00	(0.00 - 3047.89)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 5c. Comparison of Fertility Rates in Discontinuers, Subgroup Analyses

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
No Codes for Prior VTE or Anticoagulant Use								
Naïve and New Users	SEASONIQUE	11,177	482	8,797.8	54.79	(50.00 - 59.90)	0.76	(0.69 - 0.85)
	Comparator	19,436	956	13,807.0	69.24	(64.92 - 73.77)		
Naïve Users	SEASONIQUE	7,194	318	6,359.2	50.01	(44.66 - 55.82)	0.73	(0.64 - 0.84)
	Comparator	13,184	685	10,241.1	66.89	(61.97 - 72.09)		
New Users	SEASONIQUE	3,983	164	2,438.6	67.25	(57.35 - 78.37)	0.85	(0.70 - 1.03)
	Comparator	6,252	271	3,565.9	76.00	(67.22 - 85.61)		
Re-starters	SEASONIQUE	3,484	138	1,856.5	74.33	(62.45 - 87.82)	0.75	(0.61 - 0.92)
	Comparator	6,341	279	2,888.5	96.59	(85.59 - 108.61)		
Switchers	SEASONIQUE	2,709	105	1,538.4	68.25	(55.82 - 82.63)	0.63	(0.50 - 0.79)
	Comparator	4,722	248	2,343.3	105.83	(93.07 - 119.86)		
Codes for Surgery/Injury During Follow-up								
Naïve and New Users	SEASONIQUE	115	0	284.1	0.00	(0.00 - 10.54)	0.00	NA
	Comparator	156	6	405.4	14.80	(5.43 - 32.21)		
Naïve Users	SEASONIQUE	81	0	210.7	0.00	(0.00 - 14.22)	0.00	NA
	Comparator	130	5	351.0	14.24	(4.62 - 33.24)		
New Users	SEASONIQUE	34	0	73.5	0.00	(0.00 - 40.77)	0.00	NA
	Comparator	26	1	54.4	18.40	(0.47 - 102.51)		
Re-starters	SEASONIQUE	14	0	38.0	0.00	(0.00 - 78.82)	NA	NA
	Comparator	34	0	93.7	0.00	(0.00 - 31.98)		
Switchers	SEASONIQUE	13	0	28.2	0.00	(0.00 - 106.07)	NA	NA
	Comparator	31	1	87.0	11.50	(0.29 - 64.05)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 5c. Comparison of Fertility Rates in Discontinuers, Subgroup Analyses

		N	No. of Pregnancies	Person-years	IR/1,000 Person-years	95% CI	HR SEASONIQUE vs. Comparator Adjusted for PS	95% CI
No Codes for Surgery/Injury During Follow-up								
Naïve and New Users	SEASONIQUE	11,108	484	8,544.6	56.64	(51.71 - 61.92)	0.77	(0.69 - 0.86)
	Comparator	19,323	953	13,433.9	70.94	(66.51 - 75.59)		
Naïve Users	SEASONIQUE	7,146	320	6,171.6	51.85	(46.32 - 57.85)	0.74	(0.65 - 0.85)
	Comparator	13,085	682	9,919.7	68.75	(63.69 - 74.11)		
New Users	SEASONIQUE	3,962	164	2,372.9	69.11	(58.94 - 80.54)	0.86	(0.70 - 1.04)
	Comparator	6,238	271	3,514.2	77.12	(68.21 - 86.87)		
Re-starters	SEASONIQUE	3,482	139	1,827.7	76.05	(63.93 - 89.80)	0.75	(0.61 - 0.92)
	Comparator	6,329	279	2,800.6	99.62	(88.27 - 112.02)		
Switchers	SEASONIQUE	2,706	105	1,517.9	69.17	(56.58 - 83.74)	0.62	(0.50 - 0.78)
	Comparator	4,700	247	2,257.3	109.42	(96.20 - 123.96)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PS, propensity score; NA, not applicable; VTE, venous thromboembolism.

Note: Analyses within user group effectively break the matching therefore the HRs presented are propensity score-adjusted not matched HRs.

Table 6a. Delayed Pregnancy Detection: Comparison of Time Between Estimated Start of Pregnancy and First Prenatal Encounter, Current Exposure

		No. of Pregnancies	Mean Time Between Conception and First Encounter	SD	P-value* for Difference in Mean	Median Time Between Conception and First Encounter	Min, 5th Percentile, IQR, 95th Percentile, Max	P-value for Wilcoxon Rank Sum Test
Naïve and New Users	SEASONIQUE	214	74.7	40.1	0.50	64.5	20, 29, 45-103, 119, 360	0.24
	Comparator	848	72.5	52.5		61.0	-90, 25, 42-102, 119, 560	
Naïve Users	SEASONIQUE	113	74.4	33.0	0.90	65.0	20, 30, 49-103, 119, 161	0.25
	Comparator	597	73.9	55.1		62.0	-90, 25, 43-104, 119, 560	
New Users	SEASONIQUE	101	75.0	47.0	0.28	63.0	21, 28, 43-101, 119, 360	0.47
	Comparator	251	69.1	45.5		60.0	-89, 25, 40-99, 119, 426	
Re-starters	SEASONIQUE	50	72.5	39.6	0.77	61.0	22, 23, 41-102, 129, 218	0.77
	Comparator	267	74.4	45.2		66.0	16, 28, 45-103, 119, 522	
Switchers	SEASONIQUE	59	76.3	46.9	0.50	60.0	10, 26, 44-106, 150, 310	0.53
	Comparator	248	71.7	50.3		58.0	-88, 30, 43-102, 119, 478	

Abbreviations: IQR, interquartile range; SD, standard deviation.

*T-test with Satterthwaite rather than pooled p-value due to unequal variances.

Notes: Negative minimum values indicate measurement error in the estimated pregnancy start; large maximum values may be due to prenatal care codes from subsequent pregnancies.

Table 6b. Delayed Pregnancy Detection: Comparison of Time Between Estimated Start of Pregnancy and First Prenatal Encounter, Current Exposure, in Sensitivity Analyses of Naïve and New Users

		No. of Pregnancies	Mean Time Between Conception and First Encounter	SD	P-value* for Difference in Mean	Median Time Between Conception and First Encounter	Min, 5th Percentile, IQR, 95th Percentile, Max	P-value for Wilcoxon Rank Sum Test
Using 60-day Gaps for Seasonique and 28-day Gaps for Comparators	SEASONIQUE	286	71.7	39.2	0.72	62.0	20, 29, 44-96, 119, 360	0.45
	Comparator	1,092	72.8	74.0		60.0	-90, 26, 42-98, 119, 1419	
Not Censoring Comparators with Continuous Use	SEASONIQUE	214	74.7	40.1	0.49	64.5	20, 29, 45-103, 119, 360	0.23
	Comparator	870	72.4	52.1		61.0	-90, 25, 42-102, 119, 560	
Restricted to Those with at Least 24 Months of Prior Continuous Enrolment	SEASONIQUE	53	68.3	30.3	0.39	62.0	20, 29, 41-91, 119, 119	0.79
	Comparator	291	72.8	52.6		61.0	-90, 26, 43-105, 122, 560	
Restricted to Those with > 24 to ≤ 36 Months of Prior Continuous Enrolment	SEASONIQUE	17	66.0	28.2	1.00	62.0	29, 29, 40-79, 119, 119	0.97
	Comparator	79	66.0	35.3		59.0	-83, 24, 42-97, 119, 147	
Restricted to Those with a Minimum of 36 Months of Prior Continuous Enrolment	SEASONIQUE	23	64.0	29.3	0.13	55.0	26, 29, 41-91, 109, 119	0.33
	Comparator	158	76.2	61.6		62.0	-90, 24, 44-108, 128, 560	

Abbreviations: IQR, interquartile range; SD, standard deviation.

*T-test with Satterthwaite rather than pooled p-value due to unequal variances.

Notes: Negative minimum values indicate measurement error in the estimated pregnancy start; large maximum values may be due to prenatal care codes from subsequent pregnancies.

Table 6c. Delayed Pregnancy Detection: Comparison of Time Between Estimated Start of Pregnancy and First Prenatal Encounter, Current Exposure, in Subgroup Analyses of Naïve and New Users

		No. of Pregnancies	Mean Time Between Conception and First Encounter	SD	P-Value* for Difference in Mean	Median Time Between Conception and First Encounter	Min, 5th Percentile, IQR, 95th Percentile, Max	P-Value for Wilcoxon Rank Sum Test
Age 12 to ≤ 35	SEASONIQUE	192	74.2	40.9	0.70	63.5	20, 29, 45-103, 119, 360	0.38
	Comparator	736	72.8	53.8		61.0	-90, 26, 42-101, 119, 560	
Age > 35 to < 46	SEASONIQUE	22	78.7	32.7	0.29	75.0	30, 39, 45-116, 119, 133	0.25
	Comparator	112	70.0	43.0		60.5	-87, 24, 42-106, 119, 268	
Codes for Overweight/Obesity	SEASONIQUE	11	76.5	43.1	0.37	66.0	28, 28, 39-118, 158, 158	0.45
	Comparator	36	63.4	33.7		64.0	-29, 25, 39-89, 117, 117	
No Codes for Overweight/Obesity	SEASONIQUE	203	74.6	40.0	0.61	64.0	20, 29, 45-103, 119, 360	0.28
	Comparator	812	72.9	53.1		61.0	-90, 25, 43-102, 119, 560	
Codes for Tobacco Use	SEASONIQUE	20	84.2	32.3	0.30	82.0	28, 36, 62-108, 140, 161	0.03
	Comparator	50	71.1	72.4		52.5	-83, 24, 37-95, 119, 484	
No Codes for Tobacco Use	SEASONIQUE	194	73.7	40.7	0.74	63.0	20, 29, 44-103, 119, 360	0.60
	Comparator	798	72.6	51.0		62.0	-90, 25, 43-102, 119, 560	
Tobacco Users, Age > 35 years	SEASONIQUE	1	119.0	NA	NA	119.0	119, 119, 119-119, 119, 119	0.37
	Comparator	5	73.2	34.3		51.0	45, 45, 50-101, 119, 119	
Tobacco Non-users, Age > 35 years	SEASONIQUE	21	76.8	32.2	0.41	68.0	30, 39, 45-105, 119, 133	0.36
	Comparator	107	69.9	43.5		61.0	-87, 24, 41-106, 119, 268	
Tobacco Users, 12 ≤ Age ≤ 35 years	SEASONIQUE	19	82.4	32.2	0.40	77.0	28, 28, 59-103, 161, 161	0.05
	Comparator	45	70.9	75.7		54.0	-83, 24, 37-93, 119, 484	
Tobacco Non-users, 12 ≤ Age ≤ 35 years	SEASONIQUE	173	73.3	41.7	0.92	63.0	20, 29, 44-102, 119, 360	0.81
	Comparator	691	73.0	52.1		62.0	-90, 26, 43-101, 119, 560	
Codes for Prior VTE or Anticoagulant Use	SEASONIQUE	2	96.5	87.0	NA	96.5	35, 35, 35-158, 158, 158	1.00
	Comparator	1	69.0	NA		69.0	69, 69, 69-69, 69, 69	
No Codes for Prior VTE or Anticoagulant Use	SEASONIQUE	212	74.5	39.8	0.54	64.5	20, 29, 45-103, 119, 360	0.24
	Comparator	847	72.5	52.5		61.0	-90, 25, 42-102, 119, 560	
Codes for Surgery/Injury During Follow-up	SEASONIQUE	59	70.9	32.7	0.74	62.0	26, 29, 48-93, 133, 174	0.09
	Comparator	256	69.0	63.2		55.0	-53, 22, 41-84, 131, 560	
No Codes for Surgery/Injury During Follow-up	SEASONIQUE	155	76.1	42.6	0.59	66.0	20, 29, 45-106, 119, 360	0.79
	Comparator	592	74.0	47.0		64.0	-90, 27, 43-107, 119, 491	

Abbreviations: IQR, interquartile range; NA, not applicable; SD, standard deviation; VTE, venous thromboembolism.

*T-test with Satterthwaite rather than pooled p-value due to unequal variances.

Note: Rows for age 12 to < 15 years and ≥ 15 to ≤ 35 years were combined as there was only one observed pregnancy in the age group 12 to < 15 years; negative minimum values indicate measurement error in the estimated pregnancy start; large maximum values may be due to prenatal care codes from subsequent pregnancies.

Table 7a. Delayed Pregnancy Detection: Comparison of Time Between Estimated Start of Pregnancy and End of SEASONIQUE or Comparator Exposure, Current Exposure

		No. of Pregnancies	Mean Time Between Conception and End of Exposure	SD	P-value* for Difference in Mean	Median Time Between Conception and End of Exposure	Min, 5th Percentile, IQR, 95th Percentile, Max	P-value for Wilcoxon Rank Sum Test
Naïve and New Users	SEASONIQUE	221	61.8	44.3	0.03	54.0	0, 8, 27-87, 148, 210	0.00
	Comparator	868	53.7	60.9		38.0	0, 3, 17-73, 141, 955	
Naïve Users	SEASONIQUE	118	61.2	44.9	0.04	55.5	0, 5, 27-85, 154, 210	0.01
	Comparator	608	51.7	52.1		38.0	0, 3, 17-72, 132, 730	
New Users	SEASONIQUE	103	62.6	43.8	0.50	53.0	1, 12, 27-92, 141, 203	0.01
	Comparator	260	58.3	77.5		37.5	0, 4, 18-75, 169, 955	
Re-starters	SEASONIQUE	51	70.9	89.7	0.18	53.0	0, 4, 23-83, 194, 580	0.09
	Comparator	280	53.1	52.3		38.0	0, 3, 16-75, 156, 329	
Switchers	SEASONIQUE	62	59.5	43.8	0.70	47.0	0, 6, 26-84, 138, 186	0.22
	Comparator	255	56.9	57.6		41.0	0, 3, 19-78, 165, 392	

Abbreviations: IQR, interquartile range; SD, standard deviation.

*T-test with Satterthwaite rather than pooled p-value due to unequal variances.

Table 7b. Delayed Pregnancy Detection: Comparison of Time Between Estimated Start of Pregnancy and End of SEASONIQUE or Comparator Exposure, Current Exposure, in Sensitivity Analyses of Naïve and New Users

		No. of Pregnancies	Mean Time Between Conception and End of Exposure	SD	P-value* for Difference in Mean	Median Time Between Conception and End of Exposure	Min, 5th Percentile, IQR, 95th Percentile, Max	P-value for Wilcoxon Rank Sum Test
Using 60-day gaps for SEASONIQUE and 28-day gaps for Comparators	SEASONIQUE	293	77.6	62.4	0.00	66.0	0, 6, 36-108, 178, 532	0.00
	Comparator	1,119	64.1	75.5		48.0	0, 6, 25-82, 159, 1295	
Not Censoring Comparators with Continuous Use	SEASONIQUE	221	61.8	44.3	0.11	54.0	0, 8, 27-87, 148, 210	0.00
	Comparator	887	56.0	64.1		39.0	0, 3, 18-77, 146, 955	
Restricted to Those with at Least 24 Months of Prior Continuous Enrolment	SEASONIQUE	55	62.9	43.6	0.08	59.0	1, 5, 28-89, 154, 181	0.02
	Comparator	297	51.0	56.3		39.0	0, 3, 20-66, 126, 730	
Restricted to Those with > 24 to ≤ 36 Months of Prior Continuous Enrolment	SEASONIQUE	19	61.1	46.0	0.77	62.0	5, 5, 17-100, 154, 154	0.37
	Comparator	80	56.8	86.3		37.5	0, 4, 21-70, 130, 730	
Restricted to Those with a Minimum of 36 Months of Prior Continuous Enrolment	SEASONIQUE	23	65.5	48.7	0.18	57.0	1, 4, 29-96, 168, 181	0.15
	Comparator	162	50.7	38.5		41.5	1, 6, 23-64, 118, 235	
Restricted to Those with Pregnancies with Estimated Start Dates that Occur within the Last 28 Days of Supply of a Dispensing	SEASONIQUE	57	15.3	8.3	0.10	16.0	0, 1, 8-22, 27, 27	0.09
	Comparator	326	13.3	8.0		13.0	0, 1, 7-20, 26, 27	

Abbreviations: IQR, interquartile range; SD, standard deviation.

*T-test with Satterthwaite rather than pooled p-value due to unequal variances.

Table 7c. Delayed Pregnancy Detection: Comparison of Time Between Estimated Start of Pregnancy and End of SEASONIQUE or Comparator Exposure, Current Exposure, in Subgroup Analyses of Naïve and New Users

		No. of Pregnancies	Mean Time Between Conception and End of Exposure	SD	P-value* for Difference in Mean	Median Time Between Conception and End of Exposure	Min, 5th Percentile, IQR, 95th Percentile, Max	P-value for Wilcoxon Rank Sum Test
Age 12 to ≤ 35	SEASONIQUE	198	62.4	45.4	0.03	54.0	0, 6, 27-90, 155, 210	0.00
	Comparator	754	53.6	61.8		39.0	0, 3, 18-71, 135, 955	
Age > 35 to < 46	SEASONIQUE	23	56.7	34.5	0.76	60.0	1, 8, 29-73, 116, 141	0.27
	Comparator	114	54.0	54.7		32.5	1, 2, 17-80, 171, 276	
Codes for Overweight/Obesity	SEASONIQUE	11	56.1	60.5	0.94	43.0	1, 1, 6-81, 191, 191	0.76
	Comparator	36	54.5	54.9		40.0	1, 6, 24-65, 125, 306	
No Codes for Overweight/Obesity	SEASONIQUE	210	62.1	43.5	0.02	54.5	0, 8, 27-89, 148, 210	0.00
	Comparator	832	53.7	61.1		38.0	0, 3, 17-73, 141, 955	
Codes for Tobacco Use	SEASONIQUE	21	68.2	46.8	0.40	57.0	4, 5, 29-98, 129, 181	0.16
	Comparator	51	57.1	56.7		39.0	0, 3, 21-66, 190, 255	
No Codes for Tobacco Use	SEASONIQUE	200	61.2	44.1	0.04	54.0	0, 8, 27-87, 151, 210	0.00
	Comparator	817	53.5	61.1		38.0	0, 3, 17-73, 136, 955	
Tobacco Users, Age > 35 years	SEASONIQUE	1	29.0	NA	NA	29.0	29, 29, 29-29, 29, 29	1.00
	Comparator	5	66.0	106.2		27.0	8, 8, 9-31, 255, 255	
Tobacco Non-users, Age > 35 years	SEASONIQUE	22	58.0	34.8	0.61	61.0	1, 8, 42-73, 116, 141	0.27
	Comparator	109	53.5	52.1		35.0	1, 2, 17-80, 169, 276	
Tobacco Users, 12 ≤ Age ≤ 35 years	SEASONIQUE	20	70.2	47.1	0.28	65.5	4, 5, 30-103, 155, 181	0.15
	Comparator	46	56.2	50.6		40.0	0, 3, 23-66, 182, 228	
Tobacco Non-users, 12 ≤ Age ≤ 35 years	SEASONIQUE	178	61.6	45.2	0.05	52.5	0, 8, 26-89, 155, 210	0.00
	Comparator	708	53.5	62.5		38.0	0, 3, 17-72, 135, 955	
Codes for Prior VTE or Anticoagulant Use	SEASONIQUE	2	112.0	111.7	NA	112.0	33, 33, 33-191, 191, 191	1.00
	Comparator	1	42.0	NA		42.0	42, 42, 42-42, 42, 42	
No Codes for Prior VTE or Anticoagulant Use	SEASONIQUE	219	61.4	43.6	0.03	54.0	0, 6, 27-87, 148, 210	0.00
	Comparator	867	53.7	60.9		38.0	0, 3, 17-73, 141, 955	
Codes for Surgery/Injury During Follow-up	SEASONIQUE	60	52.6	44.3	0.57	35.5	0, 3, 22-79, 135, 181	0.33
	Comparator	258	48.8	60.5		34.0	0, 4, 16-64, 131, 730	
No Codes for Surgery/Injury During Follow-up	SEASONIQUE	161	65.3	44.0	0.03	57.0	2, 9, 30-89, 154, 210	0.00
	Comparator	610	55.8	61.0		40.0	0, 3, 18-78, 143, 955	

Abbreviations: IQR, interquartile range; NA, not applicable; SD, standard deviation; VTE, venous thromboembolism.

*T-test with Satterthwaite rather than pooled p-value due to unequal variances.

Note: rows for age 12 to < 15 years and ≥ 15 to ≤ 35 years were combined as there was only one observed pregnancy in the age group 12 to < 15 years.

Supplemental Table 1. Most Frequently Occurring Baseline Diagnoses Observed Among SEASONIQUE Users and Comparators Across all Six Calendar Blocks

Code Type	Code	Description
09	034	Streptococcal Sore Throat and Scarlet Fever
09	054	Herpes Simplex
09	078	Other Diseases due to Viruses and Chlamydiae
09	079	Viral and Chlamydial Infection in Conditions Classified Elsewhere and of Unspecified Site
09	112	Candidiasis
09	216	Benign Neoplasm of Skin
09	218	Uterine Leiomyoma
09	238	Neoplasm of Uncertain Behavior of Other and Unspecified Sites and Tissues
09	244	Acquired Hypothyroidism
09	256	Ovarian Dysfunction
09	268	Vitamin D Deficiency
09	272	Disorders of Lipoid Metabolism
09	276	Disorders of Fluid, Electrolyte, and Acid-Base Balance
09	278	Overweight, Obesity and Other Hyperalimentation
09	280	Iron Deficiency Anemias
09	285	Other and Unspecified Anemias
09	296	Episodic Mood Disorders
09	300	Anxiety, Dissociative and Somatoform Disorders
09	305	Nondependent Abuse of Drugs
09	307	Special Symptoms or Syndromes, not Elsewhere Classified
09	309	Adjustment Reaction
09	311	Depressive Disorder, not Elsewhere Classified
09	314	Hyperkinetic Syndrome of Childhood
09	338	Pain, not Elsewhere Classified
09	346	Migraine
09	367	Disorders of Refraction and Accommodation
09	372	Disorders of Conjunctiva
09	380	Disorders of External Ear
09	381	Nonsuppurative Otitis Media and Eustachian Tube Disorders
09	382	Suppurative and Unspecified Otitis Media
09	388	Other Disorders of Ear
09	401	Essential Hypertension
09	461	Acute Sinusitis
09	462	Acute Pharyngitis
09	463	Acute Tonsillitis
09	465	Acute Upper Respiratory Infections of Multiple or Unspecified Sites
09	466	Acute Bronchitis and Bronchiolitis
09	472	Chronic Pharyngitis and Nasopharyngitis
09	473	Chronic Sinusitis
09	477	Allergic Rhinitis
09	478	Other Diseases of Upper Respiratory Tract
09	490	Bronchitis, not Specified As Acute or Chronic
09	493	Asthma
09	530	Diseases of Esophagus
09	535	Gastritis and Duodenitis

Supplemental Table 1. Most Frequently Occurring Baseline Diagnoses Observed Among SEASONIQUE Users and Comparators Across all Six Calendar Blocks

Code Type	Code	Description
09	558	Other Noninfectious Gastroenteritis and Colitis
09	564	Functional Digestive Disorders, not Elsewhere Classified
09	595	Cystitis
09	599	Other Disorders of Urethra and Urinary Tract
09	610	Benign Mammary Dysplasias
09	611	Other Disorders of Breast
09	616	Inflammatory Disease of Cervix, Vagina, and Vulva
09	617	Endometriosis
09	620	Noninflammatory Disorders of Ovary, Fallopian Tube, and Broad Ligament
09	622	Noninflammatory Disorders of Cervix
09	623	Noninflammatory Disorders of Vagina
09	625	Pain and Other Symptoms Associated With Female Genital Organs
09	626	Disorders of Menstruation and Other Abnormal Bleeding from Female Genital Tract
09	627	Menopausal and Postmenopausal Disorders
09	682	Other Cellulitis and Abscess
09	692	Contact Dermatitis and Other Eczema
09	695	Erythematous Conditions
09	702	Other Dermatoses
09	704	Diseases of Hair and Hair Follicles
09	706	Diseases of Sebaceous Glands
09	709	Other Disorders of Skin and Subcutaneous Tissue
09	719	Other and Unspecified Disorders of Joint
09	722	Intervertebral Disc Disorders
09	723	Other Disorders of Cervical Region
09	724	Other and Unspecified Disorders of Back
09	726	Peripheral Enthesopathies and Allied Syndromes
09	727	Other Disorders of Synovium, Tendon, and Bursa
09	728	Disorders of Muscle, Ligament, and Fascia
09	729	Other Disorders of Soft Tissues
09	733	Other Disorders of Bone and Cartilage
09	739	Nonallopathic Lesions, not Elsewhere Classified
09	780	General Symptoms
09	782	Symptoms Involving Skin and Other Integumentary Tissue
09	783	Symptoms Concerning Nutrition, Metabolism, and Development
09	784	Symptoms Involving Head and Neck
09	785	Symptoms Involving Cardiovascular System
09	786	Symptoms Involving Respiratory System and Other Chest Symptoms
09	787	Symptoms Involving Digestive System
09	788	Symptoms Involving Urinary System
09	789	Other Symptoms Involving Abdomen and Pelvis
09	790	Nonspecific Findings on Examination of Blood
09	793	Nonspecific (Abnormal) Findings on Radiological and Other Examination of Body Structure
09	795	Other and Nonspecific Abnormal Cytological, Histological, Immunological and DNA Test Findings
09	796	Other Nonspecific Abnormal Findings
09	845	Sprains and Strains of Ankle and Foot

Supplemental Table 1. Most Frequently Occurring Baseline Diagnoses Observed Among SEASONIQUE Users and Comparators Across all Six Calendar Blocks

Code Type	Code	Description
09	847	Sprains and Strains of Other and Unspecified Parts of Back
09	959	Injury, Other and Unspecified
09	995	Certain Adverse Effects not Elsewhere Classified
09	V01	Contact With or Exposure to Communicable Diseases
09	V03	Need for Prophylactic Vaccination and Inoculation Against Bacterial Diseases
09	V04	Need for Prophylactic Vaccination and Inoculation Against Certain Viral Diseases
09	V05	Need for Other Prophylactic Vaccination and Inoculation Against Single Diseases
09	V06	Need for Prophylactic Vaccination and Inoculation Against Combinations of Diseases
09	V15	Other Personal History Presenting Hazards to Health
09	V16	Family History of Malignant Neoplasm
09	V20	Health Supervision of Infant or Child
09	V22	Normal Pregnancy
09	V25	Contraceptive Management
09	V27	Outcome of Delivery
09	V28	Encounter for Antenatal Screening of Mother
09	V45	Other Postprocedural Status
09	V58	Encounter for Other and Unspecified Procedure and Aftercare
09	V65	Other Persons Seeking Consultation
09	V70	General Medical Examination
09	V72	Special Investigations and Examinations
09	V73	Special Screening Examination for Viral and Chlamydial Diseases
09	V74	Special Screening Examination for Bacterial and Spirochetal Diseases
09	V76	Special Screening for Malignant Neoplasms
09	V77	Special Screening for Endocrine, Nutritional, Metabolic, and Immunity Disorders
09	V85	Body Mass Index [BMI]
10	B07	Viral Warts
10	B34	Viral Infection of Unspecified Site
10	B35	Dermatophytosis
10	B37	Candidiasis
10	D22	Melanocytic Nevi
10	D23	Other Benign Neoplasms of Skin
10	D25	Leiomyoma of Uterus
10	D48	Neoplasm of Uncertain Behavior of Other and Unspecified Sites
10	D50	Iron Deficiency Anemia
10	D64	Other Anemias
10	E03	Other Hypothyroidism
10	E04	Other Nontoxic Goiter
10	E28	Ovarian Dysfunction
10	E55	Vitamin D Deficiency
10	E66	Overweight and Obesity
10	E78	Disorders of Lipoprotein Metabolism and Other Lipidemias
10	E86	Volume Depletion
10	F17	Nicotine Dependence
10	F31	Bipolar Disorder
10	F32	Major Depressive Disorder, Single Episode

Supplemental Table 1. Most Frequently Occurring Baseline Diagnoses Observed Among SEASONIQUE Users and Comparators Across all Six Calendar Blocks

Code Type	Code	Description
10	F33	Major Depressive Disorder, Recurrent
10	F34	Persistent Mood [Affective] Disorders
10	F41	Other Anxiety Disorders
10	F43	Reaction to Severe Stress, and Adjustment Disorders
10	F90	Attention-Deficit Hyperactivity Disorders
10	G43	Migraine
10	G44	Other Headache Syndromes
10	G47	Sleep Disorders
10	G89	Pain, not Elsewhere Classified
10	H10	Conjunctivitis
10	H52	Disorders of Refraction and Accommodation
10	H53	Visual Disturbances
10	H61	Other Disorders of External Ear
10	H66	Suppurative and Unspecified Otitis Media
10	H92	Otalgia and Effusion of Ear
10	I10	Essential (Primary) Hypertension
10	J00	Acute Nasopharyngitis [Common Cold]
10	J01	Acute Sinusitis
10	J02	Acute Pharyngitis
10	J03	Acute Tonsillitis
10	J06	Acute Upper Respiratory Infections of Multiple and Unspecified Sites
10	J20	Acute Bronchitis
10	J30	Vasomotor and Allergic Rhinitis
10	J32	Chronic Sinusitis
10	J34	Other and Unspecified Disorders of Nose and Nasal Sinuses
10	J40	Bronchitis, not Specified As Acute or Chronic
10	J45	Asthma
10	K21	Gastro-Esophageal Reflux Disease
10	K29	Gastritis and Duodenitis
10	K52	Other and Unspecified Noninfective Gastroenteritis and Colitis
10	K58	Irritable Bowel Syndrome
10	K59	Other Functional Intestinal Disorders
10	K64	Hemorrhoids and Perianal Venous Thrombosis
10	L03	Cellulitis and Acute Lymphangitis
10	L29	Pruritus
10	L30	Other and Unspecified Dermatitis
10	L50	Urticaria
10	L70	Acne
10	L72	Follicular Cysts of Skin and Subcutaneous Tissue
10	L73	Other Follicular Disorders
10	L81	Other Disorders of Pigmentation
10	L82	Seborrheic Keratosis
10	M25	Other Joint Disorder, not Elsewhere Classified
10	M47	Spondylosis
10	M51	Thoracic, Thoracolumbar, and Lumbosacral Intervertebral Disc Disorders

Supplemental Table 1. Most Frequently Occurring Baseline Diagnoses Observed Among SEASONIQUE Users and Comparators Across all Six Calendar Blocks

Code Type	Code	Description
10	M54	Dorsalgia
10	M62	Other Disorders of Muscle
10	M77	Other Enthesopathies
10	M79	Other and Unspecified Soft Tissue Disorders, not Elsewhere Classified
10	M99	Biomechanical Lesions, not Elsewhere Classified
10	N30	Cystitis
10	N39	Other Disorders of Urinary System
10	N63	Unspecified Lump in Breast
10	N64	Other Disorders of Breast
10	N76	Other Inflammation of Vagina and Vulva
10	N80	Endometriosis
10	N83	Noninflammatory Disorders of Ovary, Fallopian Tube and Broad Ligament
10	N89	Other Noninflammatory Disorders of Vagina
10	N91	Absent, Scanty and Rare Menstruation
10	N92	Excessive, Frequent and Irregular Menstruation
10	N93	Other Abnormal Uterine and Vaginal Bleeding
10	N94	Pain and Other Conditions Associated With Female Genital Organs and Menstrual Cycle
10	N95	Menopausal and Other Perimenopausal Disorders
10	R00	Abnormalities of Heart Beat
10	R05	Cough
10	R06	Abnormalities of Breathing
10	R07	Pain in Throat and Chest
10	R09	Other Symptoms and Signs Involving The Circulatory and Respiratory System
10	R10	Abdominal and Pelvic Pain
10	R11	Nausea and Vomiting
10	R19	Other Symptoms and Signs Involving The Digestive System and Abdomen
10	R20	Disturbances of Skin Sensation
10	R21	Rash and Other Nonspecific Skin Eruption
10	R30	Pain Associated With Micturition
10	R31	Hematuria
10	R35	Polyuria
10	R42	Dizziness and Giddiness
10	R50	Fever of Other and Unknown Origin
10	R51	Headache
10	R53	Malaise and Fatigue
10	R55	Syncope and Collapse
10	R63	Symptoms and Signs Concerning Food and Fluid Intake
10	R68	Other General Symptoms and Signs
10	R73	Elevated Blood Glucose Level
10	R79	Other Abnormal Findings of Blood Chemistry
10	R87	Abnormal Findings in Specimens from Female Genital Organs
10	R92	Abnormal and Inconclusive Findings on Diagnostic Imaging of Breast
10	R94	Abnormal Results of Function Studies
10	S93	Dislocation and Sprain of Joints and Ligaments At Ankle, Foot and Toe Level
10	T78	Adverse Effects, not Elsewhere Classified

Supplemental Table 1. Most Frequently Occurring Baseline Diagnoses Observed Among SEASONIQUE Users and Comparators Across all Six Calendar Blocks

Code Type	Code	Description
10	Z00	Encounter for General Examination Without Complaint, Suspected or Reported Diagnosis
10	Z01	Encounter for Other Special Examination Without Complaint, Suspected or Reported Diagnosis
10	Z11	Encounter for Screening for Infectious and Parasitic Diseases
10	Z12	Encounter for Screening for Malignant Neoplasms
10	Z13	Encounter for Screening for Other Diseases and Disorders
10	Z20	Contact With and (Suspected) Exposure to Communicable Diseases
10	Z23	Encounter for Immunization
10	Z30	Encounter for Contraceptive Management
10	Z32	Encounter for Pregnancy Test and Childbirth and Childcare Instruction
10	Z34	Encounter for Supervision of Normal Pregnancy
10	Z37	Outcome of Delivery
10	Z39	Encounter for Maternal Postpartum Care and Examination
10	Z3A	Weeks of Gestation
10	Z51	Encounter for Other Aftercare and Medical Care
10	Z68	Body Mass Index [BMI]
10	Z71	Persons Encountering Health Services for Other Counseling and Medical Advice, not Elsewhere Classified
10	Z72	Problems Related to Lifestyle
10	Z76	Persons Encountering Health Services in Other Circumstances
10	Z79	Long Term (Current) Drug Therapy
10	Z80	Family History of Primary Malignant Neoplasm
10	Z86	Personal History of Certain Other Diseases
10	Z87	Personal History of Other Diseases and Conditions
10	Z88	Allergy Status to Drugs, Medicaments and Biological Substances
10	Z91	Personal Risk Factors, not Elsewhere Classified
10	Z98	Other Postprocedural States

Supplemental Table 2. Most Frequently Occurring Baseline Procedures Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Code Type	Code	Description
CPT-4	01967	Neuraxial Labor Analgesia/Anesthesia for Planned Vaginal Delivery (This Includes Any Repeat Subarachnoid Needle Placement and Drug Injection and/or Any Necessary Replacement of an Epidural Catheter During Labor)
CPT-4	1036F	Current Tobacco Non-User (Cad, Cap, Copd, Pv) (Dm) (Ibd)
CPT-4	11100	Biopsy of Skin, Subcutaneous Tissue and/or Mucous Membrane (Including Simple Closure), Unless Otherwise Listed; Single Lesion
CPT-4	17110	Destruction (Eg, Laser Surgery, Electrosurgery, Cryosurgery, Chemosurgery, Surgical Curettement), of Benign Lesions Other Than Skin Tags or Cutaneous Vascular Proliferative Lesions; Up to 14 Lesions
CPT-4	36415	Collection of Venous Blood by Venipuncture
CPT-4	36416	Collection of Capillary Blood Specimen (Eg, Finger, Heel, Ear Stick)
CPT-4	43239	Esophagogastroduodenoscopy, Flexible, Transoral; with Biopsy, Single or Multiple
CPT-4	57454	Colposcopy of the Cervix Including Upper/Adjacent Vagina; with Biopsy(s) of the Cervix and Endocervical Curettage
CPT-4	58301	Removal of Intrauterine Device (Iud)
CPT-4	70450	Computed Tomography, Head or Brain; Without Contrast Material
CPT-4	71010	Radiologic Examination, Chest; Single View, Frontal
CPT-4	71020	Radiologic Examination, Chest, 2 Views, Frontal and Lateral;
CPT-4	72100	Radiologic Examination, Spine, Lumbosacral; 2 or 3 Views
CPT-4	73610	Radiologic Examination, Ankle; Complete, Minimum of 3 Views
CPT-4	73630	Radiologic Examination, Foot; Complete, Minimum of 3 Views
CPT-4	74176	Computed Tomography, Abdomen and Pelvis; Without Contrast Material
CPT-4	74177	Computed Tomography, Abdomen and Pelvis; with Contrast Material(s)
CPT-4	76083	Screening Mammography
CPT-4	76092	Mammogram Screening
CPT-4	76499	Unlisted Diagnostic Radiographic Procedure
CPT-4	76645	Ultrasound, Breast(s) (Unilateral or Bilateral), Real Time with Image Documentation
CPT-4	76705	Ultrasound, Abdominal, Real Time with Image Documentation; Limited (Eg, Single Organ, Quadrant, Follow-Up)
CPT-4	76830	Ultrasound, Transvaginal
CPT-4	76856	Ultrasound, Pelvic (Nonobstetric), Real Time with Image Documentation; Complete
CPT-4	77052	Computer-Aided Detection (Computer Algorithm Analysis of Digital Image Data for Lesion Detection) with Further Review for Interpretation, with or Without Digitization of Film Radiographic Images; Screening Mammography (List Separately in Addition to Code for Primary Procedure)
CPT-4	77057	Screening Mammography, Bilateral (2-View Study of Each Breast)
CPT-4	77063	Screening Digital Breast Tomosynthesis, Bilateral (List Separately in Addition to Code for Primary Procedure)
CPT-4	80048	Basic Metabolic Panel (Calcium, Total) This Panel Must Include the Following: Calcium, Total (82310) Carbon Dioxide (Bicarbonate) (82374) Chloride (82435) Creatinine (82565) Glucose (82947) Potassium (84132) Sodium (84295) Urea Nitrogen (Bun) (84520)
CPT-4	80050	General Health Panel This Panel Must Include the Following: Comprehensive Metabolic Panel (80053) Blood Count, Complete (Cbc), Automated and Automated Differential Wbc Count (85025 or 85027 and 85004) or Blood Count, Complete (Cbc), Automated (85027) and Appropriate Manual Differential Wbc Count (85007 or 85009) Thyroid Stimulating Hormone (Tsh) (84443)
CPT-4	80053	Comprehensive Metabolic Panel This Panel Must Include the Following: Albumin (82040) Bilirubin, Total (82247) Calcium, Total (82310) Carbon Dioxide (Bicarbonate) (82374) Chloride (82435) Creatinine (82565) Glucose (82947) Phosphatase, Alkaline (84075) Potassium (84132) Protein, Total (84155) Sodium (84295) Transferase, Alanine Amino (Alt) (Sgpt) (84460) Transferase, Aspartate Amino (Ast) (Sgot) (84450) Urea Nitrogen (Bun) (84520)
CPT-4	80061	Lipid Panel This Panel Must Include the Following: Cholesterol, Serum, Total (82465) Lipoprotein, Direct Measurement, High Density Cholesterol (Hdl Cholesterol) (83718) Triglycerides (84478)
CPT-4	80076	Hepatic Function Panel This Panel Must Include the Following: Albumin (82040) Bilirubin, Total (82247) Bilirubin, Direct (82248) Phosphatase, Alkaline (84075) Protein, Total (84155) Transferase, Alanine Amino (Alt) (Sgpt) (84460) Transferase, Aspartate Amino (Ast) (Sgot) (84450)

Supplemental Table 2. Most Frequently Occurring Baseline Procedures Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Code Type	Code	Description
CPT-4	81000	Urinalysis, by Dip Stick or Tablet Reagent for Bilirubin, Glucose, Hemoglobin, Ketones, Leukocytes, Nitrite, Ph, Protein, Specific Gravity, Urobilinogen, Any Number of these Constituents; Non-Automated, with Microscopy
CPT-4	81001	Urinalysis, by Dip Stick or Tablet Reagent for Bilirubin, Glucose, Hemoglobin, Ketones, Leukocytes, Nitrite, Ph, Protein, Specific Gravity, Urobilinogen, Any Number of these Constituents; Automated, with Microscopy
CPT-4	81002	Urinalysis, by Dip Stick or Tablet Reagent for Bilirubin, Glucose, Hemoglobin, Ketones, Leukocytes, Nitrite, Ph, Protein, Specific Gravity, Urobilinogen, Any Number of these Constituents; Non-Automated, Without Microscopy
CPT-4	81003	Urinalysis, by Dip Stick or Tablet Reagent for Bilirubin, Glucose, Hemoglobin, Ketones, Leukocytes, Nitrite, Ph, Protein, Specific Gravity, Urobilinogen, Any Number of these Constituents; Automated, Without Microscopy
CPT-4	81025	Urine Pregnancy Test, by Visual Color Comparison Methods
CPT-4	82150	Amylase
CPT-4	82306	Vitamin D; 25 Hydroxy, Includes Fraction(s) , If Performed
CPT-4	82550	Creatine Kinase (Ck), (Cpk); Total
CPT-4	82570	Creatinine; Other Source
CPT-4	82607	Cyanocobalamin (Vitamin B-12);
CPT-4	82627	Dehydroepiandrosterone-Sulfate (Dhea-S)
CPT-4	82670	Estradiol
CPT-4	82728	Ferritin
CPT-4	82746	Folic Acid; Serum
CPT-4	82784	Gammaglobulin (Immunoglobulin); Iga, Igd, Igg, Igm, Each
CPT-4	82947	Glucose; Quantitative, Blood (Except Reagent Strip)
CPT-4	82950	Glucose; Post Glucose Dose (Includes Glucose)
CPT-4	83001	Gonadotropin; Follicle Stimulating Hormone (FSH)
CPT-4	83002	Gonadotropin; Luteinizing Hormone (Lh)
CPT-4	83036	Hemoglobin; Glycosylated (A1c)
CPT-4	83516	Immunoassay for Analyte Other Than Infectious Agent Antibody or Infectious Agent Antigen; Qualitative or Semiquantitative, Multiple Step Method
CPT-4	83540	Iron
CPT-4	83550	Iron Binding Capacity
CPT-4	83690	Lipase
CPT-4	83735	Magnesium
CPT-4	84100	Phosphorus Inorganic (Phosphate);
CPT-4	84144	Progesterone
CPT-4	84146	Prolactin
CPT-4	84403	Testosterone; Total
CPT-4	84436	Thyroxine; Total
CPT-4	84439	Thyroxine; Free
CPT-4	84443	Thyroid Stimulating Hormone (Tsh)
CPT-4	84479	Thyroid Hormone (T3 or T4) Uptake or Thyroid Hormone Binding Ratio (Thbr)
CPT-4	84480	Triiodothyronine T3; Total (Tt-3)
CPT-4	84481	Triiodothyronine T3; Free
CPT-4	84484	Troponin, Quantitative
CPT-4	84550	Uric Acid; Blood
CPT-4	84702	Gonadotropin, Chorionic (Hcg); Quantitative
CPT-4	84703	Gonadotropin, Chorionic (Hcg); Qualitative
CPT-4	85018	Blood Count; Hemoglobin (Hgb)

Supplemental Table 2. Most Frequently Occurring Baseline Procedures Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Code Type	Code	Description
CPT-4	85025	Blood Count; Complete (Cbc), Automated (Hgb, Hct, Rbc, Wbc and Platelet Count) and Automated Differential White Blood Cell Count
CPT-4	85027	Blood Count; Complete (Cbc), Automated (Hgb, Hct, Rbc, Wbc and Platelet Count)
CPT-4	85610	Prothrombin Time;
CPT-4	85652	Sedimentation Rate, Erythrocyte; Automated
CPT-4	85730	Thromboplastin Time, Partial (Ptt); Plasma or Whole Blood
CPT-4	86038	Antinuclear Antibodies (Ana);
CPT-4	86140	C-Reactive Protein;
CPT-4	86308	Heterophile Antibodies; Screening
CPT-4	86376	Microsomal Antibodies (Eg, Thyroid or Liver-Kidney), Each
CPT-4	86431	Rheumatoid Factor; Quantitative
CPT-4	86580	Skin Test; Tuberculosis, Intradermal
CPT-4	86592	Syphilis Test, Non-Treponemal Antibody; Qualitative (Eg, Vdrl, Rpr, Art)
CPT-4	86695	Antibody; Herpes Simplex, Type 1
CPT-4	86696	Antibody; Herpes Simplex, Type 2
CPT-4	86701	Antibody; HIV-1
CPT-4	86703	Antibody; HIV-1 and HIV-2, Single Result
CPT-4	86800	Thyroglobulin Antibody
CPT-4	86803	Hepatitis C Antibody;
CPT-4	86850	Antibody Screen, Rbc, Each Serum Technique
CPT-4	86900	Blood Typing, Serologic; Abo
CPT-4	86901	Blood Typing, Serologic; Rh (D)
CPT-4	87070	Culture, Bacterial; Any Other Source Except Urine, Blood or Stool, Aerobic, with Isolation and Presumptive Identification of Isolates
CPT-4	87077	Culture, Bacterial; Aerobic Isolate, Additional Methods Required for Definitive Identification, Each Isolate
CPT-4	87081	Culture, Presumptive, Pathogenic Organisms, Screening Only;
CPT-4	87086	Culture, Bacterial; Quantitative Colony Count, Urine
CPT-4	87088	Culture, Bacterial; with Isolation and Presumptive Identification of Each Isolate, Urine
CPT-4	87186	Susceptibility Studies, Antimicrobial Agent; Microdilution or Agar Dilution (Minimum Inhibitory Concentration [mic] or Breakpoint), Each Multi-Antimicrobial, Per Plate
CPT-4	87210	Smear, Primary Source with Interpretation; Wet Mount for Infectious Agents (Eg, Saline, India Ink, Koh Preps)
CPT-4	87340	Infectious Agent Antigen Detection by Immunoassay Technique, (Eg, Enzyme Immunoassay [eia], Enzyme-Linked Immunosorbent Assay [elisa], Immunochemiluminometric Assay [imca]) Qualitative or Semiquantitative, Multiple-Step Method; Hepatitis B Surface Antigen (Hbsag)
CPT-4	87389	Infectious Agent Antigen Detection by Immunoassay Technique, (Eg, Enzyme Immunoassay [eia], Enzyme-Linked Immunosorbent Assay [elisa], Immunochemiluminometric Assay [imca]) Qualitative or Semiquantitative, Multiple-Step Method; HIV-1 Antigen(s) , with HIV-1 and HIV-2 Antibodies, Single Result
CPT-4	87480	Infectious Agent Detection by Nucleic Acid (Dna or Rna); Candida Species, Direct Probe Technique
CPT-4	87481	Infectious Agent Detection by Nucleic Acid (Dna or Rna); Candida Species, Amplified Probe Technique
CPT-4	87491	Infectious Agent Detection by Nucleic Acid (Dna or Rna); Chlamydia Trachomatis, Amplified Probe Technique
CPT-4	87510	Infectious Agent Detection by Nucleic Acid (Dna or Rna); Gardnerella Vaginalis, Direct Probe Technique
CPT-4	87591	Infectious Agent Detection by Nucleic Acid (Dna or Rna); Neisseria Gonorrhoeae, Amplified Probe Technique
CPT-4	87621	Infectious Agent Detection by Nucleic Acid (Dna or Rna); Papillomavirus, Human, Amplified Probe Technique
CPT-4	87624	Infectious Agent Detection by Nucleic Acid (Dna or Rna); Human Papillomavirus (Hpv), High-Risk Types (Eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
CPT-4	87660	Infectious Agent Detection by Nucleic Acid (Dna or Rna); Trichomonas Vaginalis, Direct Probe Technique

Supplemental Table 2. Most Frequently Occurring Baseline Procedures Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Code Type	Code	Description
CPT-4	87661	Infectious Agent Detection by Nucleic Acid (Dna or Rna); Trichomonas Vaginalis, Amplified Probe Technique
CPT-4	87798	Infectious Agent Detection by Nucleic Acid (Dna or Rna), Not Otherwise Specified; Amplified Probe Technique, Each Organism
CPT-4	87804	Infectious Agent Antigen Detection by Immunoassay with Direct Optical Observation; Influenza
CPT-4	87880	Infectious Agent Antigen Detection by Immunoassay with Direct Optical Observation; Streptococcus, Group A
CPT-4	88141	Cytopathology, Cervical or Vaginal (Any Reporting System), Requiring Interpretation by Physician
CPT-4	88142	Cytopathology, Cervical or Vaginal (Any Reporting System), Collected in Preservative Fluid, Automated Thin Layer Preparation; Manual Screening Under Physician Supervision
CPT-4	88175	Cytopathology, Cervical or Vaginal (Any Reporting System), Collected in Preservative Fluid, Automated Thin Layer Preparation; with Screening by Automated System and Manual Rescreening or Review, Under Physician Supervision
CPT-4	88304	Level III - Surgical Pathology, Gross and Microscopic Examination Abortion, Induced Abscess Aneurysm - Arterial/Ventricular Anus, Tag Appendix, Other Than Incidental Artery, Atheromatous Plaque Bartholin's Gland Cyst Bone Fragment(s) , Other Than Pathologic Fracture Bursa/Synovial Cyst Carpal Tunnel Tissue Cartilage, Shavings Cholesteatoma Colon, Colostomy Stoma Conjunctiva - Biopsy/Pterygium Cornea Diverticulum - Esophagus/Small Intestine Dupuytren's Contracture Tissue Femoral Head, Other Than Fracture Fissure/Fistula Foreskin, Other Than Newborn Gallbladder Ganglion Cyst Hematoma Hemorrhoids Hydatid of Morgagni Intervertebral Disc Joint, Loose Body Meniscus Mucocele, Salivary Neuroma - Morton's/Traumatic Pilonidal Cyst/Sinus Polyps, Inflammatory - Nasal/Sinusoidal Skin - Cyst/Tag/Debridement Soft Tissue, Debridement Soft Tissue, Lipoma Spermatocele Tendon/Tendon Sheath Testicular Appendage Thrombus or Embolus Tonsil and/or Adenoids Varicocele Vas Deferens, Other Than Sterilization Vein, Varicosity
CPT-4	88305	Level IV - Surgical Pathology, Gross and Microscopic Examination Abortion - Spontaneous/Missed Artery, Biopsy Bone Marrow, Biopsy Bone Exostosis Brain/Meninges, Other Than for Tumor Resection Breast, Biopsy, Not Requiring Microscopic Evaluation of Surgical Margins Breast, Reduction Mammoplasty Bronchus, Biopsy Cell Block, Any Source Cervix, Biopsy Colon, Biopsy Duodenum, Biopsy Endocervix, Curettings/Biopsy Endometrium, Curettings/Biopsy Esophagus, Biopsy Extremity, Amputation, Traumatic Fallopian Tube, Biopsy Fallopian Tube, Ectopic Pregnancy Femoral Head, Fracture Fingers/Toes, Amputation, Non-Traumatic Gingiva/Oral Mucosa, Biopsy Heart Valve Joint, Resection Kidney, Biopsy Larynx, Biopsy Leiomyoma(s) , Uterine Myomectomy - Without Uterus Lip, Biopsy/Wedge Resection Lung, Transbronchial Biopsy Lymph Node, Biopsy Muscle, Biopsy Nasal Mucosa, Biopsy Nasopharynx/Oropharynx, Biopsy Nerve, Biopsy Odontogenic/Dental Cyst Omentum, Biopsy Ovary with or Without Tube, Non-Neoplastic Ovary, Biopsy/Wedge Resection Parathyroid Gland Peritoneum, Biopsy Pituitary Tumor Placenta, Other Than Third Trimester Pleura/Pericardium - Biopsy/Tissue Polyp, Cervical/Endometrial Polyp, Colorectal Polyp, Stomach/Small Intestine Prostate, Needle Biopsy Prostate, Tur Salivary Gland, Biopsy Sinus, Paranasal Biopsy Skin, Other Than Cyst/Tag/Debridement/Plastic Repair Small Intestine, Biopsy Soft Tissue, Other Than Tumor/Mass/Lipoma/Debridement Spleen Stomach, Biopsy Synovium Testis, Other Than Tumor/Biopsy/Castration Thyroglossal Duct/Brachial Cleft Cyst Tongue, Biopsy Tonsil, Biopsy Trachea, Biopsy Ureter, Biopsy Urethra, Biopsy Urinary Bladder, Biopsy Uterus, with or Without Tubes and Ovaries, for Prolapse Vagina, Biopsy Vulva/Labia, Biopsy
CPT-4	89240	Unlisted Miscellaneous Pathology Test
CPT-4	90460	Immunization Administration Through 18 Years of Age Via Any Route of Administration, with Counseling by Physician or Other Qualified Health Care Professional; First or Only Component of Each Vaccine or Toxoid Administered
CPT-4	90471	Immunization Administration (Includes Percutaneous, Intradermal, Subcutaneous, or Intramuscular Injections); 1 Vaccine (Single or Combination Vaccine/Toxoid)
CPT-4	90472	Immunization Administration (Includes Percutaneous, Intradermal, Subcutaneous, or Intramuscular Injections); Each Additional Vaccine (Single or Combination Vaccine/Toxoid) (List Separately in Addition to Code for Primary Procedure)
CPT-4	90649	Human Papillomavirus Vaccine, Types 6, 11, 16, 18, Quadrivalent (4vhpv), 3 Dose Schedule, for Intramuscular Use
CPT-4	90651	Human Papillomavirus Vaccine Types 6, 11, 16, 18, 31, 33, 45, 52, 58, Nonavalent (9vhpv), 3 Dose Schedule, for Intramuscular Use
CPT-4	90656	Influenza Virus Vaccine, Trivalent (Iiv3), Split Virus, Preservative Free, 0.5 Ml Dosage, for Intramuscular Use
CPT-4	90658	Influenza Virus Vaccine, Trivalent (Iiv3), Split Virus, 0.5 Ml Dosage, for Intramuscular Use
CPT-4	90686	Influenza Virus Vaccine, Quadrivalent (Iiv4), Split Virus, Preservative Free, 0.5 Ml Dosage, for Intramuscular Use
CPT-4	90688	Influenza Virus Vaccine, Quadrivalent (Iiv4), Split Virus, 0.5 Ml Dosage, for Intramuscular Use
CPT-4	90715	Tetanus, Diphtheria Toxoids and Acellular Pertussis Vaccine (Tdap), When Administered to Individuals 7 Years or Older, for Intramuscular Use
CPT-4	90734	Meningococcal Conjugate Vaccine, Serogroups A, C, Y and W-135, Quadrivalent (Mcv4 or Menacwy), for Intramuscular Use
CPT-4	90772	Ther/Proph/Diag Inj, Sc/Im

Supplemental Table 2. Most Frequently Occurring Baseline Procedures Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Code Type	Code	Description
CPT-4	90774	Ther Prop Diag Inj Intravenous Push
CPT-4	90791	Psychiatric Diagnostic Evaluation
CPT-4	90792	Psychiatric Diagnostic Evaluation with Medical Services
CPT-4	90801	Psychiatric Diagnostic Interview Examination
CPT-4	90806	Individual Psychotherapy, Insight Oriented, Behavior Modifying and/or Supportive, in an Office or Outpatient Facility, Approximately 45 to 50 Minutes Face-to-Face with the Patient;
CPT-4	90833	Psychotherapy, 30 Minutes with Patient When Performed with an Evaluation and Management Service (List Separately in Addition to the Code for Primary Procedure)
CPT-4	90834	Psychotherapy, 45 Minutes with Patient
CPT-4	90837	Psychotherapy, 60 Minutes with Patient
CPT-4	90862	Pharmacologic Management, Including Prescription, Use, and Review of Medication with No More Than Minimal Medical Psychotherapy
CPT-4	91000	Esophageal Intubation and Collection of Washings for Cytology, Including Preparation of Specimens (Separate Procedure)
CPT-4	92004	Ophthalmological Services: Medical Examination and Evaluation with Initiation of Diagnostic and Treatment Program; Comprehensive, New Patient, 1 or More Visits
CPT-4	92014	Ophthalmological Services: Medical Examination and Evaluation, with Initiation or Continuation of Diagnostic and Treatment Program; Comprehensive, Established Patient, 1 or More Visits
CPT-4	92015	Determination of Refractive State
CPT-4	93000	Electrocardiogram, Routine Ecg with at Least 12 Leads; with Interpretation and Report
CPT-4	93005	Electrocardiogram, Routine Ecg with at Least 12 Leads; Tracing Only, Without Interpretation and Report
CPT-4	93010	Electrocardiogram, Routine Ecg with at Least 12 Leads; Interpretation and Report Only
CPT-4	93306	Echocardiography, Transthoracic, Real-Time with Image Documentation (2d), Includes M-Mode Recording, When Performed, Complete, with Spectral Doppler Echocardiography, and with Color Flow Doppler Echocardiography
CPT-4	94010	Spirometry, Including Graphic Record, Total and Timed Vital Capacity, Expiratory Flow Rate Measurement(s) , with or Without Maximal Voluntary Ventilation
CPT-4	94640	Pressurized or Nonpressurized Inhalation Treatment for Acute Airway Obstruction for Therapeutic Purposes and/or for Diagnostic Purposes Such As Sputum Induction with an Aerosol Generator, Nebulizer, Metered Dose Inhaler or Intermittent Positive Pressure Breathing (Ippb) Device
CPT-4	94760	Noninvasive Ear or Pulse Oximetry for Oxygen Saturation; Single Determination
CPT-4	95004	Percutaneous Tests (Scratch, Puncture, Prick) with Allergenic Extracts, Immediate Type Reaction, Including Test Interpretation and Report, Specify Number of Tests
CPT-4	96361	Intravenous Infusion, Hydration; Each Additional Hour (List Separately in Addition to Code for Primary Procedure)
CPT-4	96365	Intravenous Infusion, for Therapy, Prophylaxis, or Diagnosis (Specify Substance or Drug); Initial, Up to 1 Hour
CPT-4	96372	Therapeutic, Prophylactic, or Diagnostic Injection (Specify Substance or Drug); Subcutaneous or Intramuscular
CPT-4	96374	Therapeutic, Prophylactic, or Diagnostic Injection (Specify Substance or Drug); Intravenous Push, Single or Initial Substance/Drug
CPT-4	96375	Therapeutic, Prophylactic, or Diagnostic Injection (Specify Substance or Drug); Each Additional Sequential Intravenous Push of A New Substance/Drug (List Separately in Addition to Code for Primary Procedure)
CPT-4	97001	Physical Therapy Evaluation
CPT-4	97010	Application of A Modality to 1 or More Areas; Hot or Cold Packs
CPT-4	97012	Application of A Modality to 1 or More Areas; Traction, Mechanical
CPT-4	97014	Application of A Modality to 1 or More Areas; Electrical Stimulation (Unattended)
CPT-4	97035	Application of A Modality to 1 or More Areas; Ultrasound, Each 15 Minutes
CPT-4	97110	Therapeutic Procedure, 1 or More Areas, Each 15 Minutes; Therapeutic Exercises to Develop Strength and Endurance, Range of Motion and Flexibility
CPT-4	97112	Therapeutic Procedure, 1 or More Areas, Each 15 Minutes; Neuromuscular Reeducation of Movement, Balance, Coordination, Kinesthetic Sense, Posture, and/or Proprioception for Sitting and/or Standing Activities

Supplemental Table 2. Most Frequently Occurring Baseline Procedures Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Code Type	Code	Description
CPT-4	97140	Manual Therapy Techniques (Eg, Mobilization/ Manipulation, Manual Lymphatic Drainage, Manual Traction), 1 or More Regions, Each 15 Minutes
CPT-4	97530	Therapeutic Activities, Direct (One-On-One) Patient Contact (Use of Dynamic Activities to Improve Functional Performance), Each 15 Minutes
CPT-4	98940	Chiropractic Manipulative Treatment (Cmt); Spinal, 1-2 Regions
CPT-4	98941	Chiropractic Manipulative Treatment (Cmt); Spinal, 3-4 Regions
CPT-4	99000	Handling and/or Conveyance of Specimen for Transfer From the Office to A Laboratory
CPT-4	99051	Service(s) Provided in the Office During Regularly Scheduled Evening, Weekend, or Holiday Office Hours, in Addition to Basic Service
CPT-4	99053	Service(s) Provided Between 10:00 Pm and 8:00 Am at 24-Hour Facility, in Addition to Basic Service
CPT-4	99201	Office or Other Outpatient Visit for the Evaluation and Management of A New Patient, which Requires these 3 Key Components: A Problem Focused History; A Problem Focused Examination; Straightforward Medical Decision Making. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are Self Limited or Minor. Typically, 10 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99202	Office or Other Outpatient Visit for the Evaluation and Management of A New Patient, which Requires these 3 Key Components: an Expanded Problem Focused History; an Expanded Problem Focused Examination; Straightforward Medical Decision Making. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Low to Moderate Severity. Typically, 20 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99203	Office or Other Outpatient Visit for the Evaluation and Management of A New Patient, which Requires these 3 Key Components: A Detailed History; A Detailed Examination; Medical Decision Making of Low Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Moderate Severity. Typically, 30 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99204	Office or Other Outpatient Visit for the Evaluation and Management of A New Patient, which Requires these 3 Key Components: A Comprehensive History; A Comprehensive Examination; Medical Decision Making of Moderate Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Moderate to High Severity. Typically, 45 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99205	Office or Other Outpatient Visit for the Evaluation and Management of A New Patient, which Requires these 3 Key Components: A Comprehensive History; A Comprehensive Examination; Medical Decision Making of High Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Moderate to High Severity. Typically, 60 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99211	Office or Other Outpatient Visit for the Evaluation and Management of an Established Patient, That May Not Require the Presence of A Physician or Other Qualified Health Care Professional. Usually, the Presenting Problem(s) are Minimal. Typically, 5 Minutes are Spent Performing or Supervising these Services.
CPT-4	99212	Office or Other Outpatient Visit for the Evaluation and Management of an Established Patient, which Requires at Least 2 of these 3 Key Components: A Problem Focused History; A Problem Focused Examination; Straightforward Medical Decision Making. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are Self Limited or Minor. Typically, 10 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99213	Office or Other Outpatient Visit for the Evaluation and Management of an Established Patient, which Requires at Least 2 of these 3 Key Components: an Expanded Problem Focused History; an Expanded Problem Focused Examination; Medical Decision Making of Low Complexity. Counseling and Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Low to Moderate Severity. Typically, 15 Minutes are Spent Face-to-Face with the Patient and/or Family.

Supplemental Table 2. Most Frequently Occurring Baseline Procedures Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Code Type	Code	Description
CPT-4	99214	Office or Other Outpatient Visit for the Evaluation and Management of an Established Patient, which Requires at Least 2 of these 3 Key Components: A Detailed History; A Detailed Examination; Medical Decision Making of Moderate Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Moderate to High Severity. Typically, 25 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99215	Office or Other Outpatient Visit for the Evaluation and Management of an Established Patient, which Requires at Least 2 of these 3 Key Components: A Comprehensive History; A Comprehensive Examination; Medical Decision Making of High Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Moderate to High Severity. Typically, 40 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99243	Office Consultation for A New or Established Patient, which Requires these 3 Key Components: A Detailed History; A Detailed Examination; and Medical Decision Making of Low Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Moderate Severity. Typically, 40 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99244	Office Consultation for A New or Established Patient, which Requires these 3 Key Components: A Comprehensive History; A Comprehensive Examination; and Medical Decision Making of Moderate Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Moderate to High Severity. Typically, 60 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99245	Office Consultation for A New or Established Patient, which Requires these 3 Key Components: A Comprehensive History; A Comprehensive Examination; and Medical Decision Making of High Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Moderate to High Severity. Typically, 80 Minutes are Spent Face-to-Face with the Patient and/or Family.
CPT-4	99282	Emergency Department Visit for the Evaluation and Management of A Patient, which Requires these 3 Key Components: an Expanded Problem Focused History; an Expanded Problem Focused Examination; and Medical Decision Making of Low Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Low to Moderate Severity.
CPT-4	99283	Emergency Department Visit for the Evaluation and Management of A Patient, which Requires these 3 Key Components: an Expanded Problem Focused History; an Expanded Problem Focused Examination; and Medical Decision Making of Moderate Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of Moderate Severity.
CPT-4	99284	Emergency Department Visit for the Evaluation and Management of A Patient, which Requires these 3 Key Components: A Detailed History; A Detailed Examination; and Medical Decision Making of Moderate Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of High Severity, and Require Urgent Evaluation by the Physician or Other Qualified Health Care Professionals But Do Not Pose an Immediate Significant Threat to Life or Physiologic Function.
CPT-4	99285	Emergency Department Visit for the Evaluation and Management of A Patient, which Requires these 3 Key Components Within the Constraints Imposed by the Urgency of the Patient's Clinical Condition and/or Mental Status: A Comprehensive History; A Comprehensive Examination; and Medical Decision Making of High Complexity. Counseling and/or Coordination of Care with Other Physicians, Other Qualified Health Care Professionals, or Agencies are Provided Consistent with the Nature of the Problem(s) and the Patient's and/or Family's Needs. Usually, the Presenting Problem(s) are of High Severity and Pose an Immediate Significant Threat to Life or Physiologic Function.
CPT-4	99385	Initial Comprehensive Preventive Medicine Evaluation and Management of an Individual Including an Age and Gender Appropriate History, Examination, Counseling/Anticipatory Guidance/Risk Factor Reduction Interventions, and the Ordering of Laboratory/Diagnostic Procedures, New Patient; 18-39 Years
CPT-4	99386	Initial Comprehensive Preventive Medicine Evaluation and Management of an Individual Including an Age and Gender Appropriate History, Examination, Counseling/Anticipatory Guidance/Risk Factor Reduction Interventions, and the Ordering of Laboratory/Diagnostic Procedures, New Patient; 40-64 Years

Supplemental Table 2. Most Frequently Occurring Baseline Procedures Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Code Type	Code	Description
CPT-4	99394	Periodic Comprehensive Preventive Medicine Reevaluation and Management of an Individual Including an Age and Gender Appropriate History, Examination, Counseling/Anticipatory Guidance/Risk Factor Reduction Interventions, and the Ordering of Laboratory/Diagnostic Procedures, Established Patient; Adolescent (Age 12 Through 17 Years)
CPT-4	99395	Periodic Comprehensive Preventive Medicine Reevaluation and Management of an Individual Including an Age and Gender Appropriate History, Examination, Counseling/Anticipatory Guidance/Risk Factor Reduction Interventions, and the Ordering of Laboratory/Diagnostic Procedures, Established Patient; 18-39 Years
CPT-4	99396	Periodic Comprehensive Preventive Medicine Reevaluation and Management of an Individual Including an Age and Gender Appropriate History, Examination, Counseling/Anticipatory Guidance/Risk Factor Reduction Interventions, and the Ordering of Laboratory/Diagnostic Procedures, Established Patient; 40-64 Years
HCPCS	A0425	Ground Mileage, Per Statute Mile
HCPCS	G0202	Screening Mammography, Bilateral (2-View Study of Each Breast), Including Computer-Aided Detection (Cad) When Performed
HCPCS	G0283	Electrical Stimulation (Unattended), to One or More Areas for Indication(s) Other Than Wound Care, As Part of A Therapy Plan of Care
HCPCS	G8427	Eligible Clinician Attests to Documenting in the Medical Record They Obtained, Updated, or Reviewed the Patient's Current Medications
HCPCS	J0696	Injection, Ceftriaxone Sodium, Per 250 Mg
HCPCS	J1100	Injection, Dexamethasone Sodium Phosphate, 1 Mg
HCPCS	J1170	Injection, Hydromorphone, Up to 4 Mg
HCPCS	J1200	Injection, Diphenhydramine Hcl, Up to 50 Mg
HCPCS	J1885	Injection, Ketorolac Tromethamine, Per 15 Mg
HCPCS	J2250	Injection, Midazolam Hcl, Per 1 Mg
HCPCS	J2270	Injection, Morphine Sulfate, Up to 10 Mg
HCPCS	J2405	Injection, Ondansetron Hcl, Per 1 Mg
HCPCS	J2550	Injection, Promethazine Hcl, Up to 50 Mg
HCPCS	J2704	Injection Propofol 10 Mg
HCPCS	J3010	Injection, Fentanyl Citrate, 0.1 Mg
HCPCS	J3301	Injection, Triamcinolone Acetonide, Not Otherwise Specified, 10 Mg
HCPCS	J7030	Infusion, Normal Saline Solution, 1,000 Cc
HCPCS	J7120	Ringers Lactate Infusion, Up to 1,000 Cc
HCPCS	Q0091	Screening Papanicolaou Smear; Obtaining, Preparing and Conveyance of Cervical or Vaginal Smear to Laboratory
HCPCS	Q9967	Low Osmolar Contrast Material, 300-399 Mg/Ml Iodine Concentration, Per Ml
HCPCS	S9083	Global Fee Urgent Care Centers

Supplemental Table 3. Most Frequently Occurring Baseline Medications Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Medications
Acetaminophen with Codeine
Acyclovir
Adapalene
Adapalene/Benzoyl Peroxide
Albuterol
Albuterol Sulfate
Alprazolam
Aluminum Chloride
Amitriptyline Hcl
Amlodipine Besylate
Amoxicillin
Amoxicillin/Potassium Clav
Amphet Asp/Amphet/D-Amphet
Aripiprazole
Atenolol
Atomoxetine Hcl
Atorvastatin Calcium
Azelastine Hcl
Azithromycin
Baclofen
Beclomethasone Dipropionate
Benzonatate
Blood Sugar Diagnostic
Budesonide
Bupropion Hcl
Buspirone Hcl
Butalb/Acetaminophen/Caffeine
Carisoprodol
Cefdinir
Cefprozil
Cefuroxime Axetil
Celecoxib
Cephalexin Monohydrate
Cetirizine Hcl
Chlorhexidine Gluconate
Ciprofloxacin Hcl
Ciprofloxacin Hcl/Dexameth
Citalopram Hydrobromide
Clarithromycin
Clindamycin Hcl
Clindamycin Phos/Benzoyl Perox
Clindamycin Phosphate
Clobetasol Propionate
Clonazepam
Clonidine Hcl
Clotrimazole/Betamet Diprop
Cyclobenzaprine Hcl
Dapsone
Desog-E.Estradiol/E.Estradiol
Desogestrel-Ethinyl Estradiol
Desonide

Supplemental Table 3. Most Frequently Occurring Baseline Medications Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Medications
Desvenlafaxine Succinate
Dexamethasone
Dexlansoprazole
Diazepam
Diclofenac Potassium
Diclofenac Sodium
Dicyclomine Hcl
Divalproex Sodium
D-Methorphan Hb/P-Epd Hcl/Bpm
Doxycycline Hyclate
Doxycycline Monohydrate
Duloxetine Hcl
Eletriptan Hbr
Eletriptan Hydrobromide
Epinephrine
Ergocalciferol (Vitamin D2)
Erythromycin Base
Escitalopram Oxalate
Esomeprazole Magnesium
Estradiol
Eszopiclone
Ethinyl Estradiol/Drospirenone
Ethynodiol D-Ethinyl Estradiol
Etonogestrel/Ethinyl Estradiol
Fexofenadine Hcl
Fexofenadine/Pseudoephedrine
Fluconazole
Fluocinonide
Fluoxetine Hcl
Fluticasone Propionate
Fluticasone/Salmeterol
Folic Acid
Gabapentin
Gentamicin Sulfate
Guaifenesin/Codeine Phos
Guaifenesin/Codeine Phosphate
Guaifenesin/Hydrocodone Bit
Guaifenesin/P-Ephed Hcl
Guaifenesin/Phenylephrine Hcl
Guanfacine Hcl
Hydrochlorothiazide
Hydrocodone Bit/Acetaminophen
Hydrocodone Bit/Homatrop Me-Br
Hydrocodone Bit/Homatropine
Hydrocodone/Chlorphen P-Stirex
Hydrocortisone
Hydromorphone Hcl
Hydroxychloroquine Sulfate
Hydroxyzine Hcl
Hydroxyzine Pamoate
Hyoscyamine Sulfate

Supplemental Table 3. Most Frequently Occurring Baseline Medications Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Medications
Ibuprofen
Inhaler, Assist Devices
Ipratropium Bromide
Isotretinoin
Ketoconazole
Ketorolac Tromethamine
Lamotrigine
Lancets
Levocetirizine Dihydrochloride
Levofloxacin
Levonorgestrel-Ethin Estradiol
Levothyroxine Sodium
Lidocaine
Lidocaine Hcl
Lisdexamfetamine Dimesylate
Lisinopril
Lisinopril/Hydrochlorothiazide
Lithium Carbonate
L-Norgest/E.Estradiol-E.Estrad
Lorazepam
Losartan Potassium
Medroxyprogesterone Acetate
Meloxicam
Metaxalone
Metformin Hcl
Methocarbamol
Methylphenidate Hcl
Methylprednisolone
Metoclopramide Hcl
Metoprolol Succinate
Metronidazole
Minocycline Hcl
Misoprostol
Mometasone Furoate
Mometasone/Formoterol
Montelukast Sodium
Moxifloxacin Hcl
Mupirocin
Nabumetone
Naproxen
Naproxen Sodium
Neo/Polymyx B Sulf/Dexameth
Neomycin/Polymyxin B/Hydrocort
Nitrofurantoin Macrocrystal
Nitrofurantoin/Nitrofuran Mac
Norelgestromin/Ethin.Estradiol
Norethindrone
Norethindrone Ac-Eth Estradiol
Norethindrone-E.Estradiol-Iron
Norethindrone-Ethinyl Estrad
Norgestimate-Ethinyl Estradiol

Supplemental Table 3. Most Frequently Occurring Baseline Medications Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Medications
Norgestrel-Ethinyl Estradiol
Nortriptyline Hcl
Nystatin
Nystatin/Triamcin
Ofloxacin
Olopatadine Hcl
Omeprazole
Ondansetron
Ondansetron Hcl
Oseltamivir Phosphate
Oxycodone Hcl
Oxycodone Hcl/Acetaminophen
Pantoprazole Sodium
Paroxetine Hcl
Penicillin V Potassium
P-Ephed Hcl/Cetirizine Hcl
Phenazopyridine Hcl
Polyethylene Glycol 3350
Polymyxin B Sulfate/Tmp
Potassium Chloride
Prednisolone Acetate
Prednisone
Prochlorperazine Maleate
Promethazine Hcl
Promethazine Hcl/Codeine
Promethazine/Dextromethorphan
Propoxyphene/Acetaminophen
Propranolol Hcl
Quetiapine Fumarate
Rizatriptan Benzoate
Scopolamine
Sertraline Hcl
Silver Sulfadiazine
Sodium Fluoride
Sodium,potassium,&mag Sulfates
Spironolactone
Sucralfate
Sulfacetamide Sodium
Sulfacetamide Sodium/Sulfur
Sulfamethoxazole/Trimethoprim
Sumatriptan Succinate
Tamsulosin Hcl
Tazarotene
Temazepam
Terconazole
Thyroid,pork
Tizanidine Hcl
Tobramycin
Tobramycin/Dexamethasone
Topiramate
Tramadol Hcl

Supplemental Table 3. Most Frequently Occurring Baseline Medications Observed Among SEASONIQUE Users and Comparators Across All Six Calendar Blocks

Medications
Trazodone Hcl
Tretinoin
Triamcinolone Acetonide
Triamterene/Hydrochlorothiazid
Triazolam
Valacyclovir Hcl
Venlafaxine Hcl
Verapamil Hcl
Zolmitriptan
Zolpidem Tartrate

Annex 3. Figures

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Figure 1a. Kernel Density Estimates Before Matching

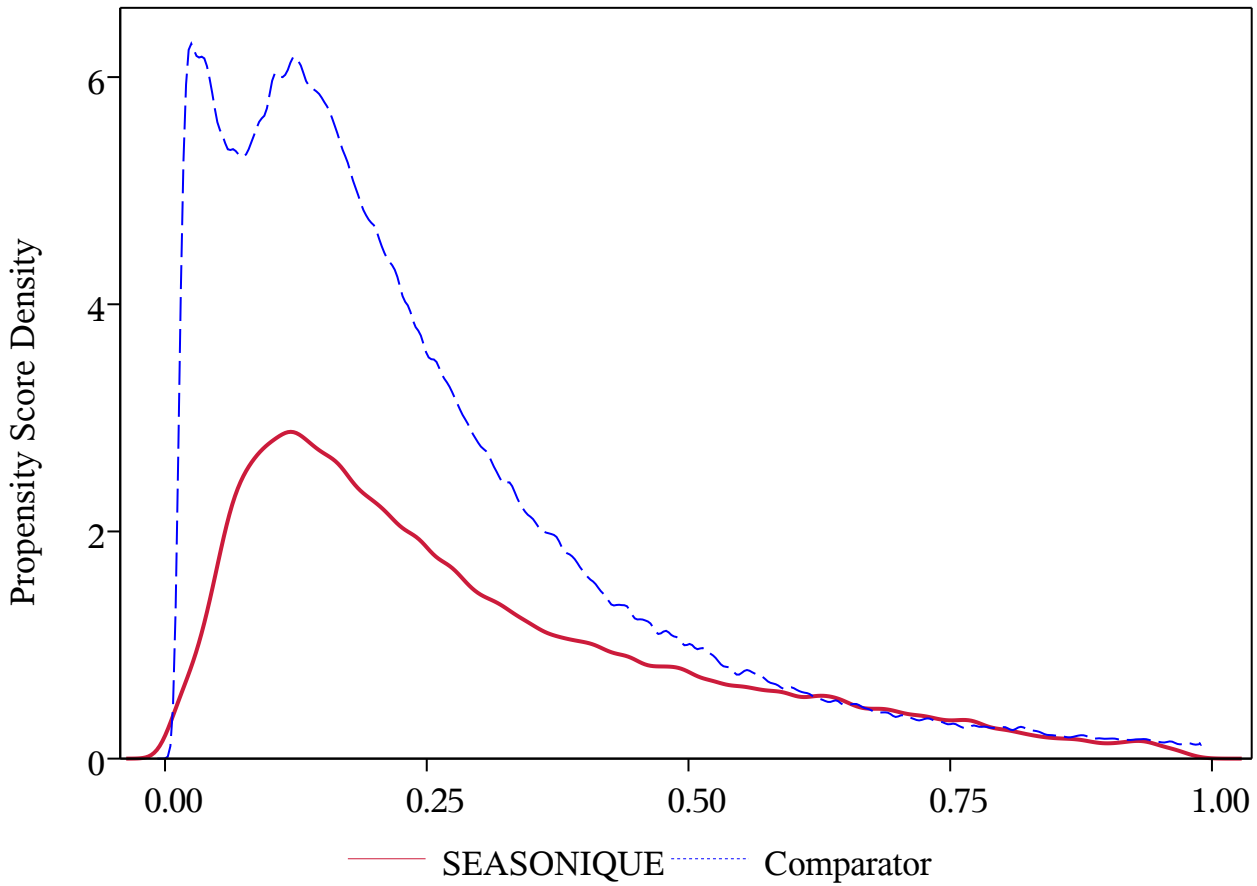


Figure 1b. Kernel Density Estimates After Matching

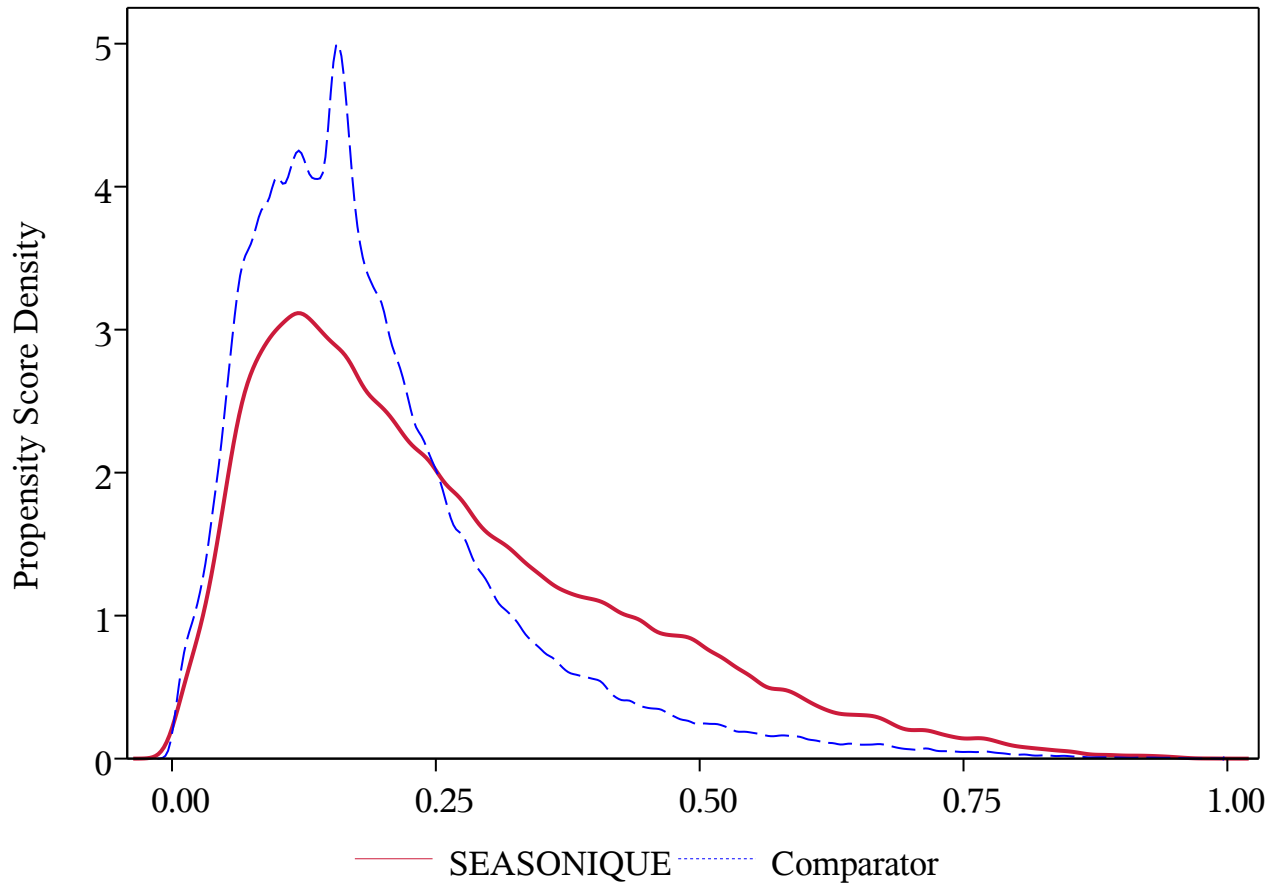


Figure 2a. Log-log Survival Curves, VTE (Main Definition), Current Exposure

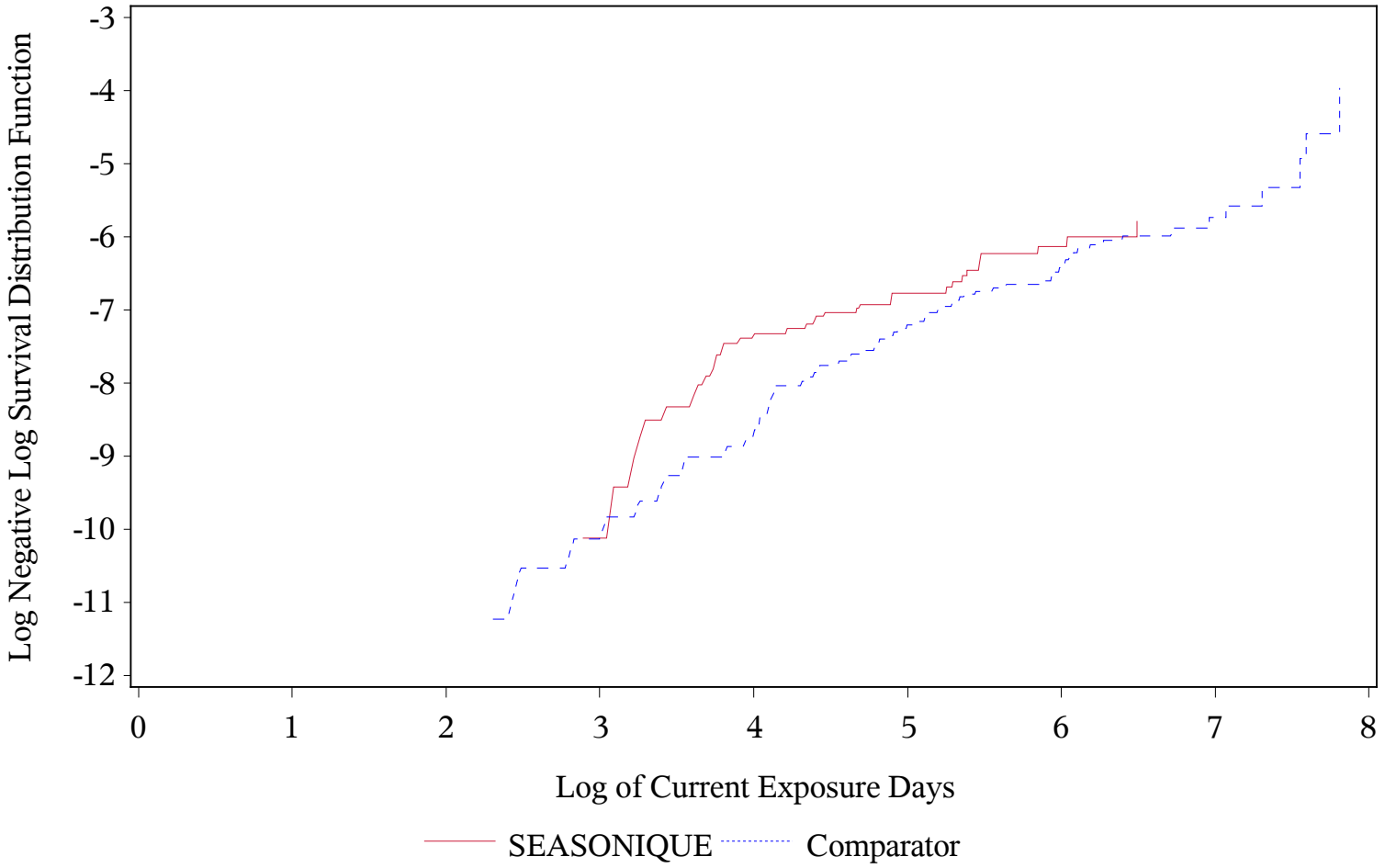


Figure 2b. Survival Curves, VTE (Main Definition), Current Exposure

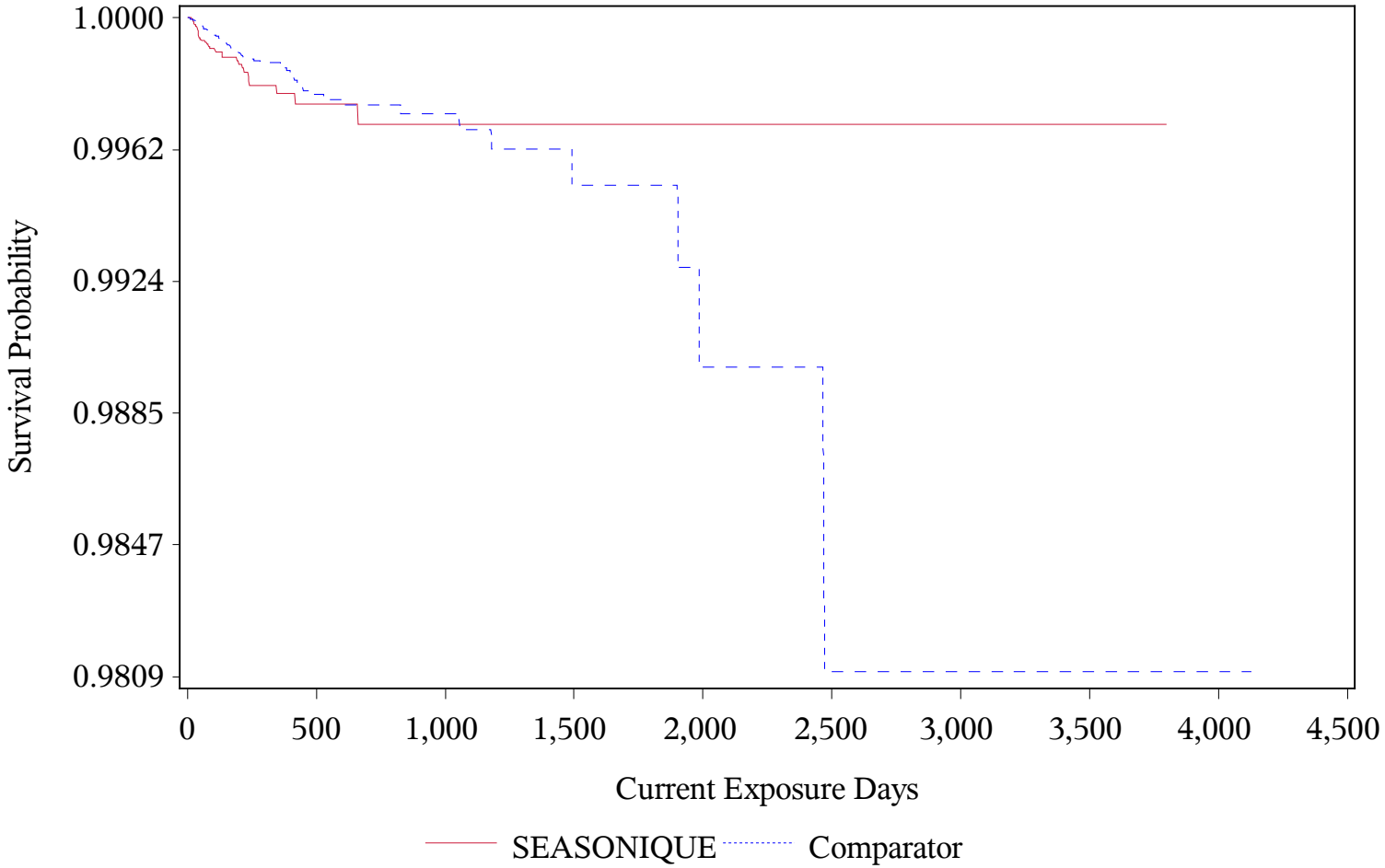


Figure 2c. Log-log Survival Curves, VTE (Main Definition), Recent Exposure

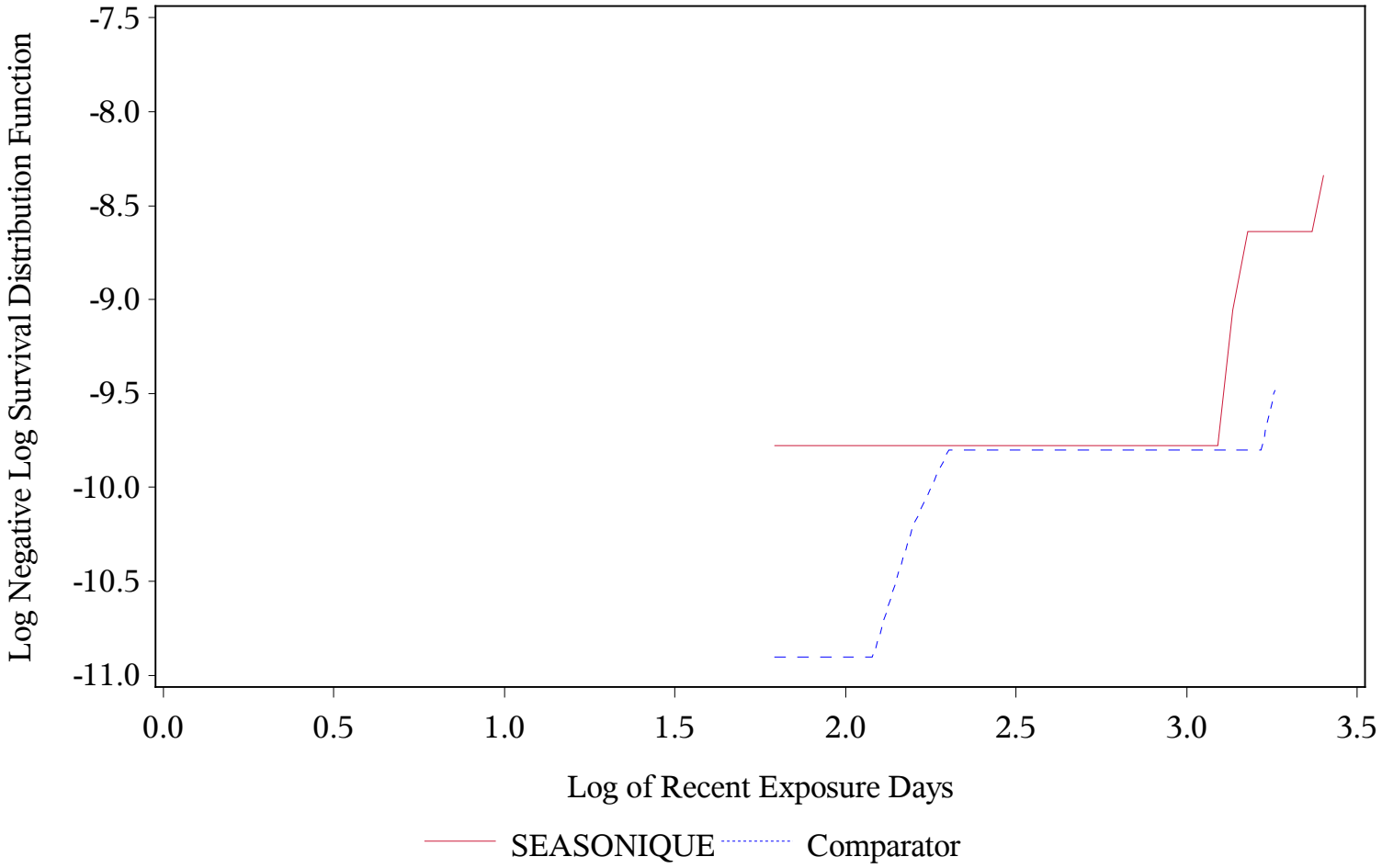


Figure 2d. Survival Curves, VTE (Main Definition), Recent Exposure

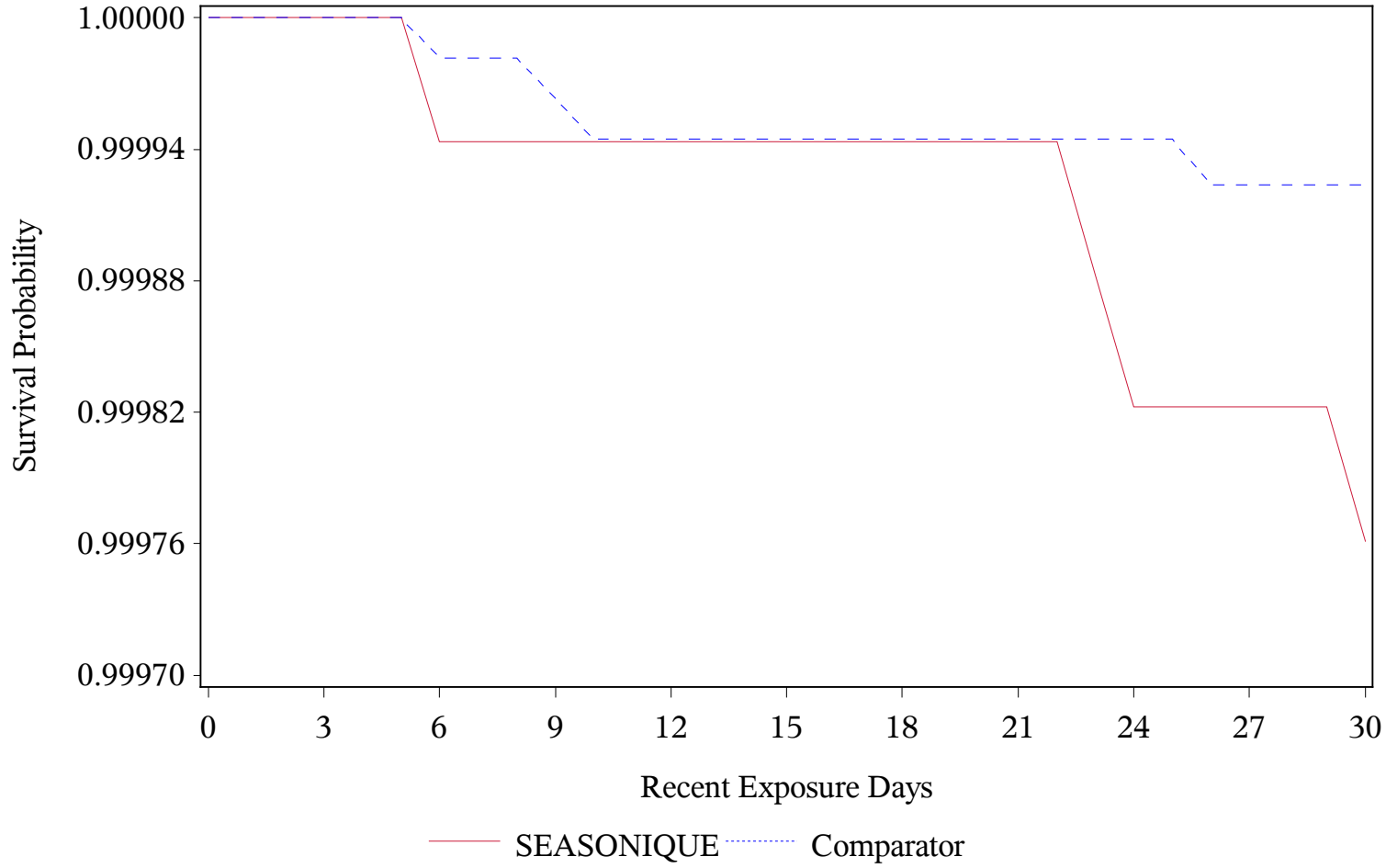


Figure 2e. Log-log Survival Curves, VTE (Main Definition), Intermediate Exposure

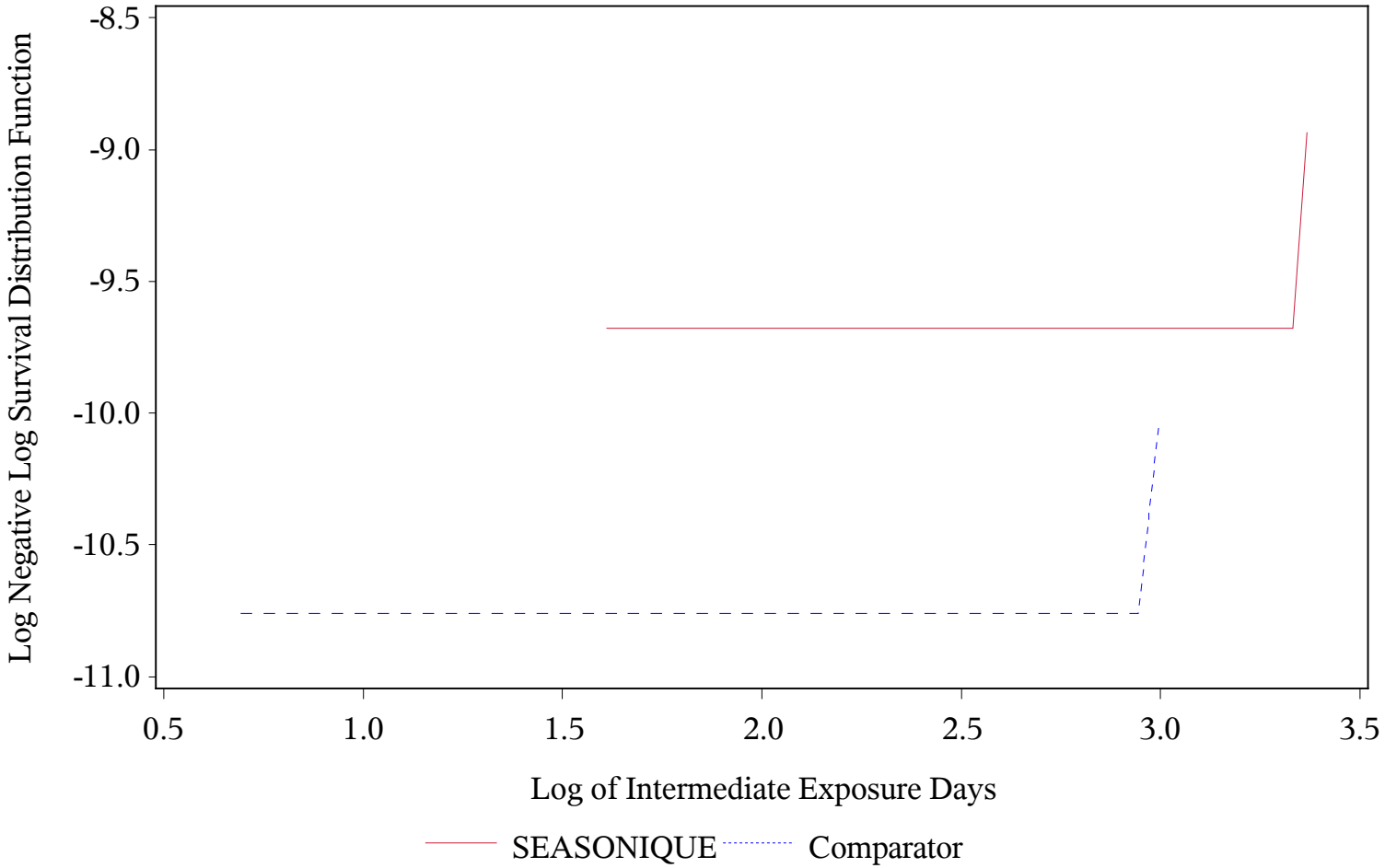


Figure 2f. Survival Curves, VTE (Main Definition), Intermediate Exposure

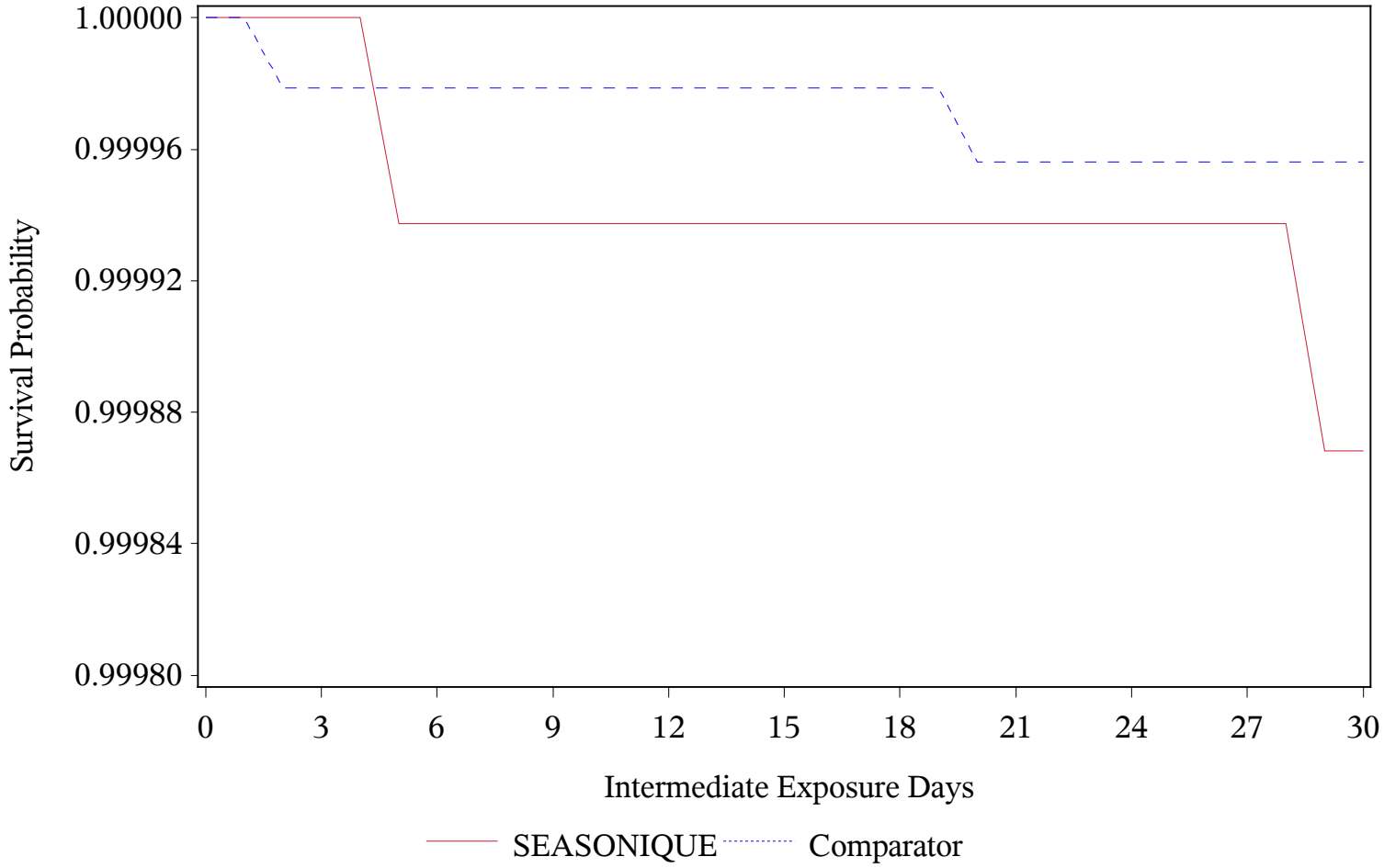


Figure 2g. Log-log Survival Curves, VTE (Main Definition), Remote Exposure

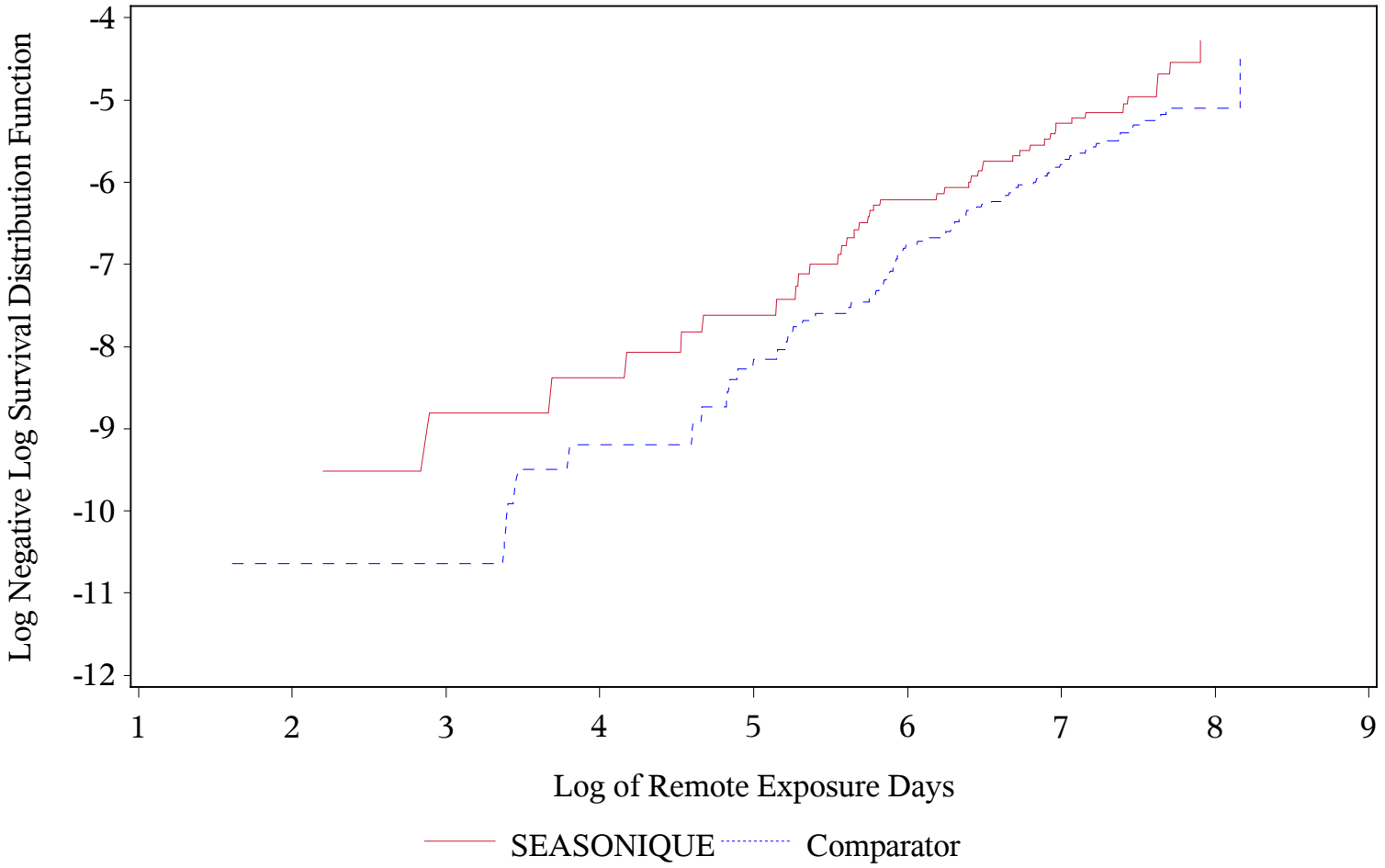


Figure 2h. Survival Curves, VTE (Main Definition), Remote Exposure

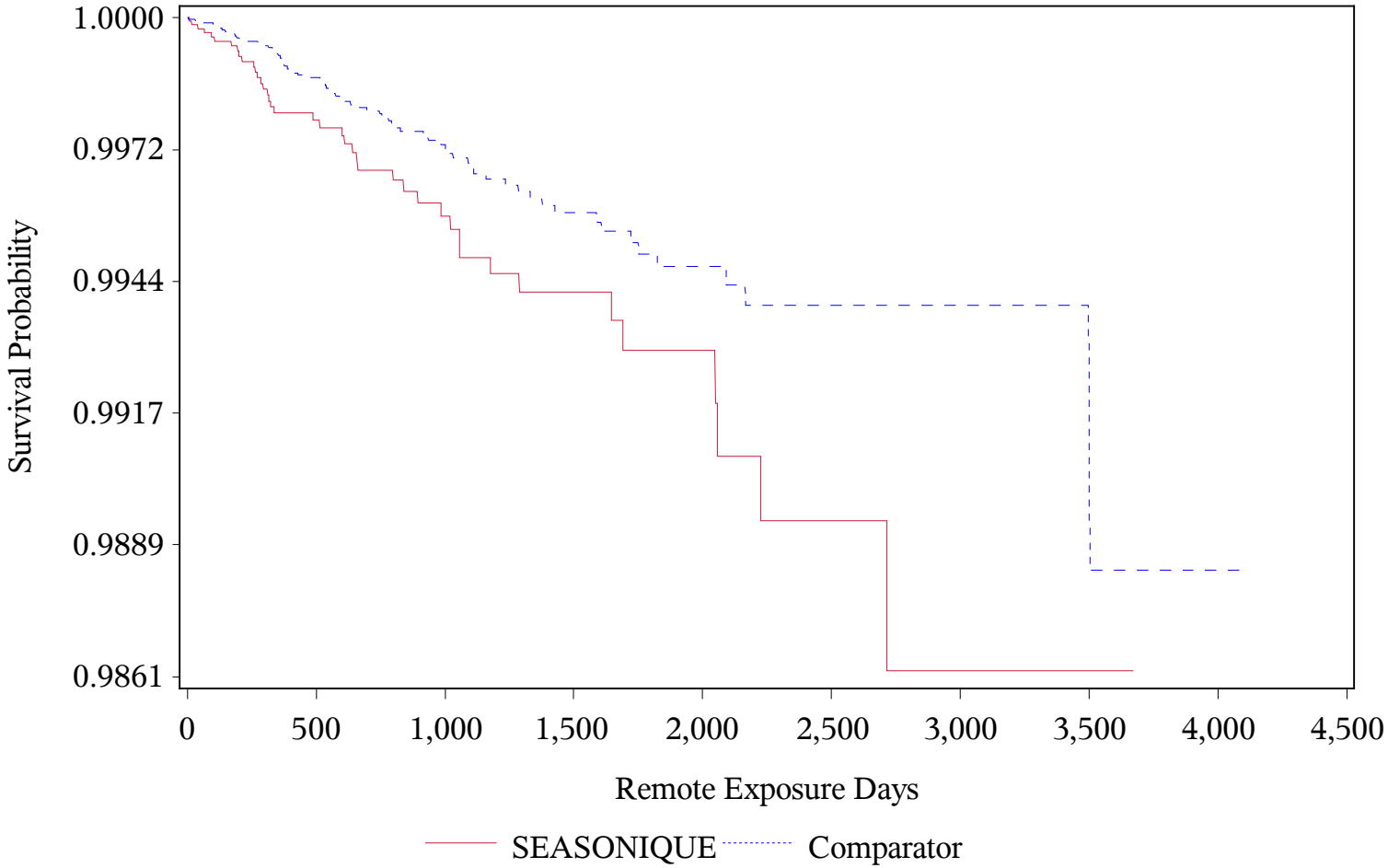


Figure 3a. Log-log Survival Curves, VTE (Sensitivity Definition), Current Exposure

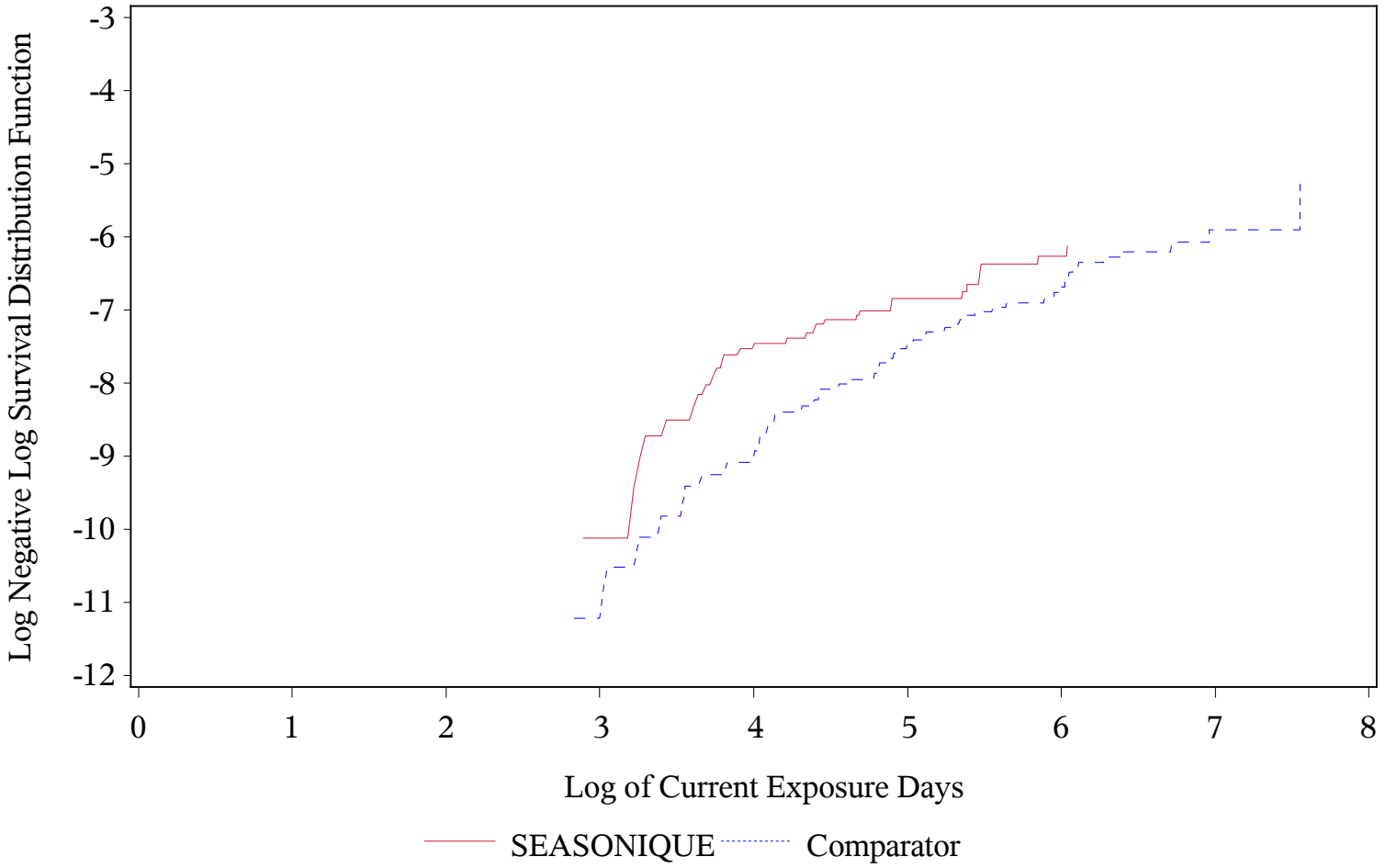


Figure 3b. Survival Curves, VTE (Sensitivity Definition), Current Exposure

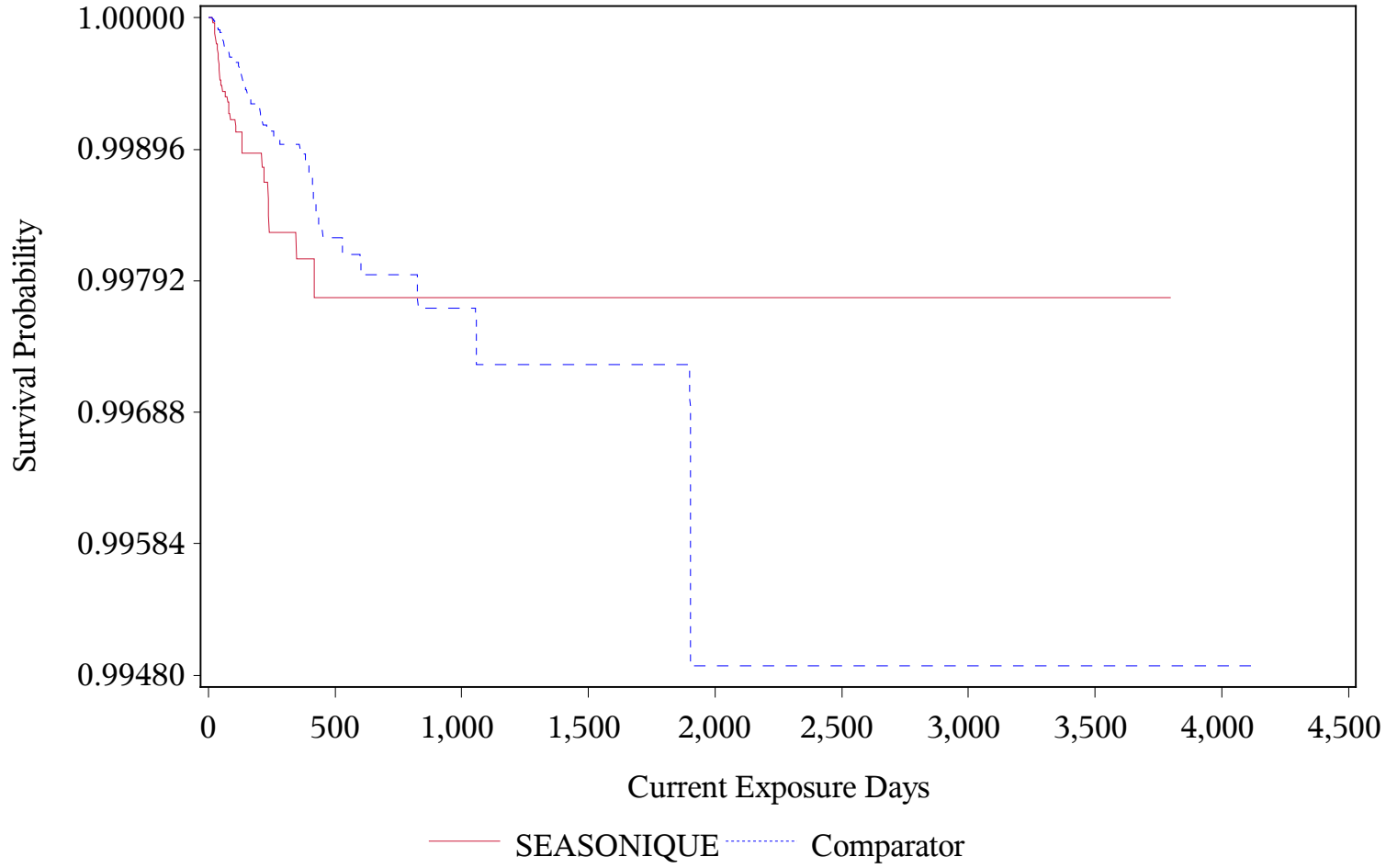


Figure 3c. Log-log Survival Curves, VTE (Sensitivity Definition), Recent Exposure

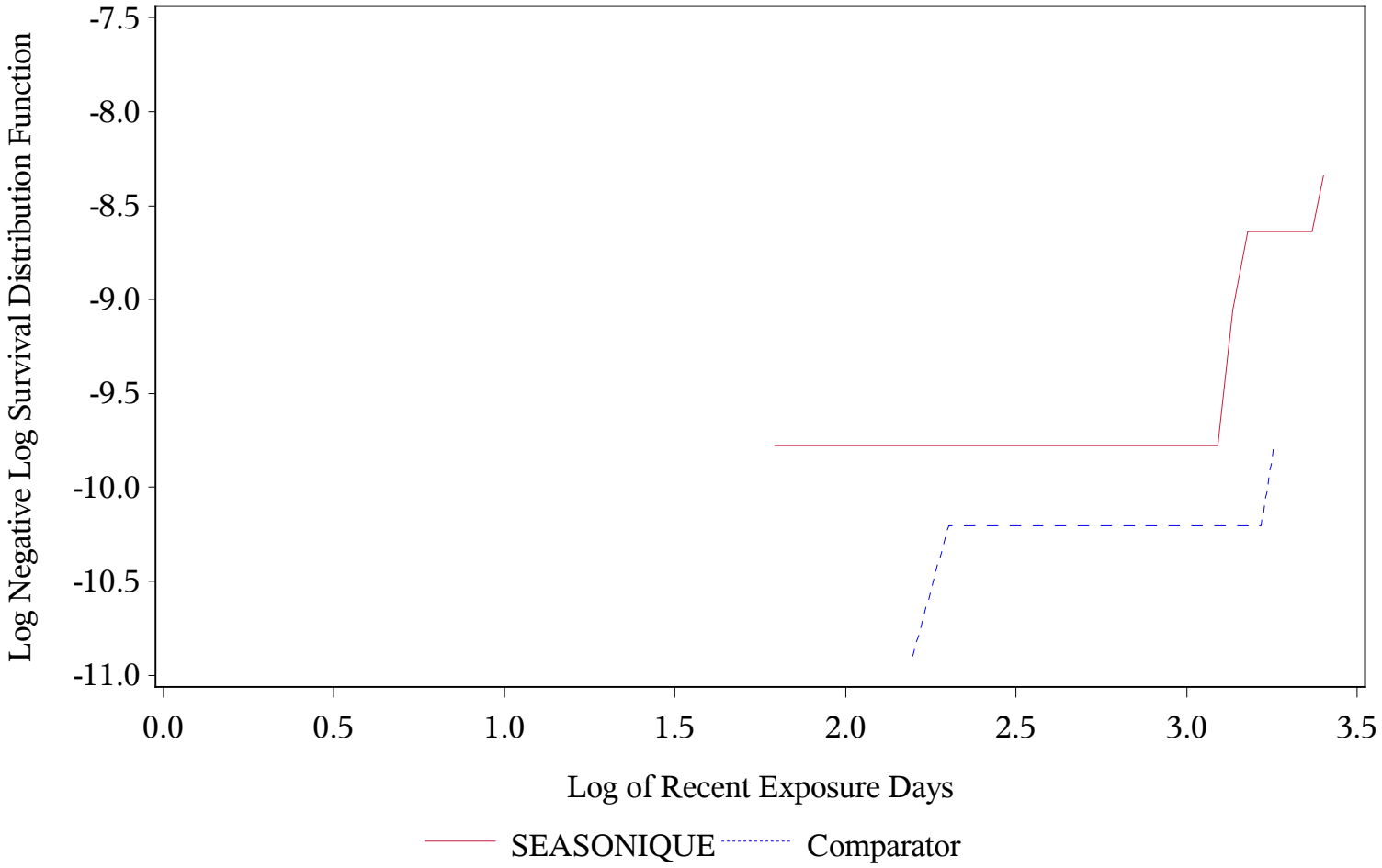


Figure 3d. Survival Curves, VTE (Sensitivity Definition), Recent Exposure

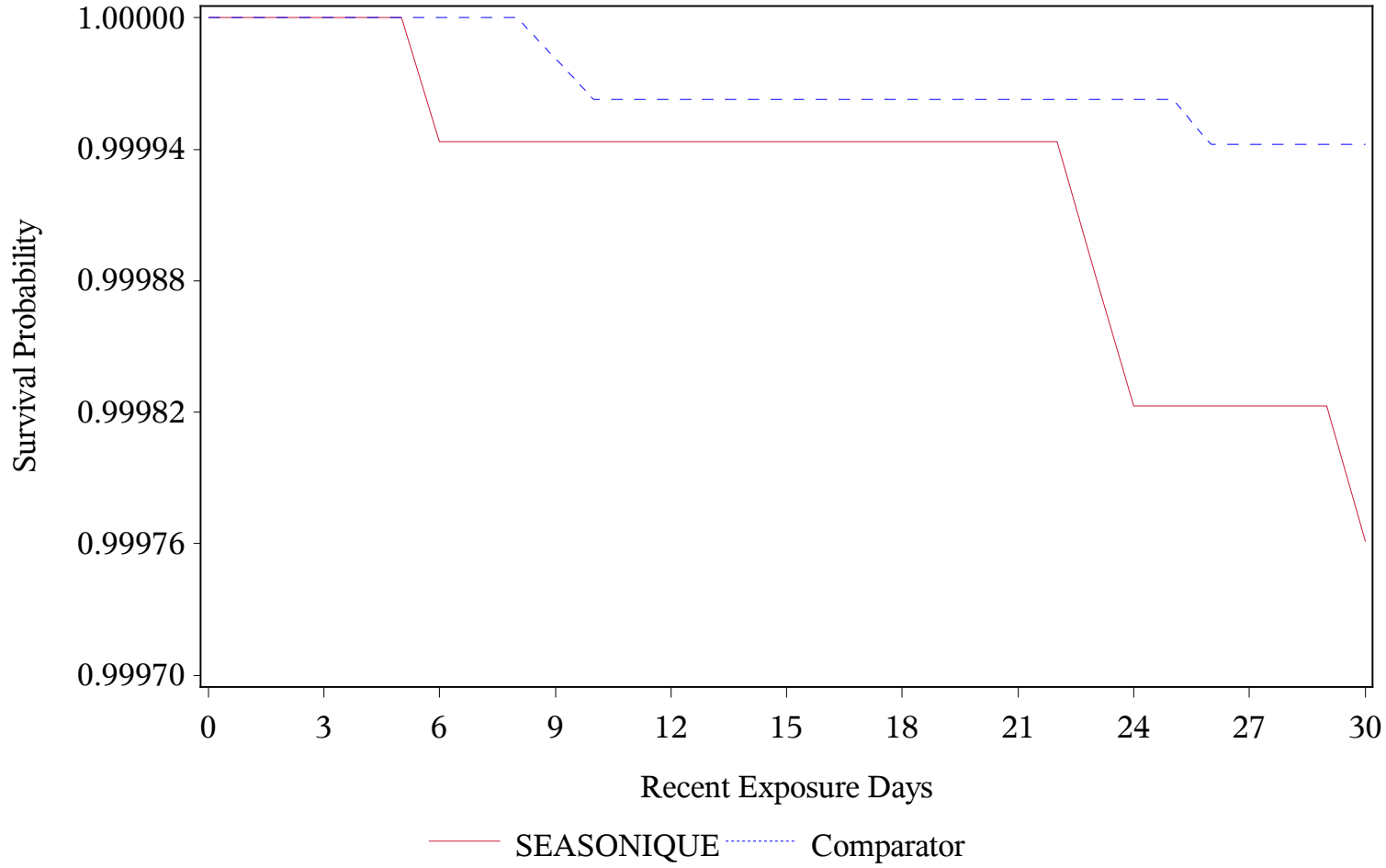


Figure 3e. Log-log Survival Curves, VTE (Sensitivity Definition), Intermediate Exposure

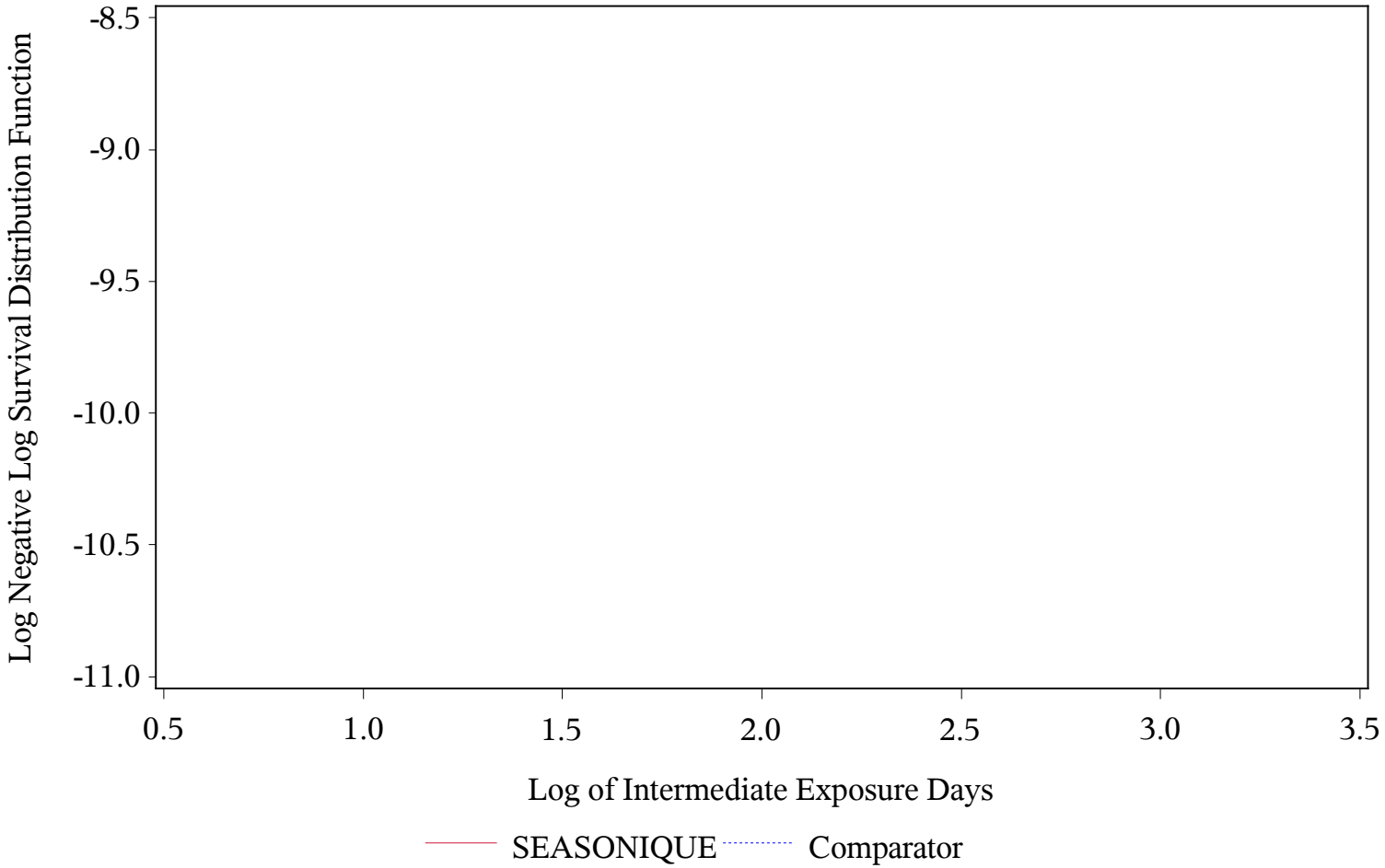


Figure 3f. Survival Curves, VTE (Sensitivity Definition), Intermediate Exposure

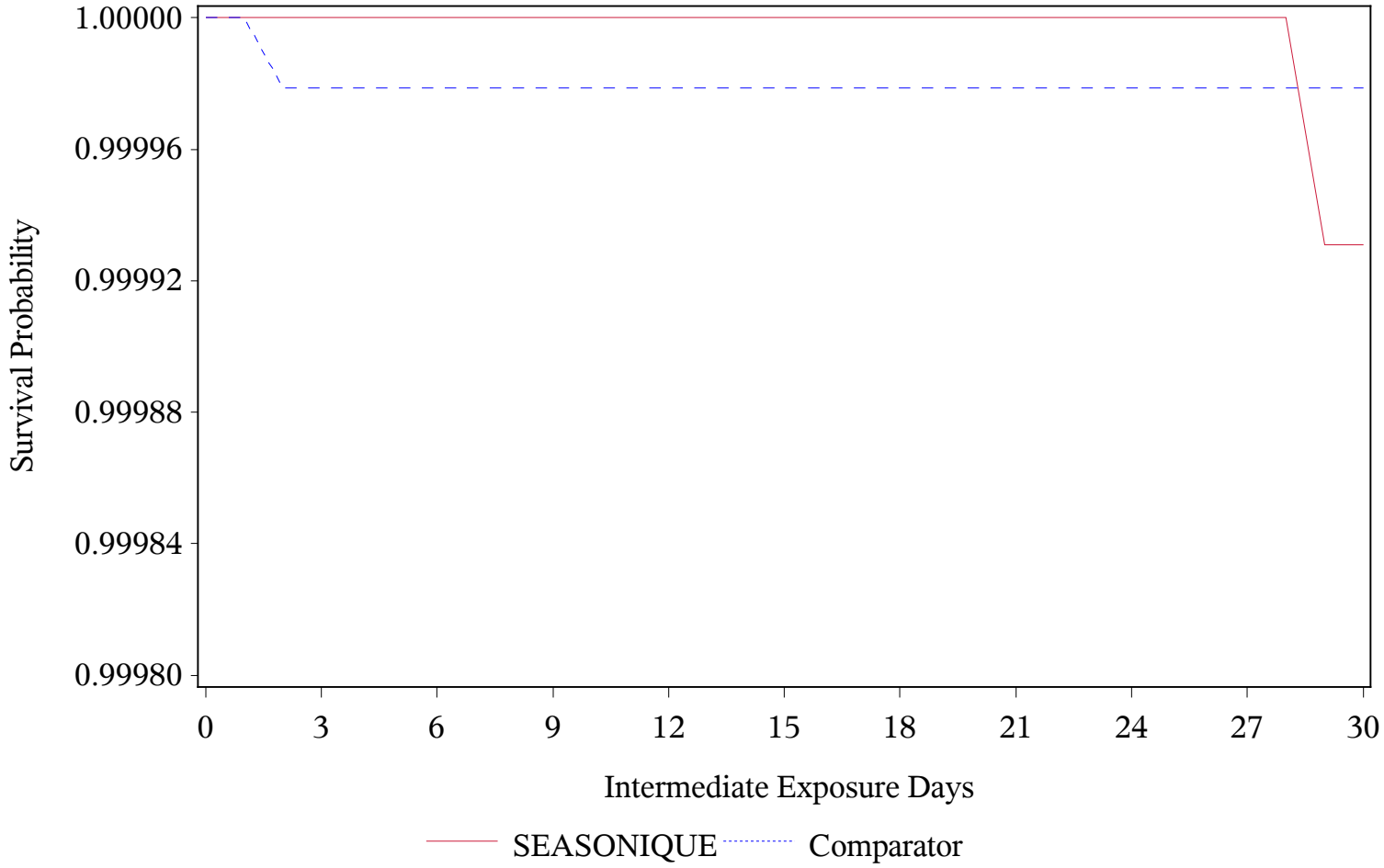


Figure 3g. Log-log Survival Curves, VTE (Sensitivity Definition), Remote Exposure

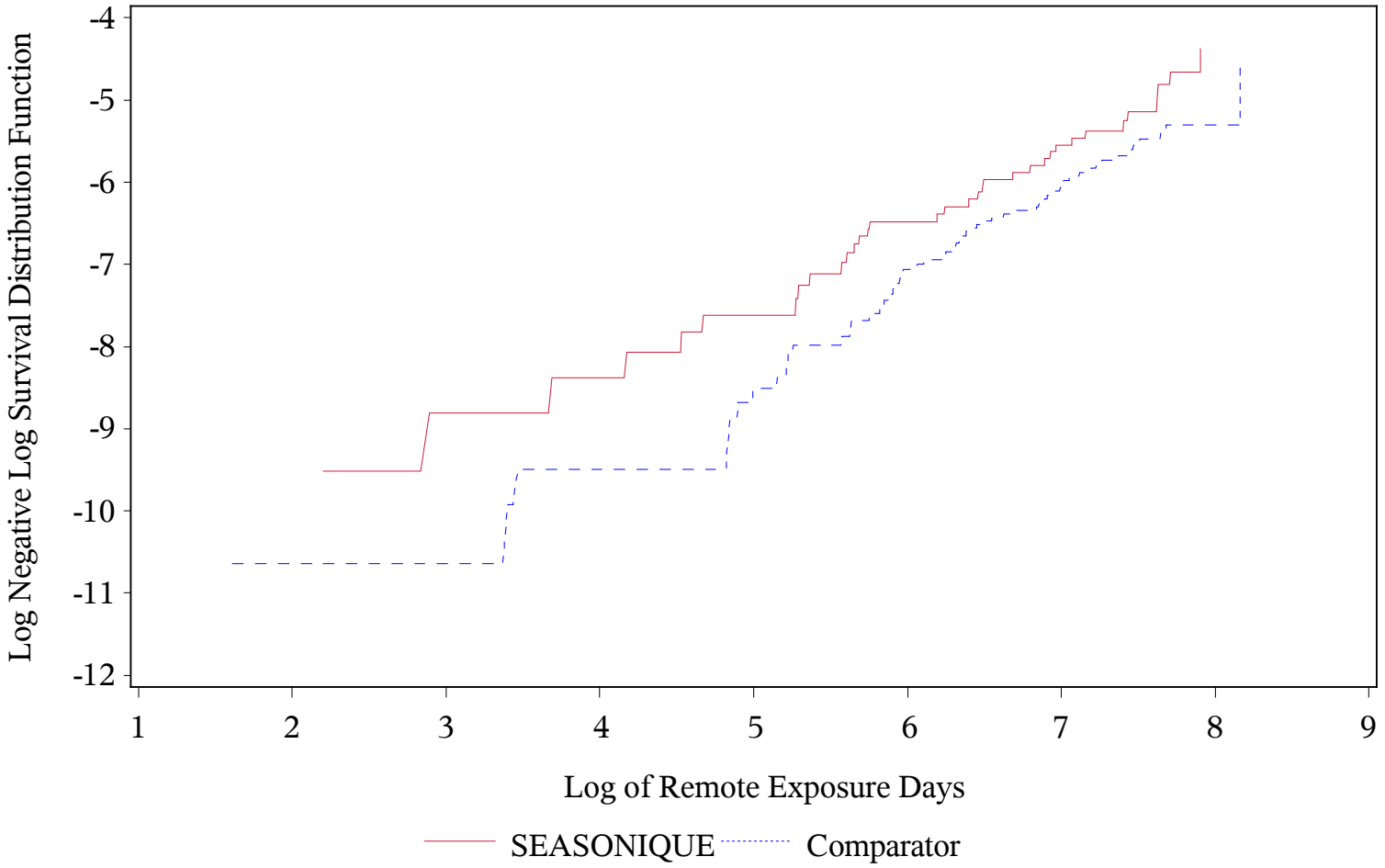


Figure 3h. Survival Curves, VTE (Sensitivity Definition), Remote Exposure

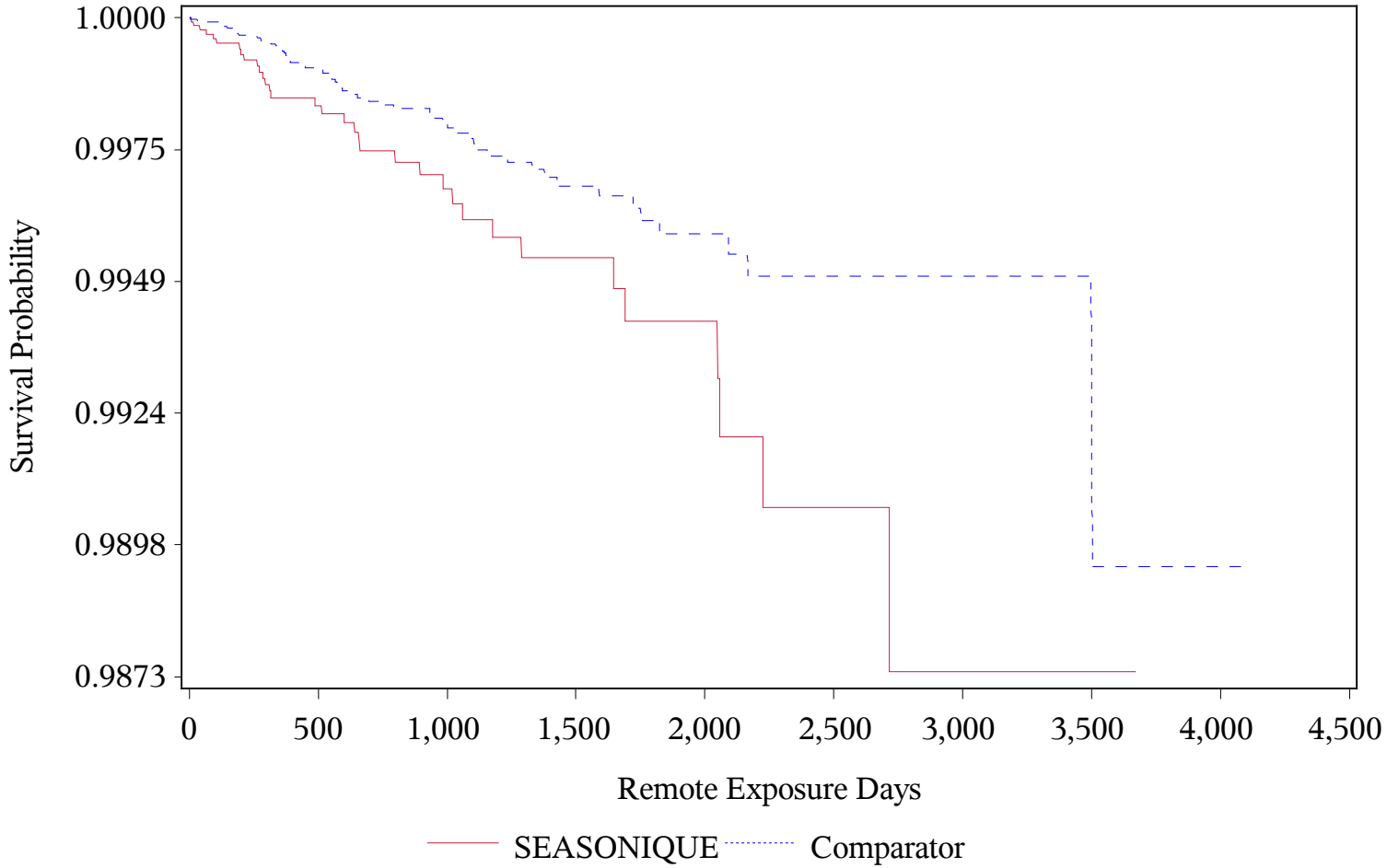


Figure 4a. Log-log Survival Curves, ATE, Current Exposure

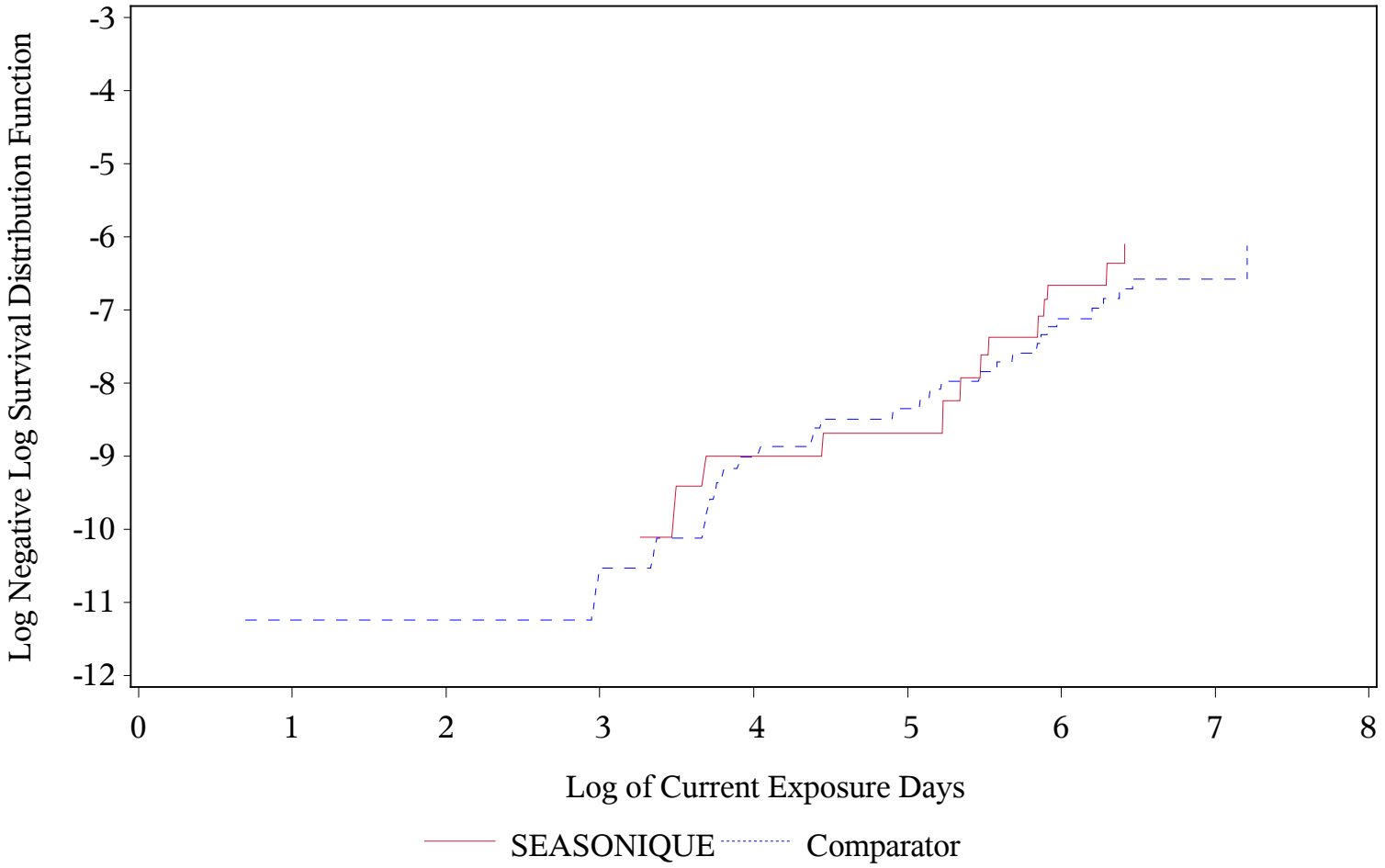


Figure 4b. Survival Curves, ATE, Current Exposure

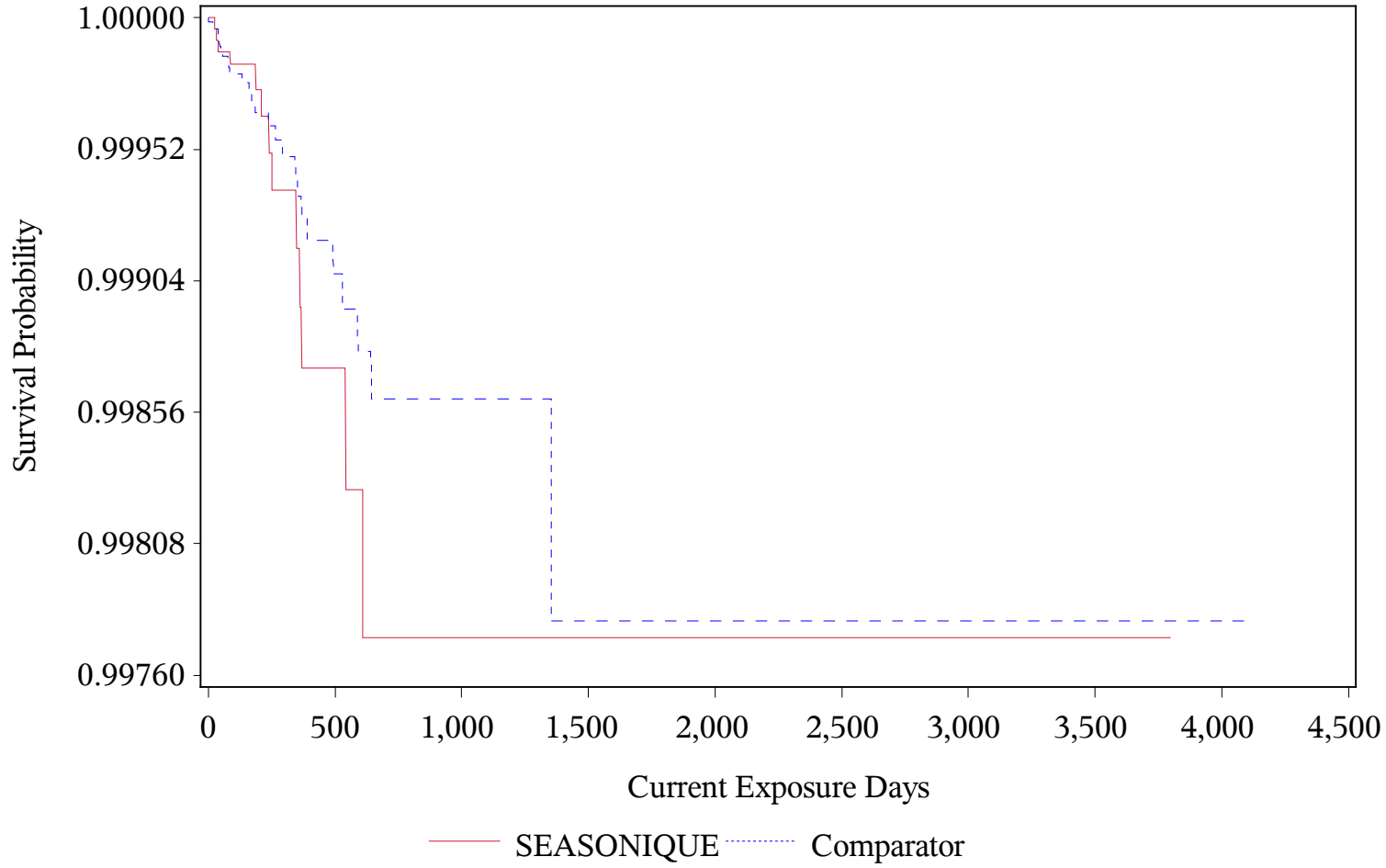


Figure 4c. Log-log Survival Curves, ATE, Recent Exposure

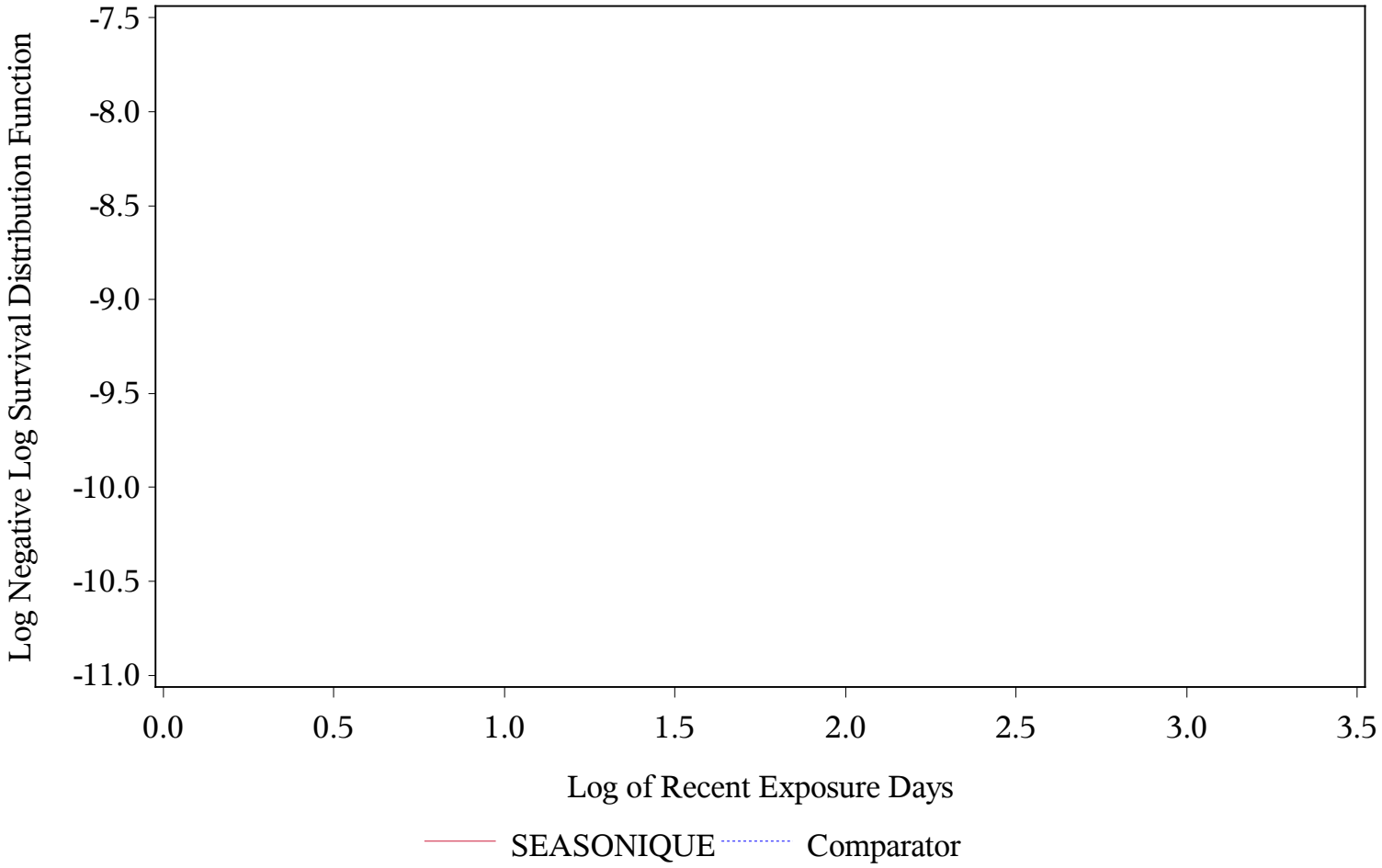


Figure 4d. Survival Curves, ATE, Recent Exposure

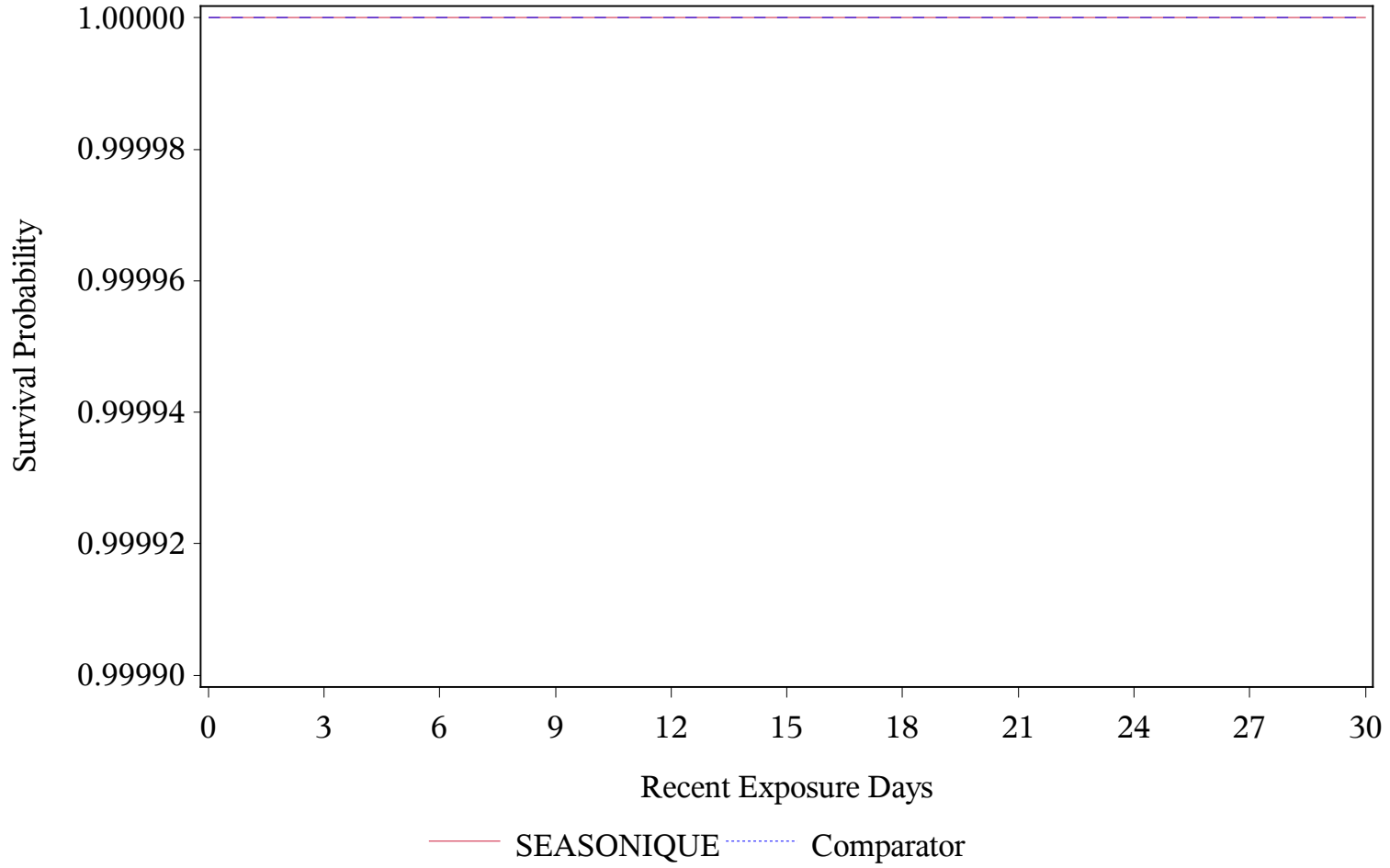


Figure 4e. Log-log Survival Curves, ATE, Intermediate Exposure

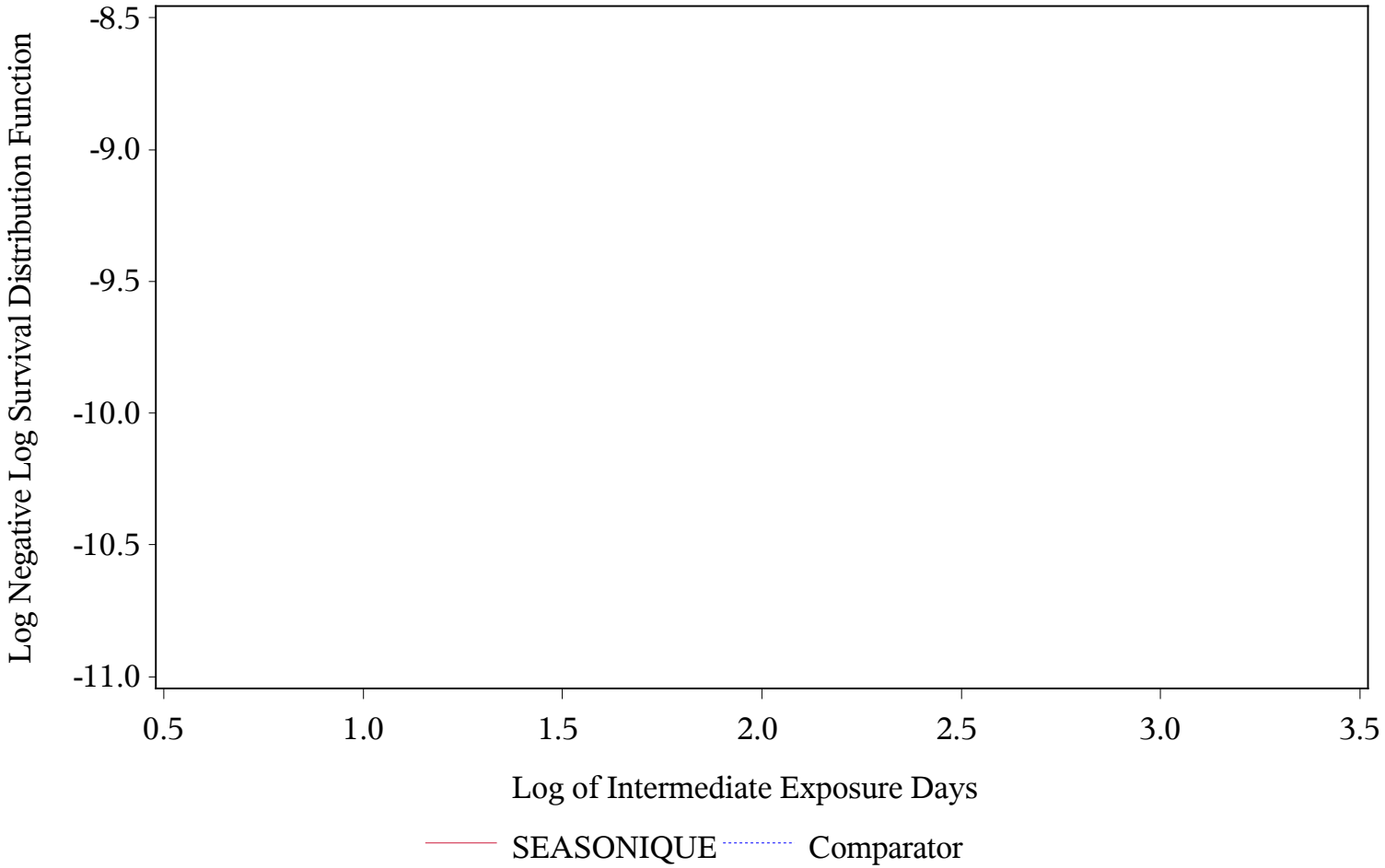


Figure 4f. Survival Curves, ATE, Intermediate Exposure

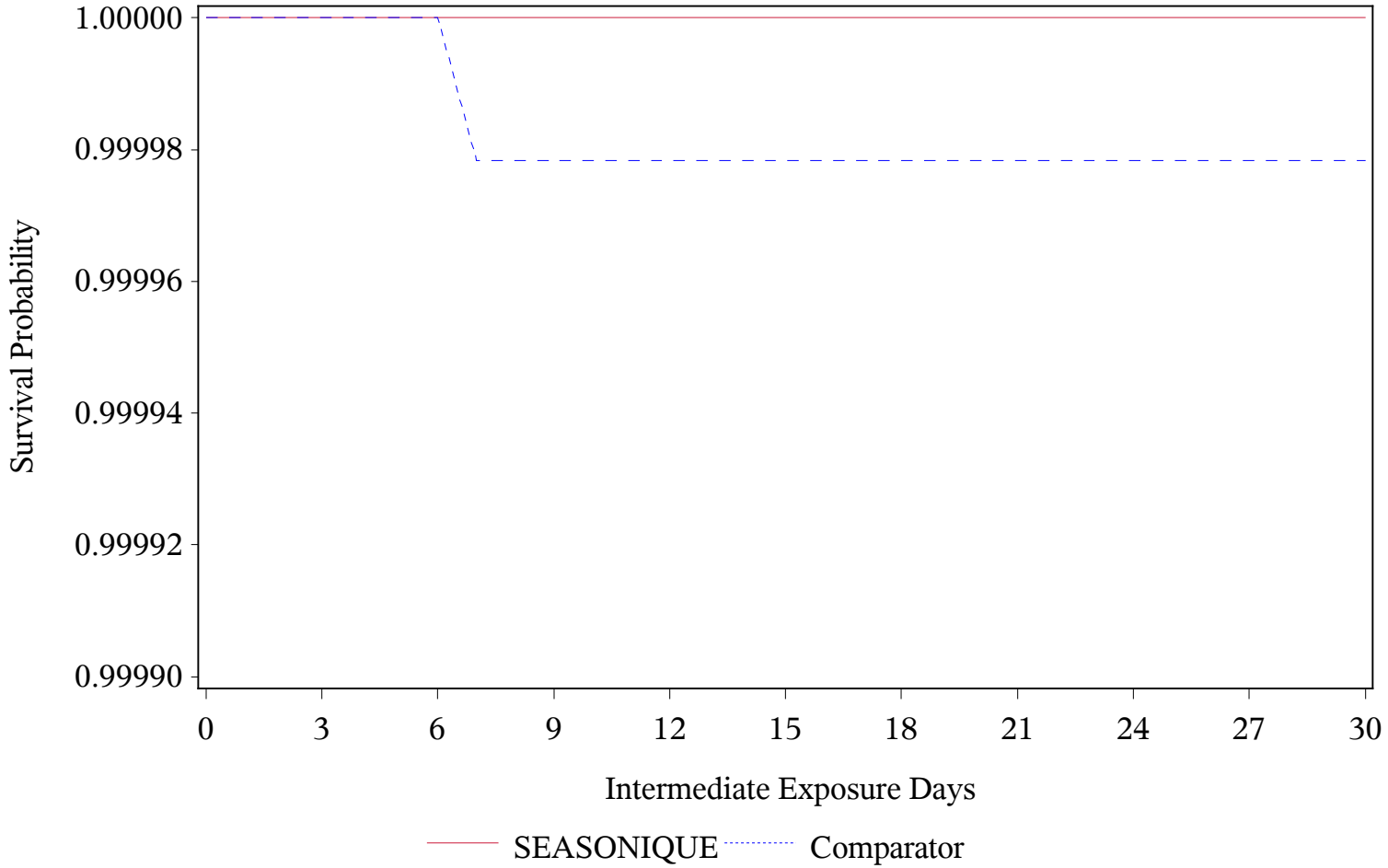


Figure 4g. Log-log Survival Curves, ATE, Remote Exposure

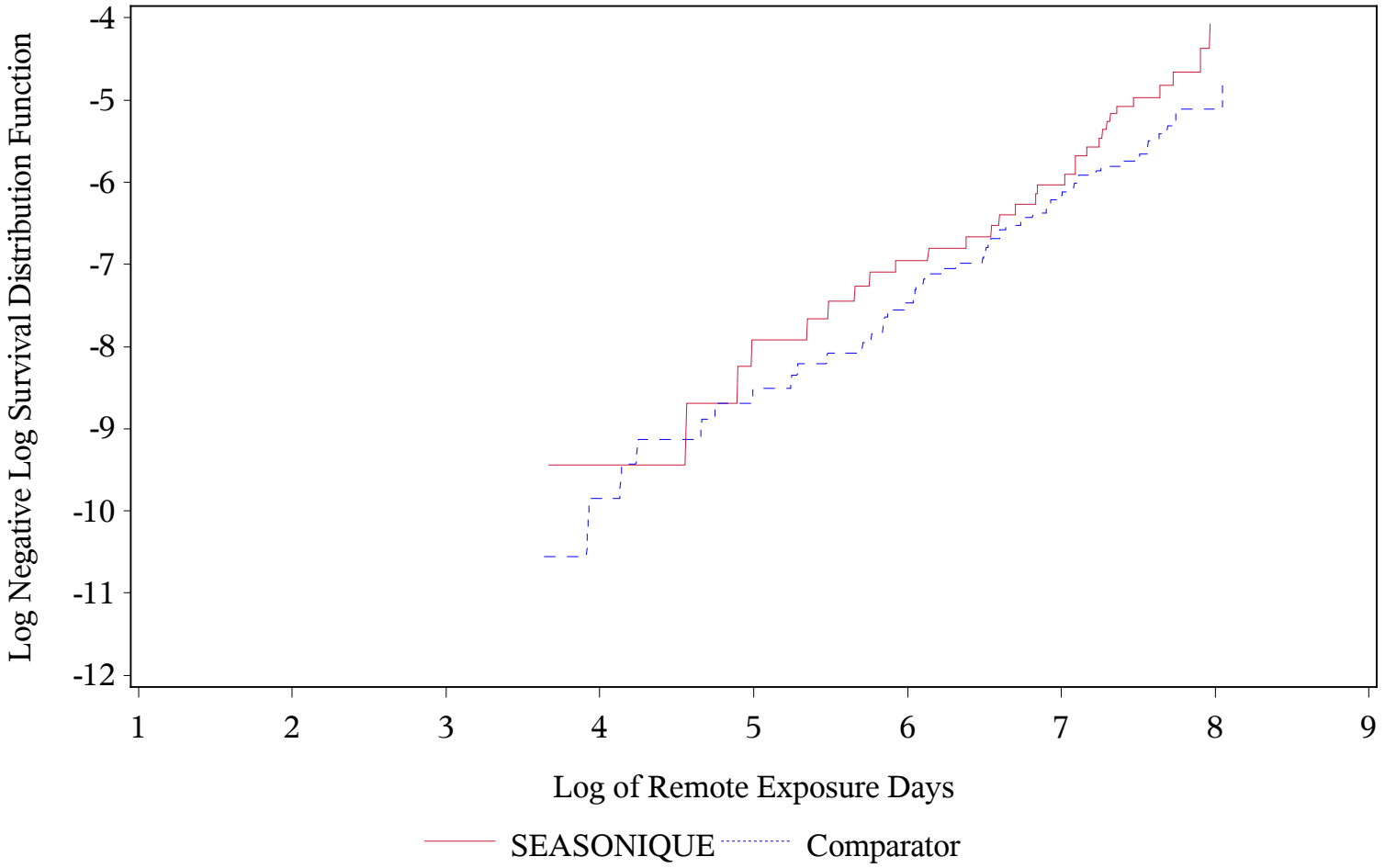


Figure 4h. Survival Curves, ATE, Remote Exposure

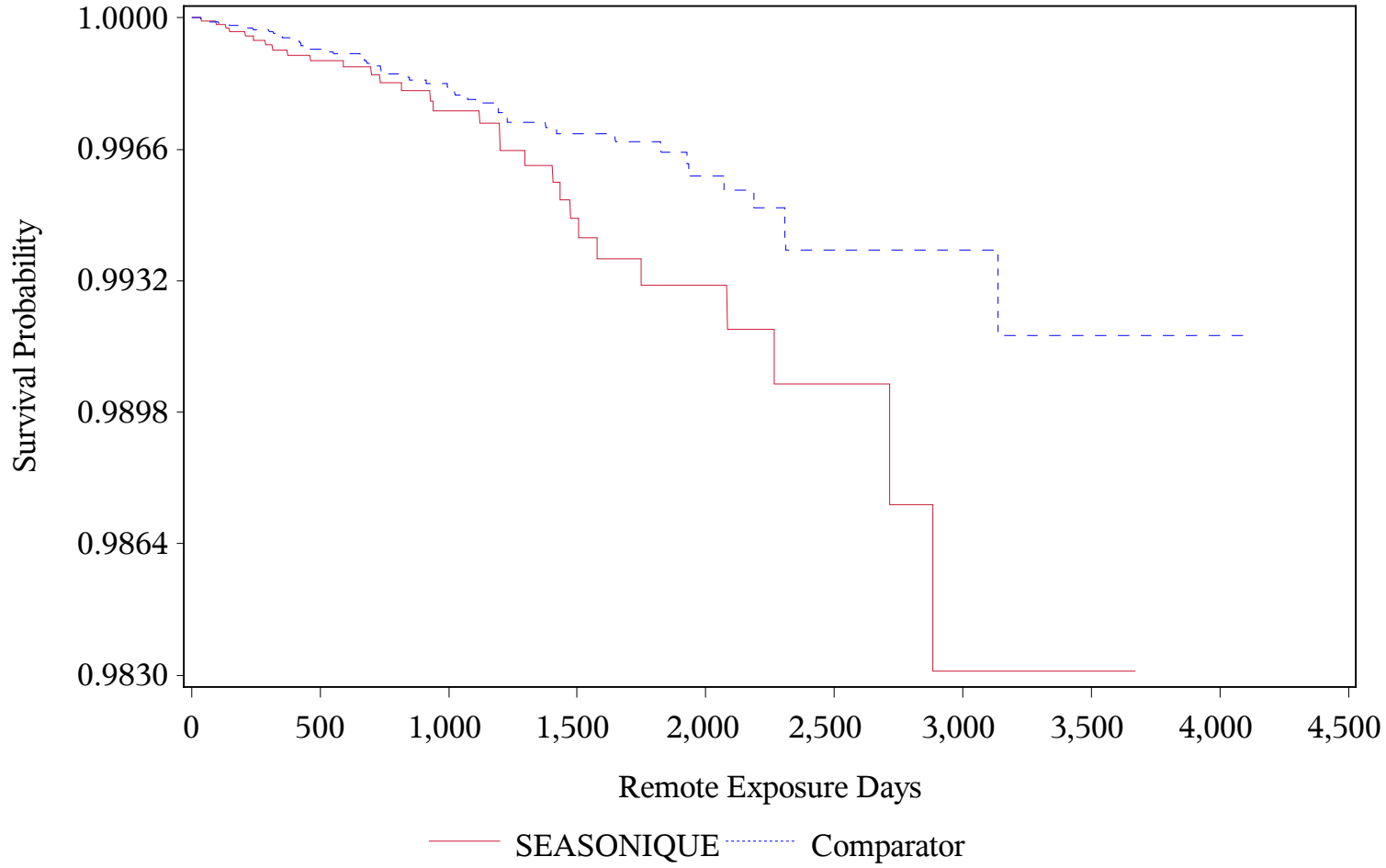


Figure 5a. Log-log Survival Curves, Breast Cancer, Current Exposure

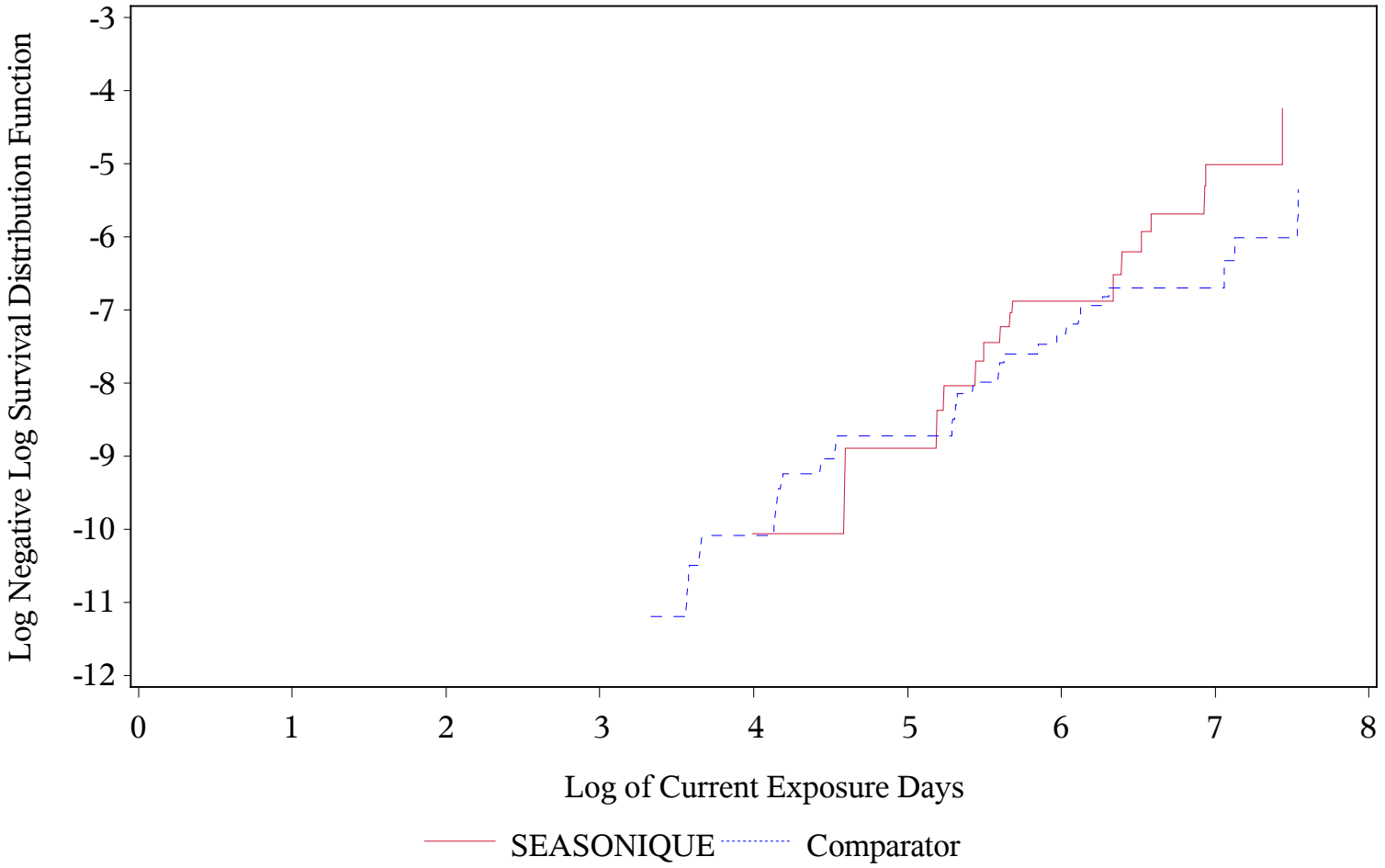


Figure 5b. Survival Curves, Breast Cancer, Current Exposure

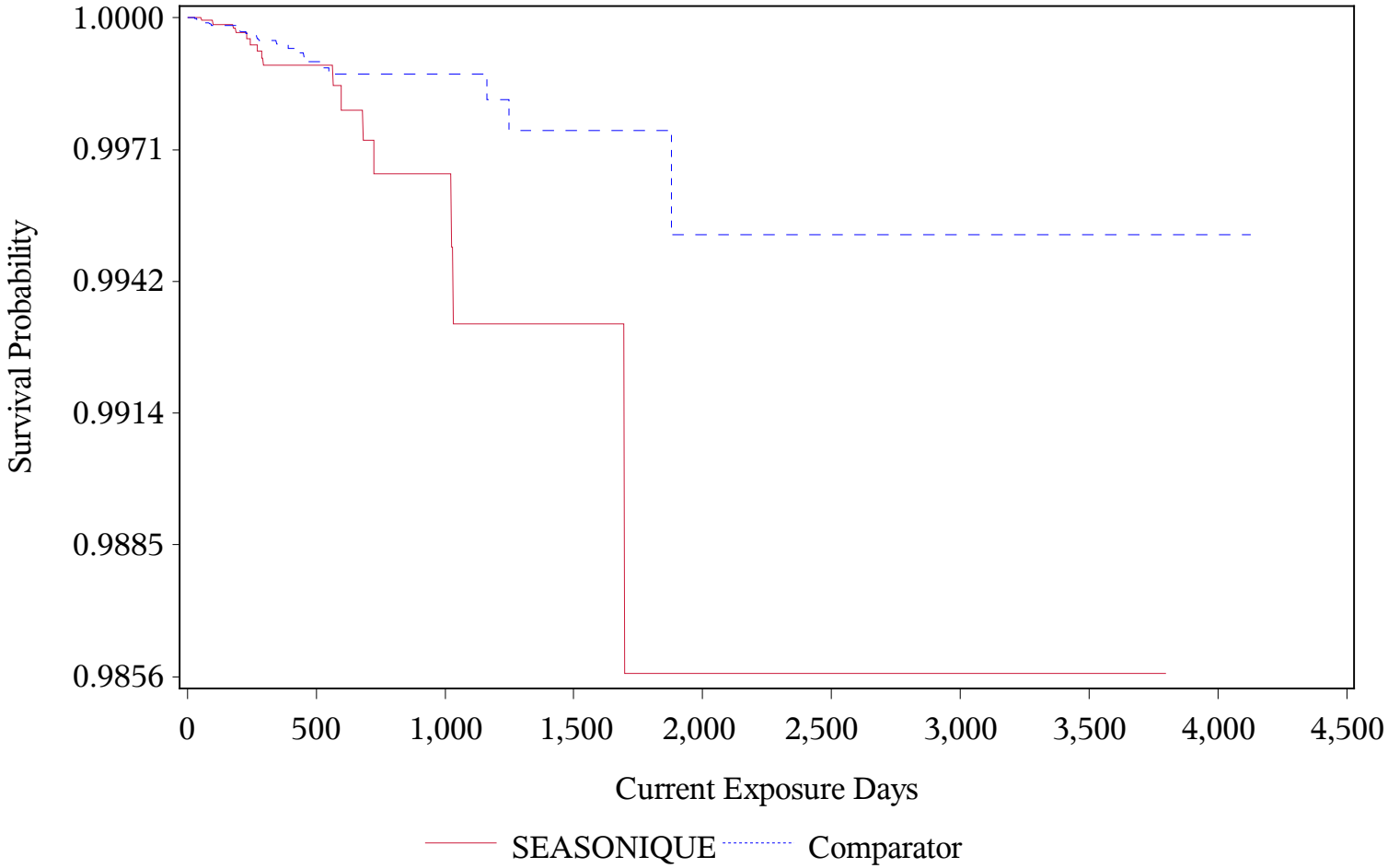


Figure 5c. Log-log Survival Curves, Breast Cancer, Recent Exposure

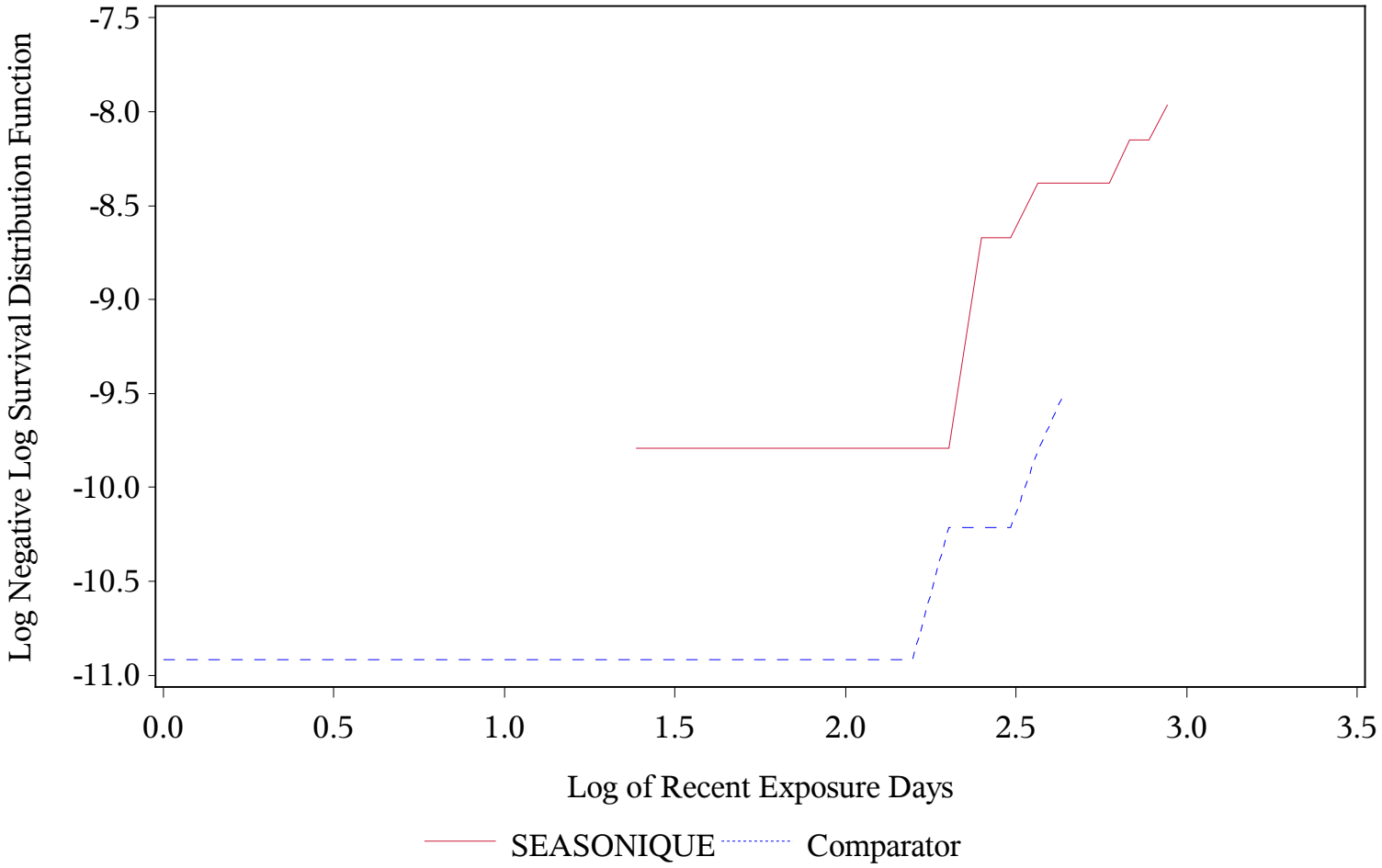


Figure 5d. Survival Curves, Breast Cancer, Recent Exposure

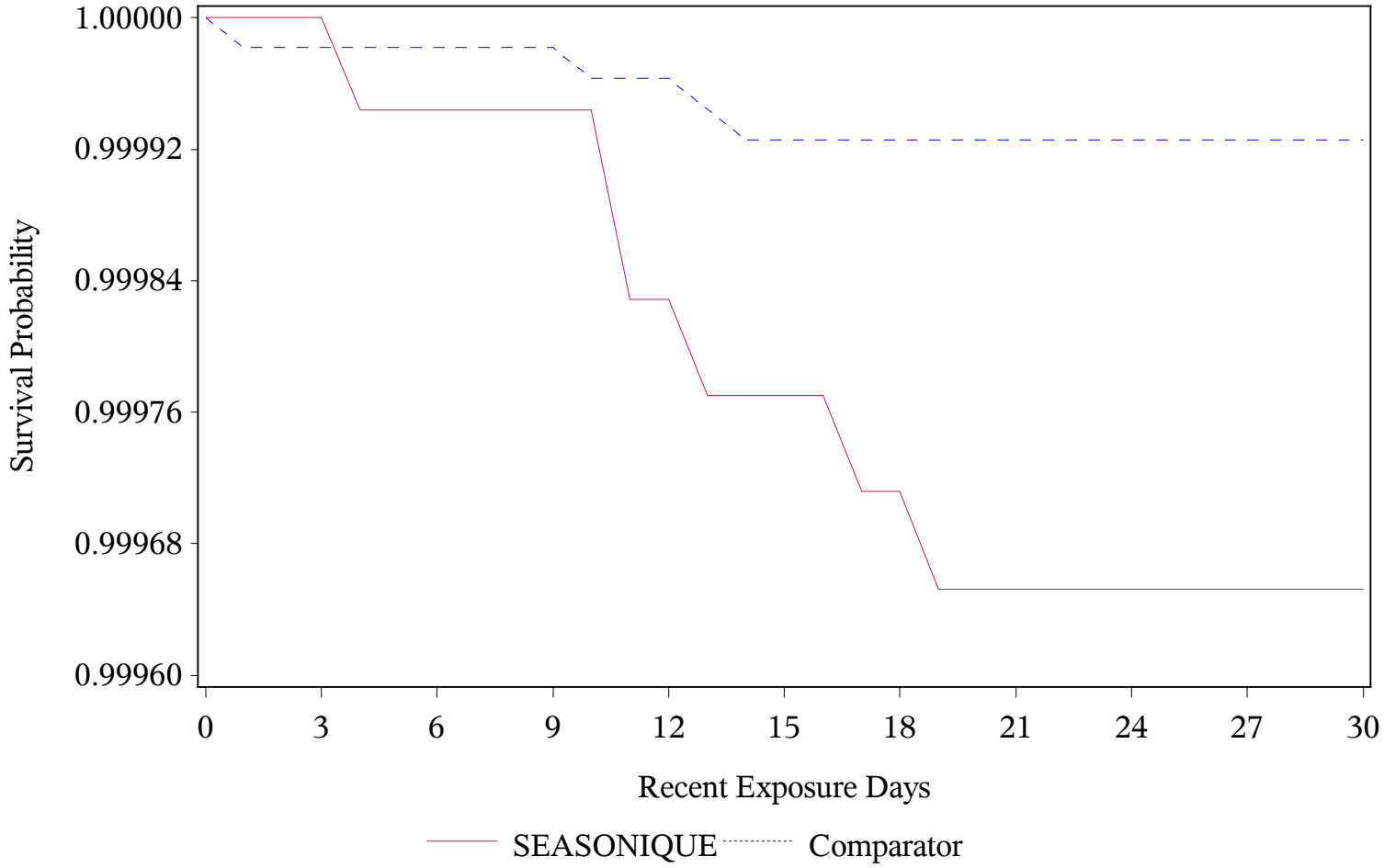


Figure 5e. Log-log Survival Curves, Breast Cancer, Intermediate Exposure

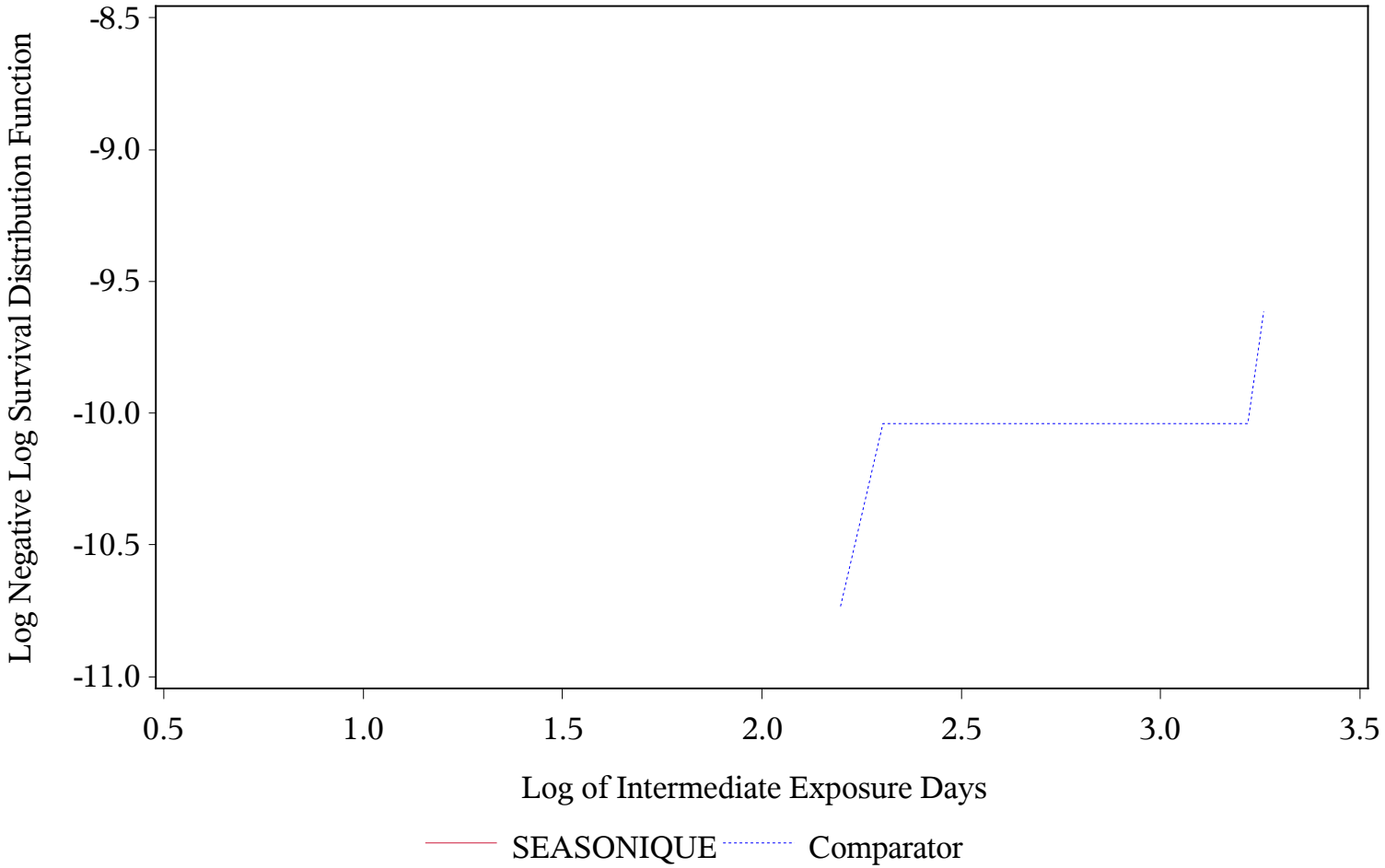


Figure 5f. Survival Curves, Breast Cancer, Intermediate Exposure

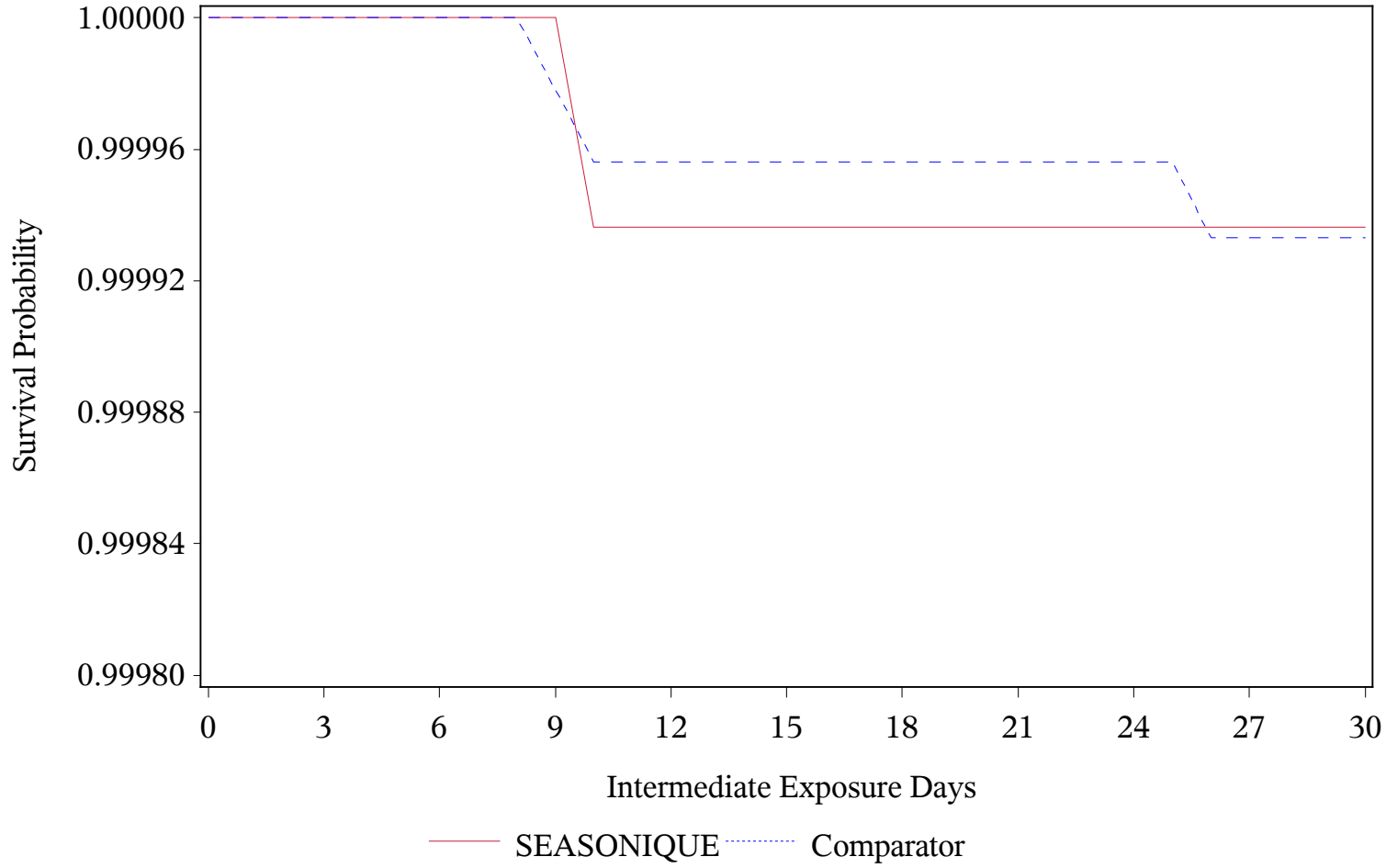


Figure 5g. Log-log Survival Curves, Breast Cancer, Remote Exposure

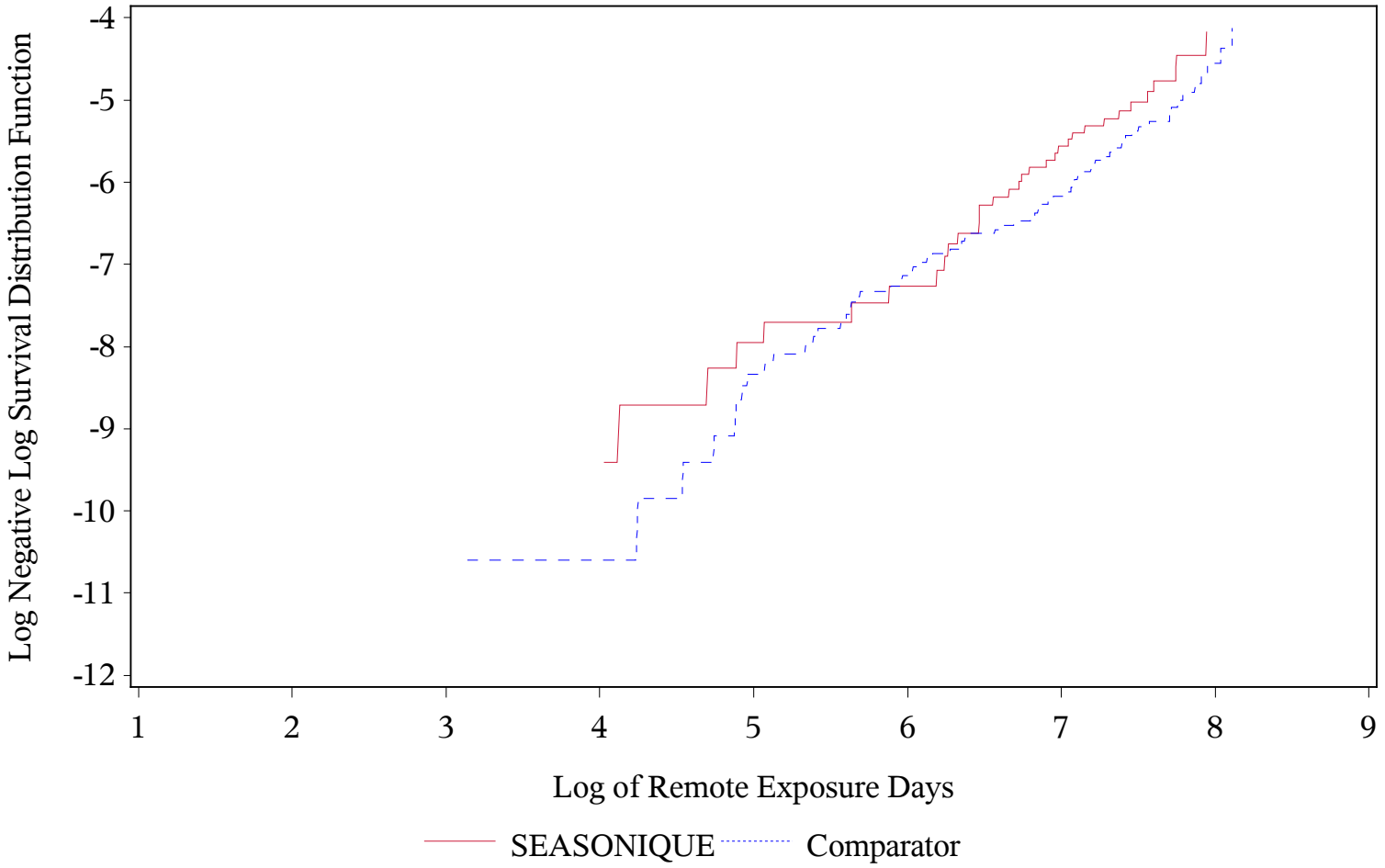


Figure 5h. Survival Curves, Breast Cancer, Remote Exposure

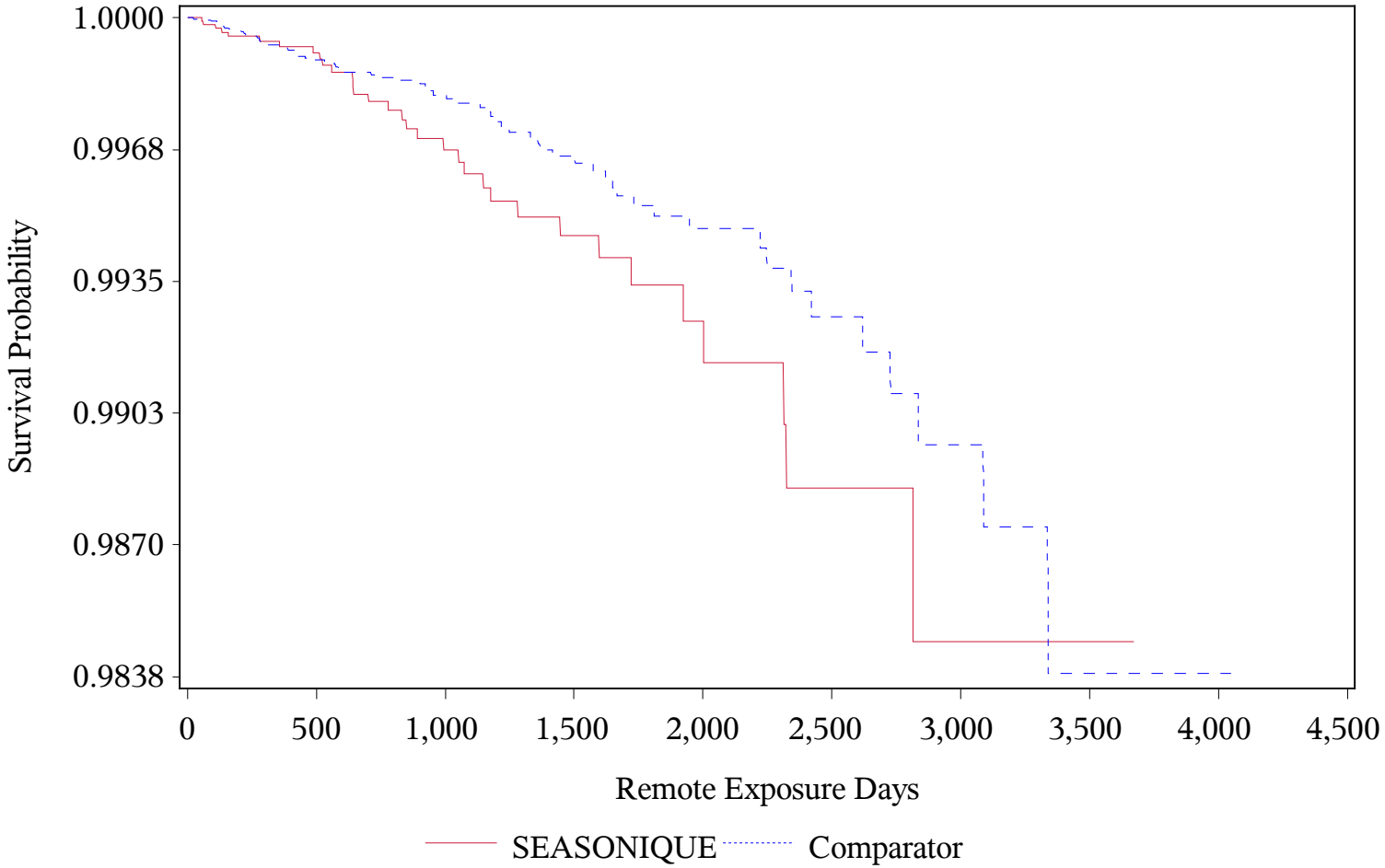


Figure 6a. Log-log Survival Curves, Cervical Cancer, Current Exposure

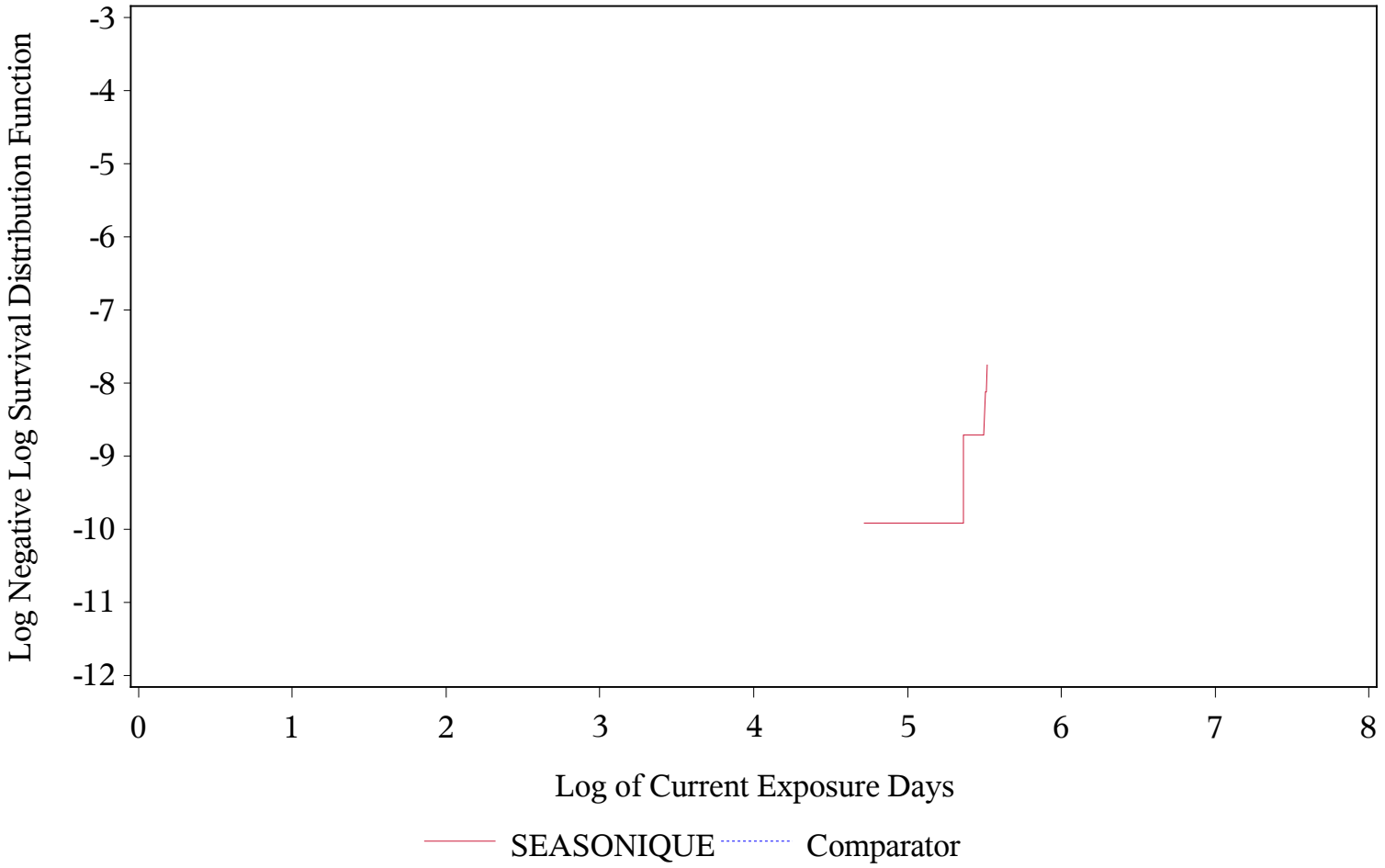


Figure 6b. Survival Curves, Cervical Cancer, Current Exposure

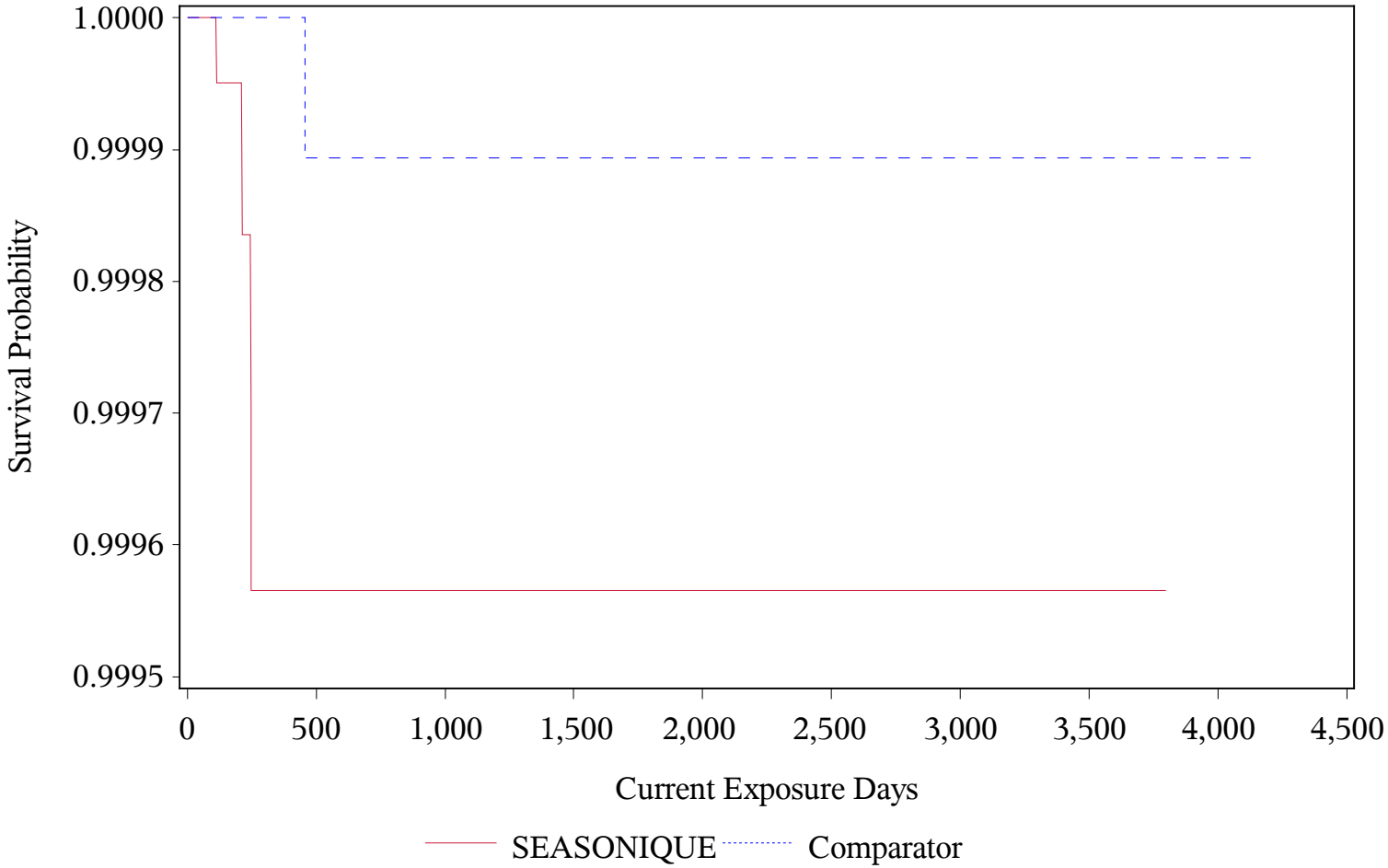


Figure 6c. Log-log Survival Curves, Cervical Cancer, Recent Exposure

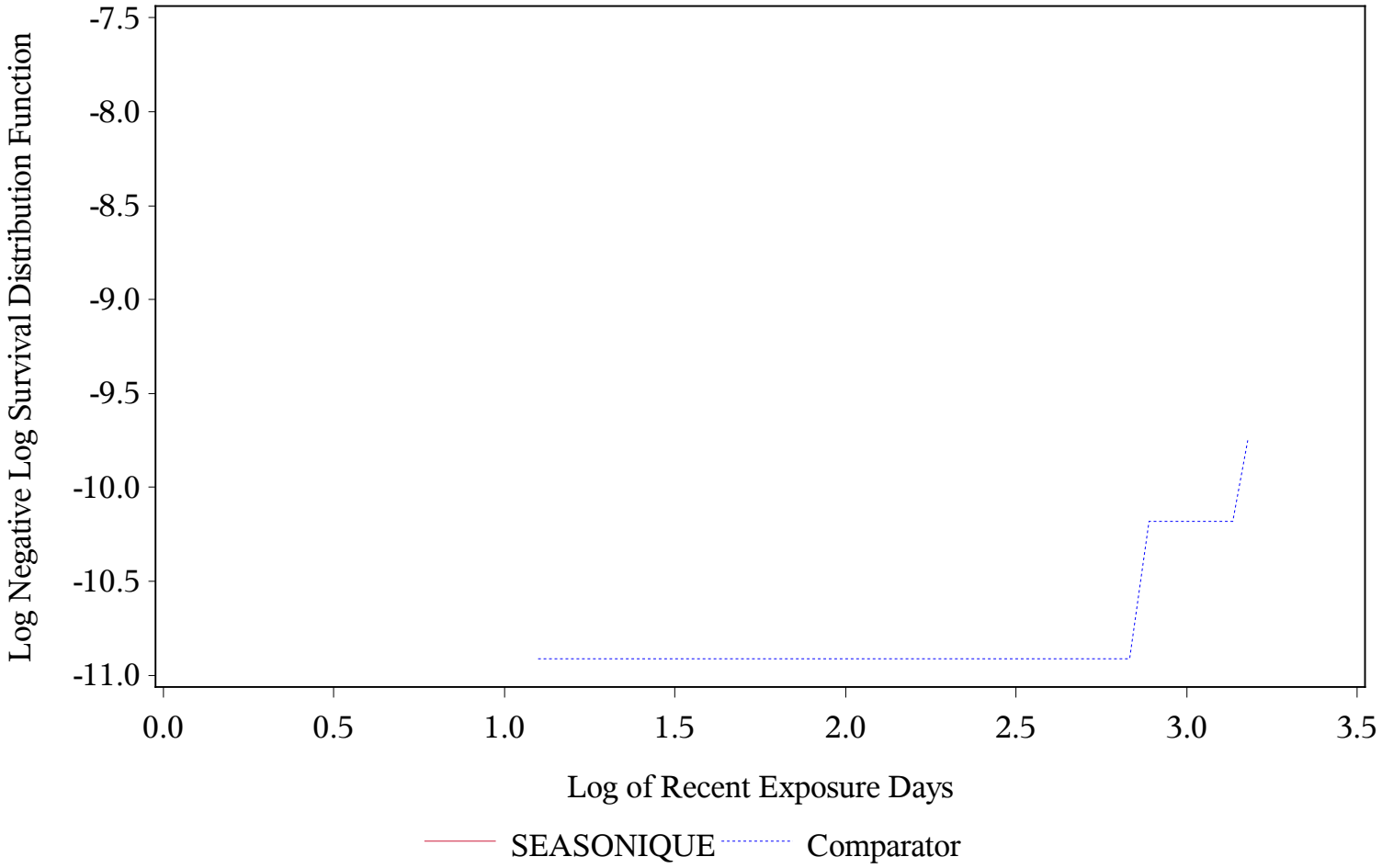


Figure 6d. Survival Curves, Cervical Cancer, Recent Exposure

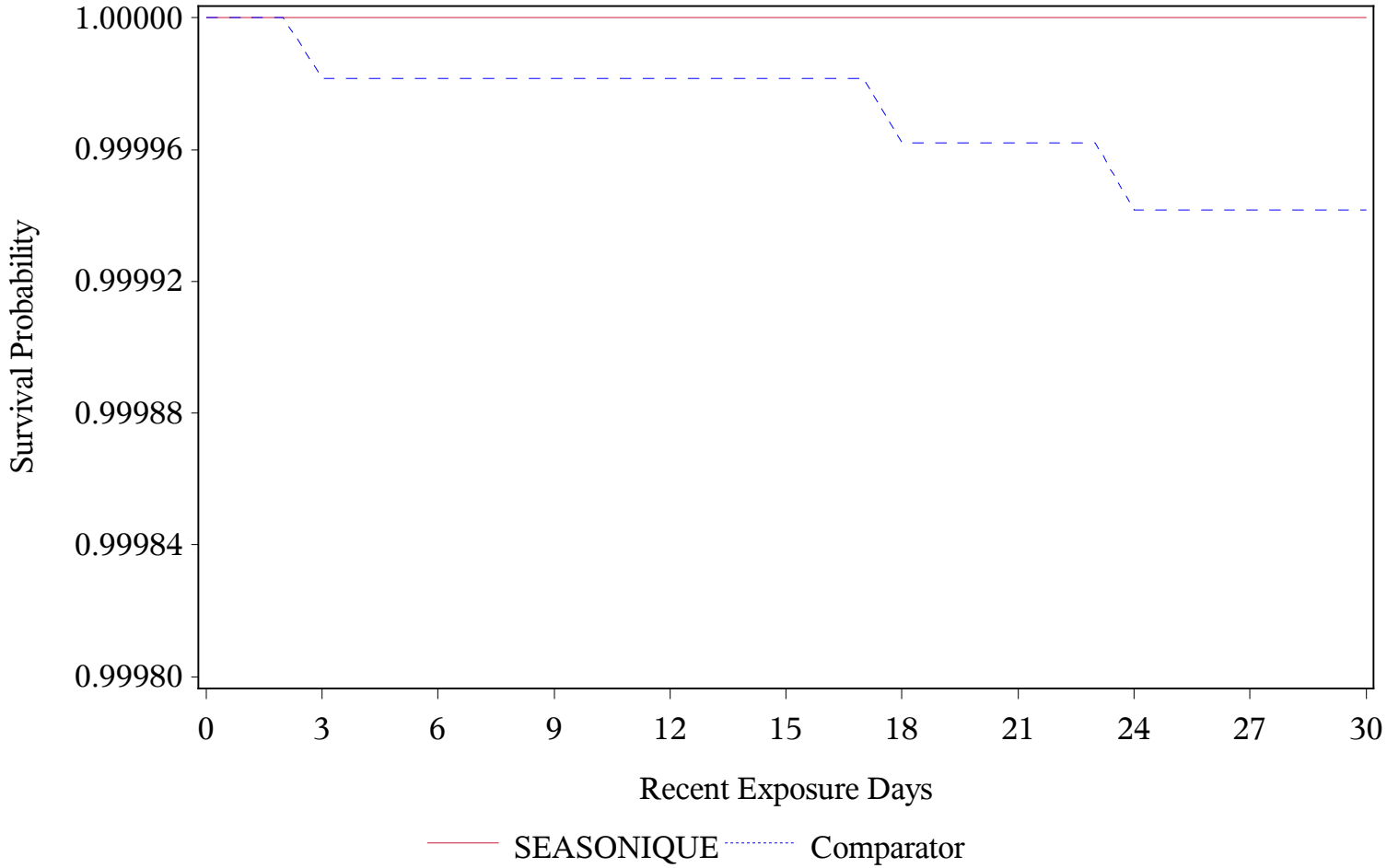


Figure 6e. Log-log Survival Curves, Cervical Cancer, Intermediate Exposure

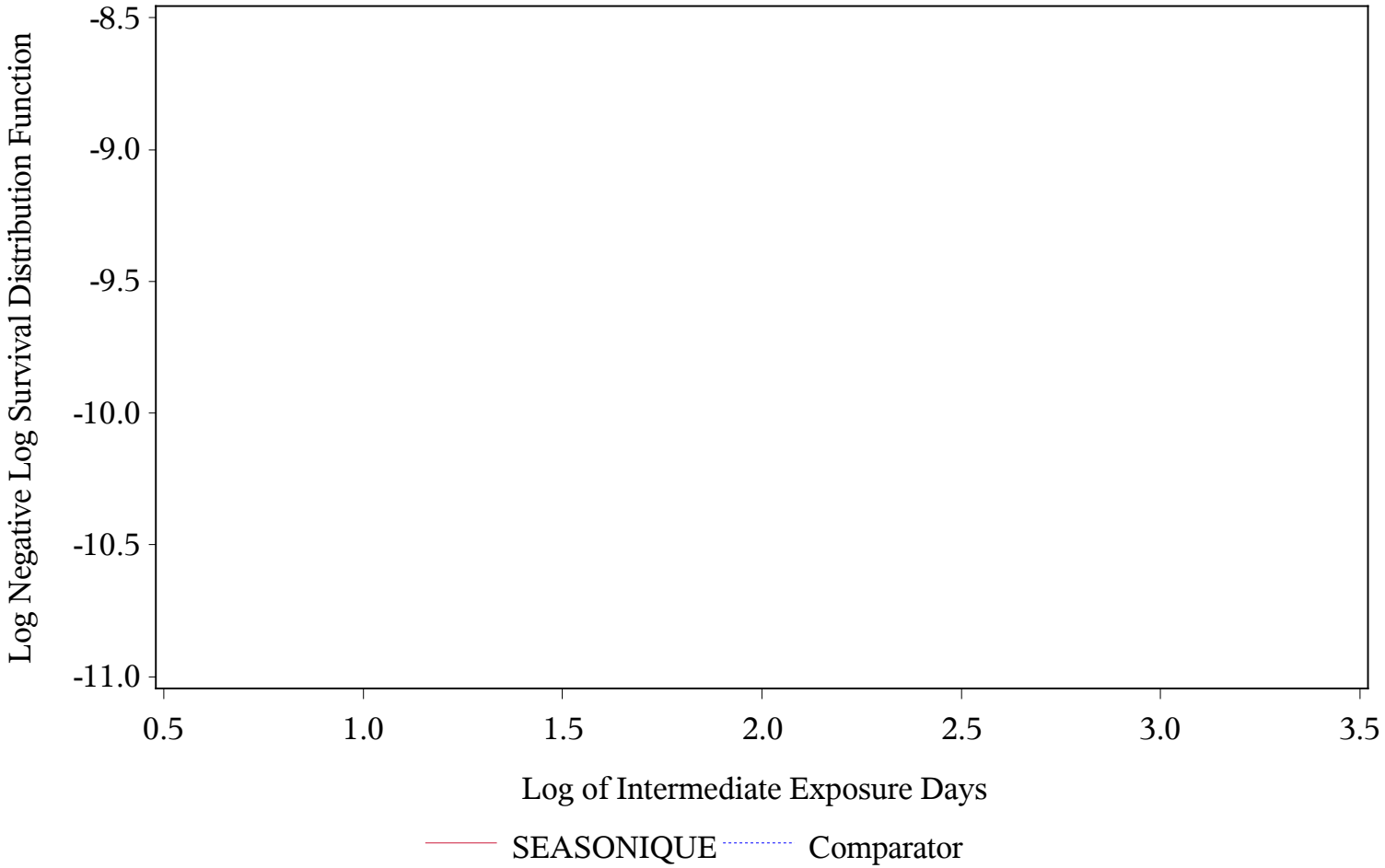


Figure 6f. Survival Curves, Cervical Cancer, Intermediate Exposure

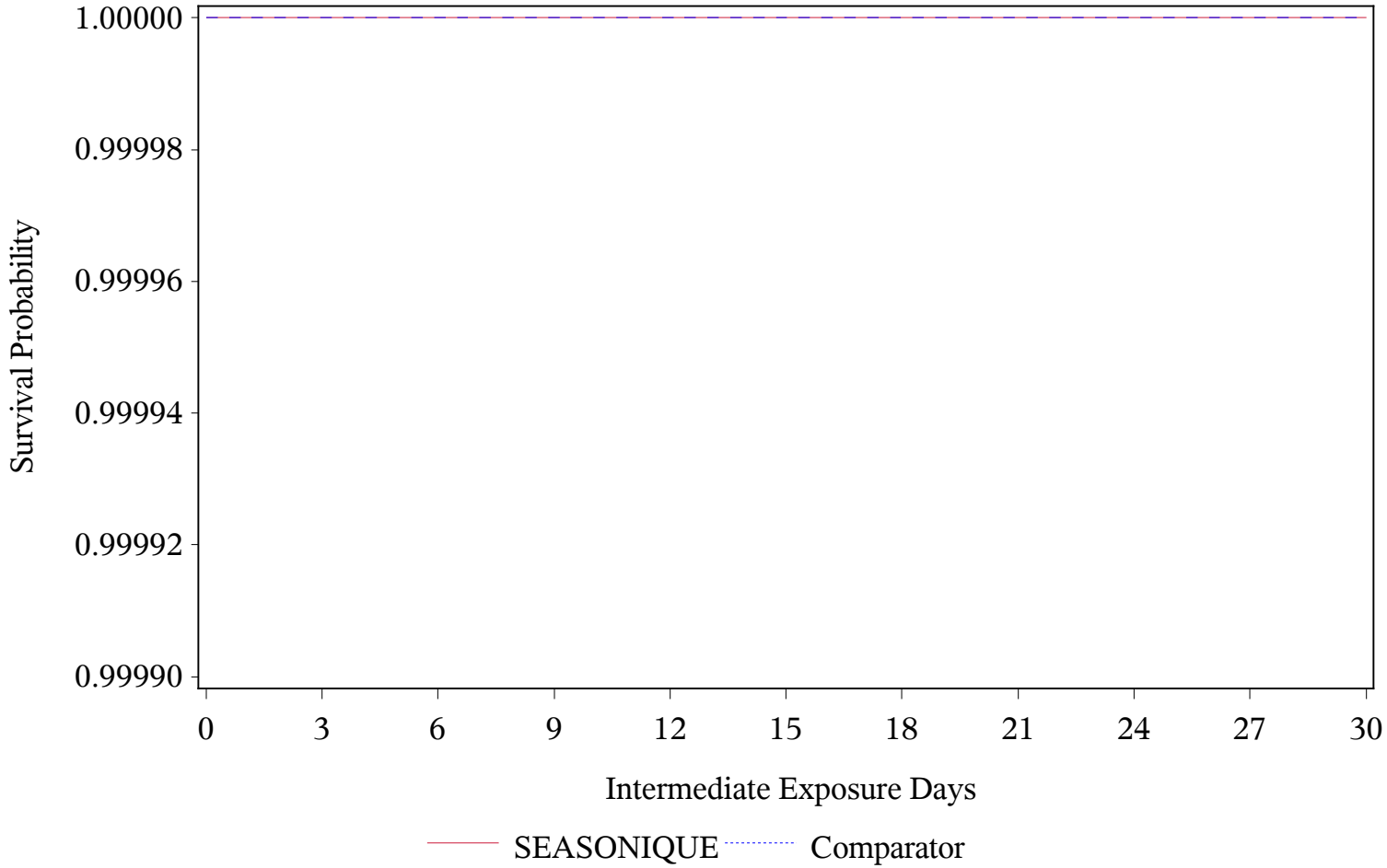


Figure 6g. Log-log Survival Curves, Cervical Cancer, Remote Exposure

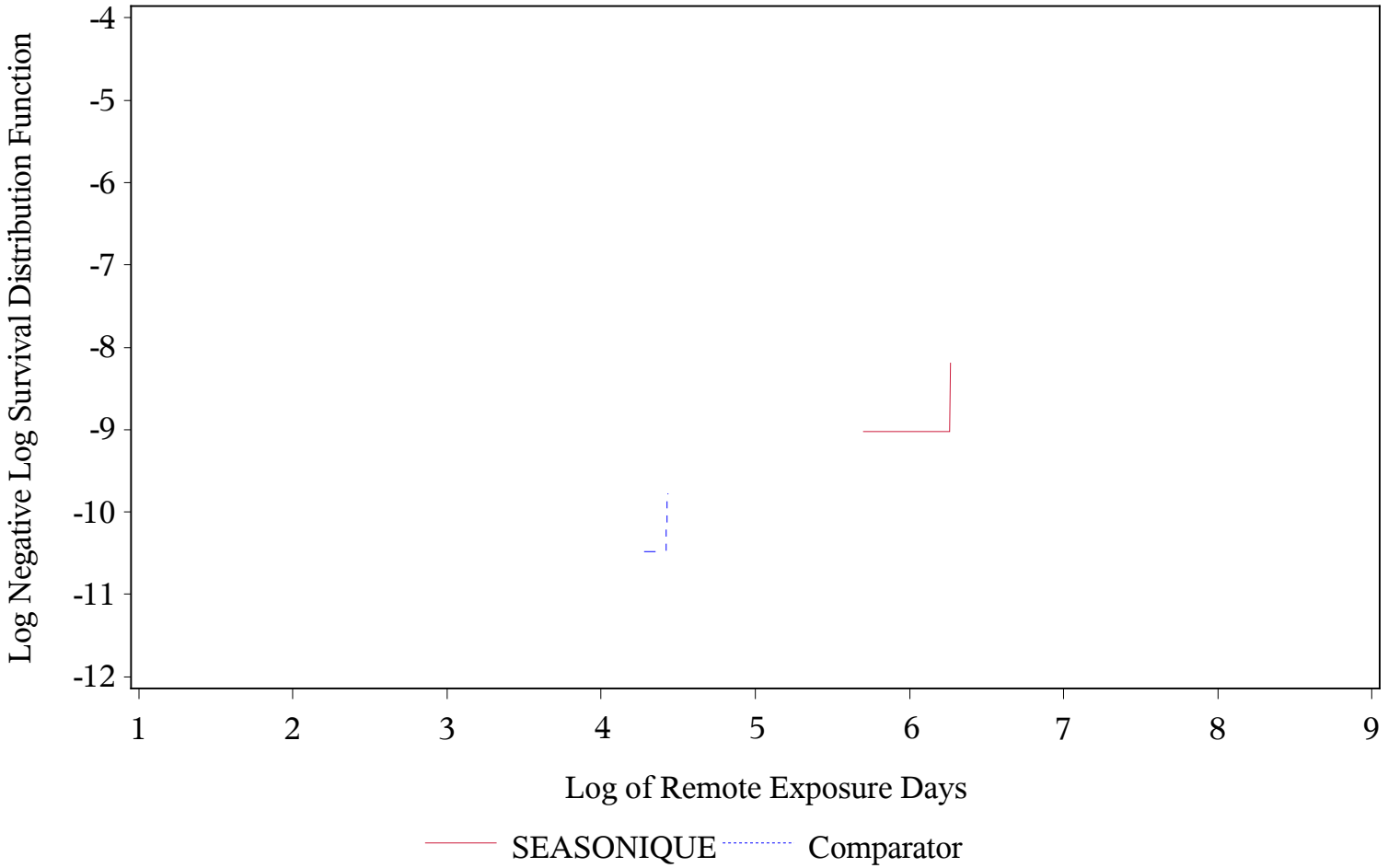


Figure 6h. Survival Curves, Cervical Cancer, Remote Exposure

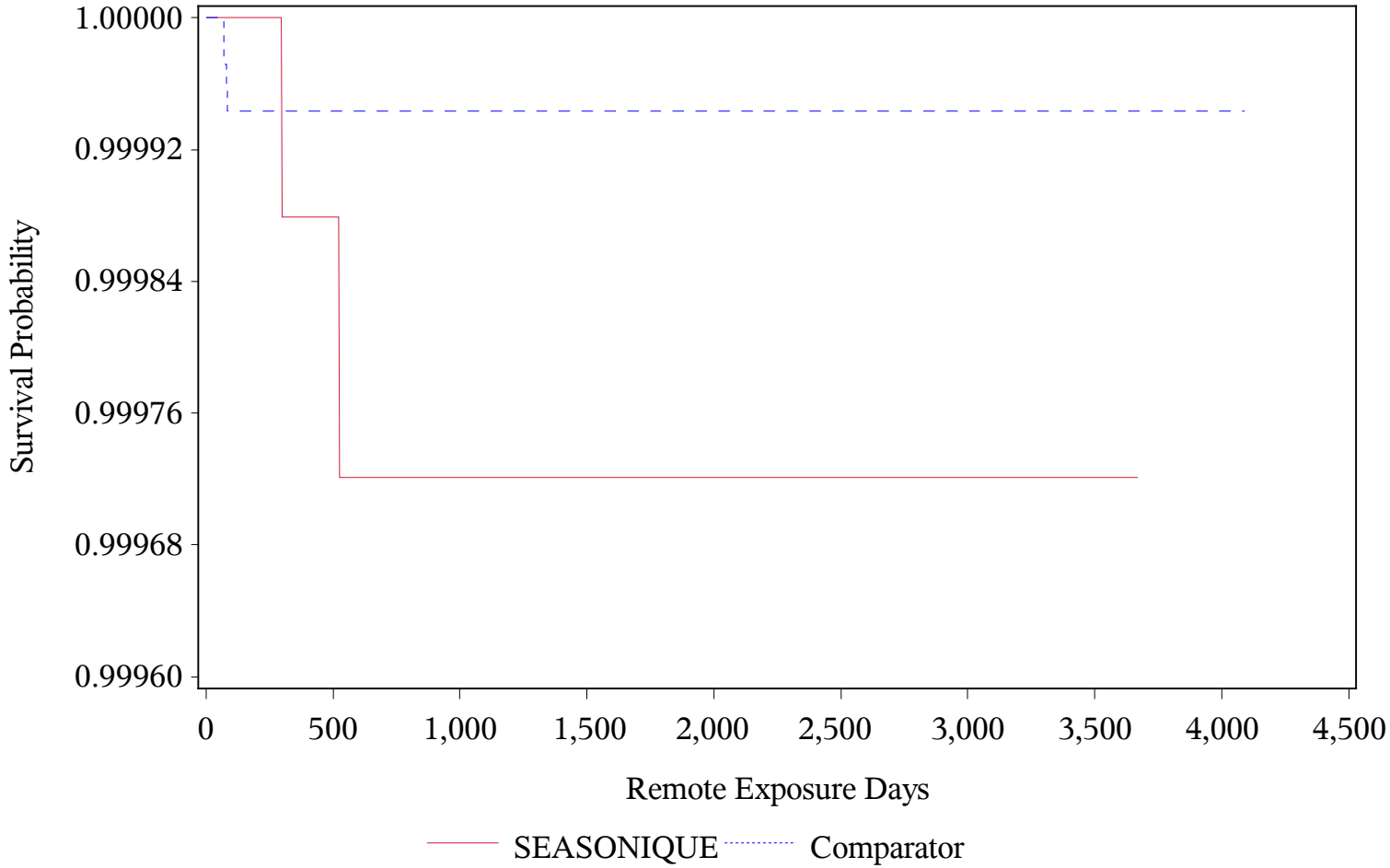


Figure 7a. Log-log Survival Curves, Endometrial Cancer, Current Exposure

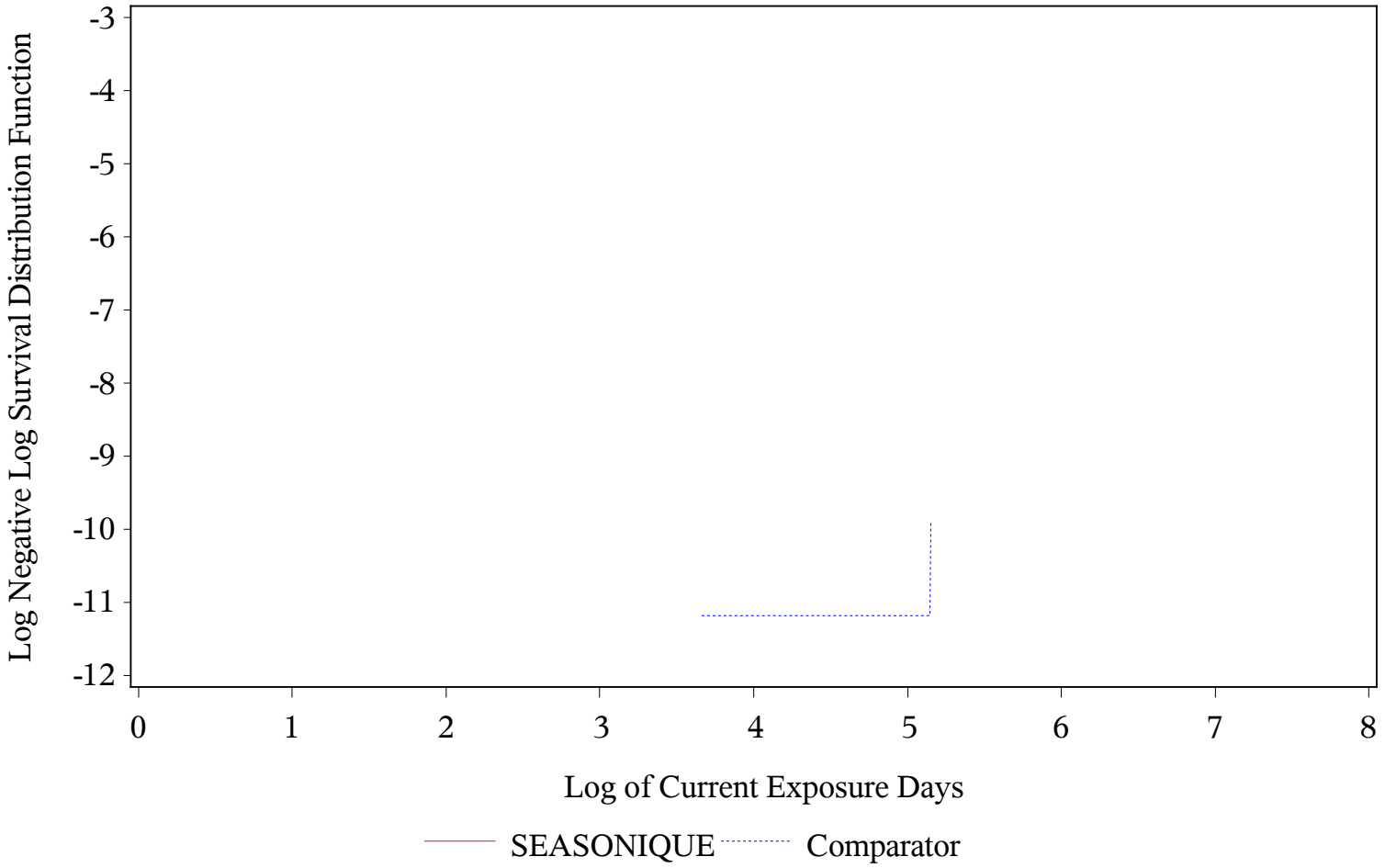


Figure 7b. Survival Curves, Endometrial Cancer, Current Exposure

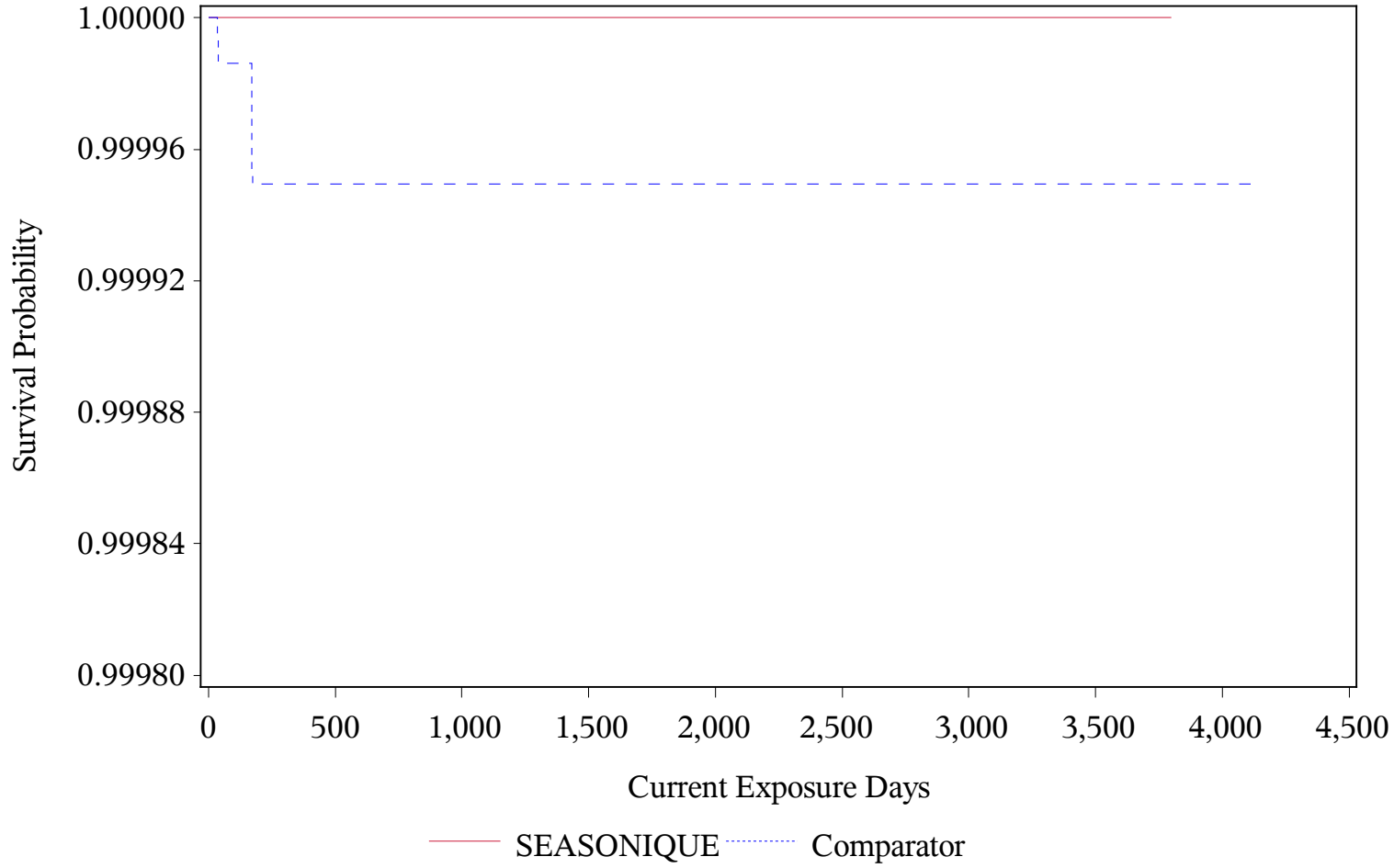


Figure 7c. Log-log Survival Curves, Endometrial Cancer, Recent Exposure

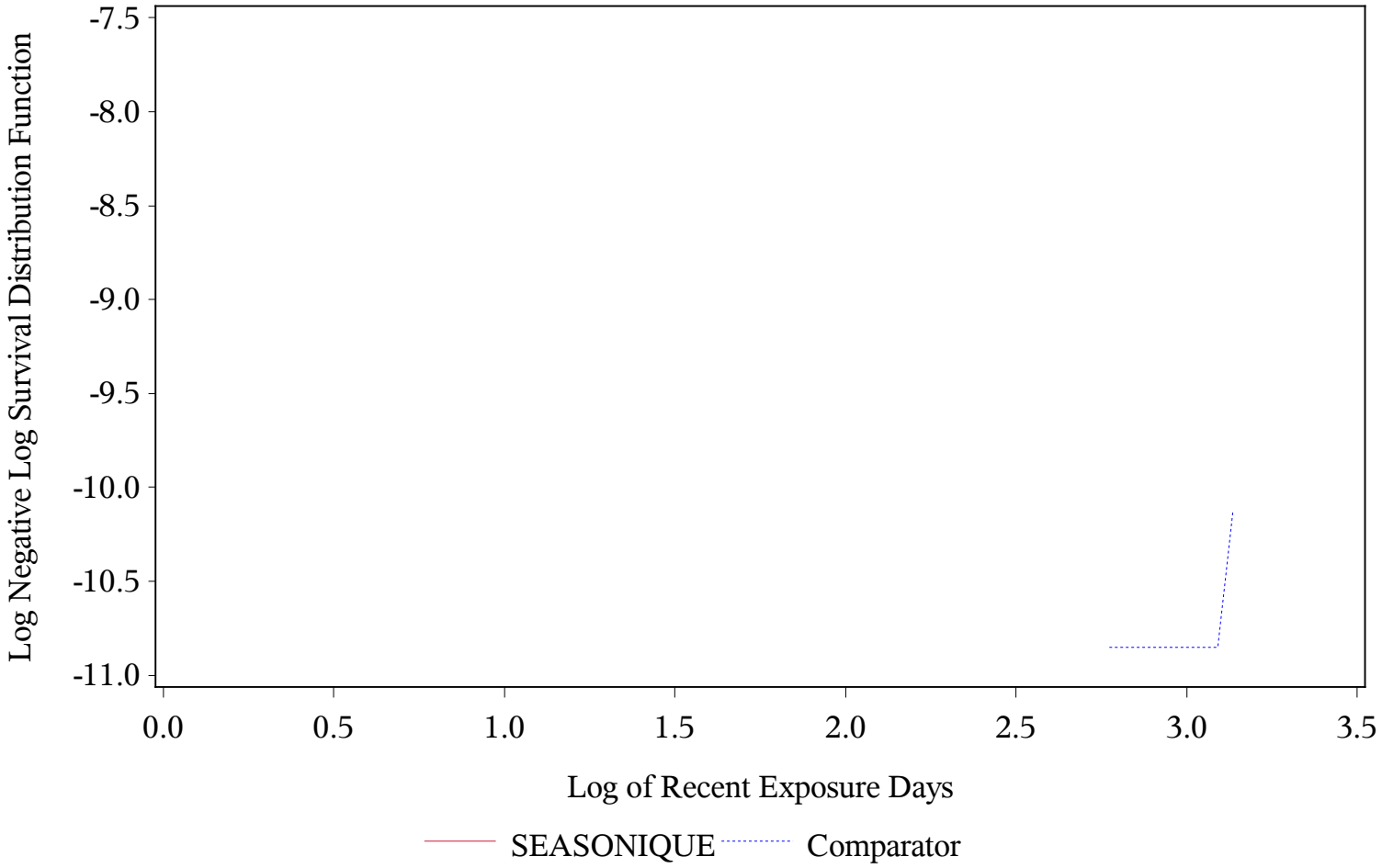


Figure 7d. Survival Curves, Endometrial Cancer, Recent Exposure

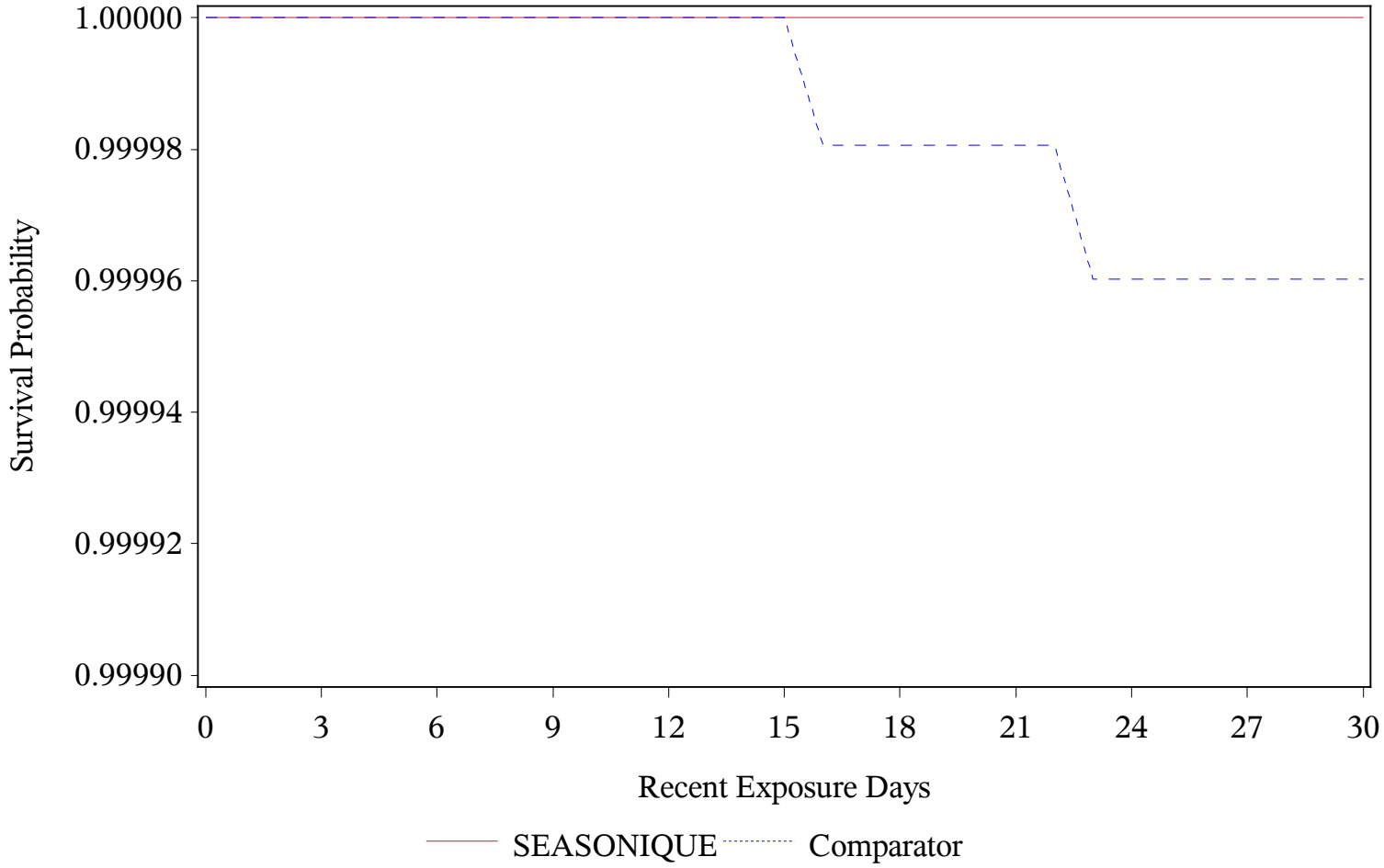


Figure 7e. Log-log Survival Curves, Endometrial Cancer, Intermediate Exposure

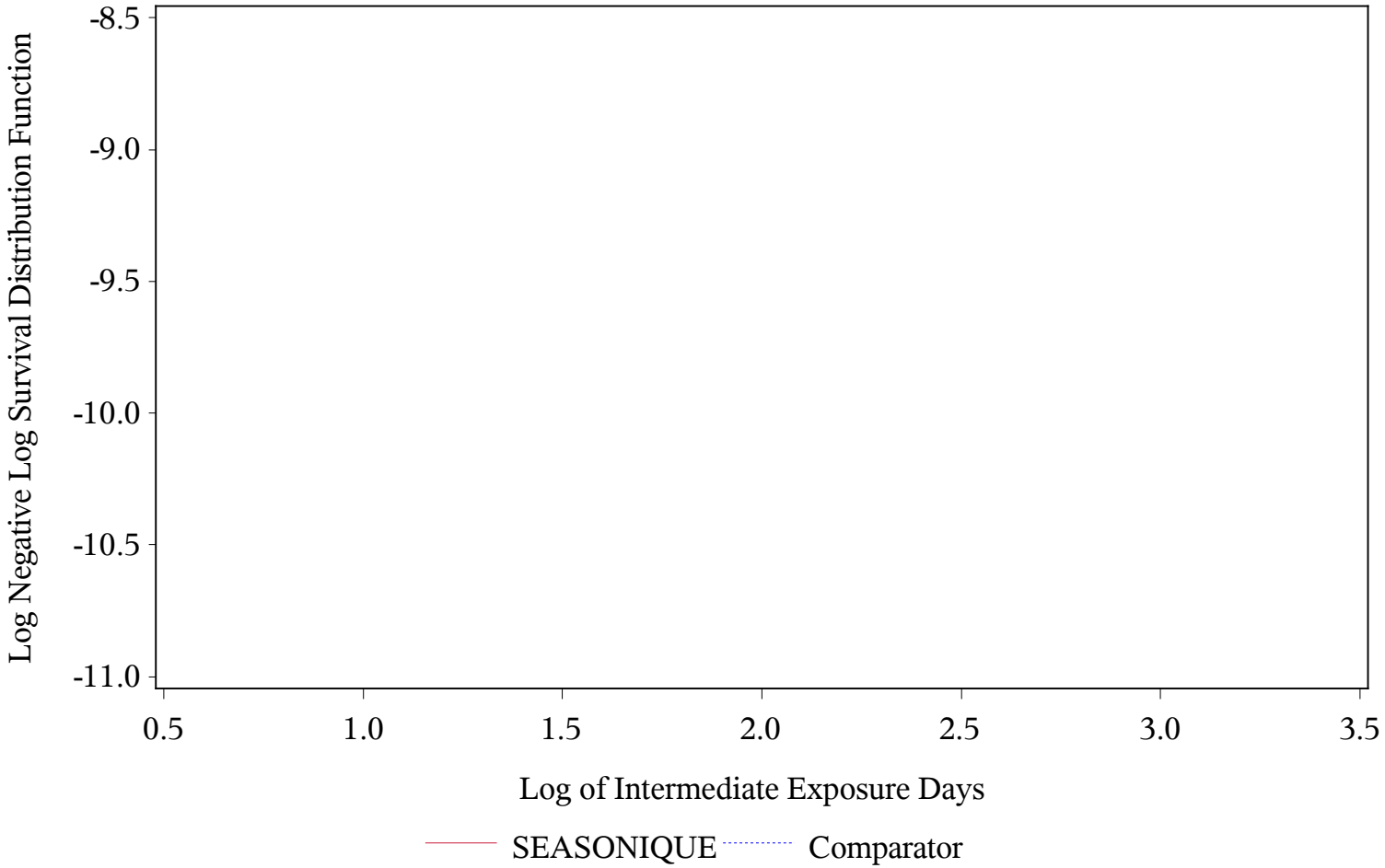


Figure 7f. Survival Curves, Endometrial Cancer, Intermediate Exposure

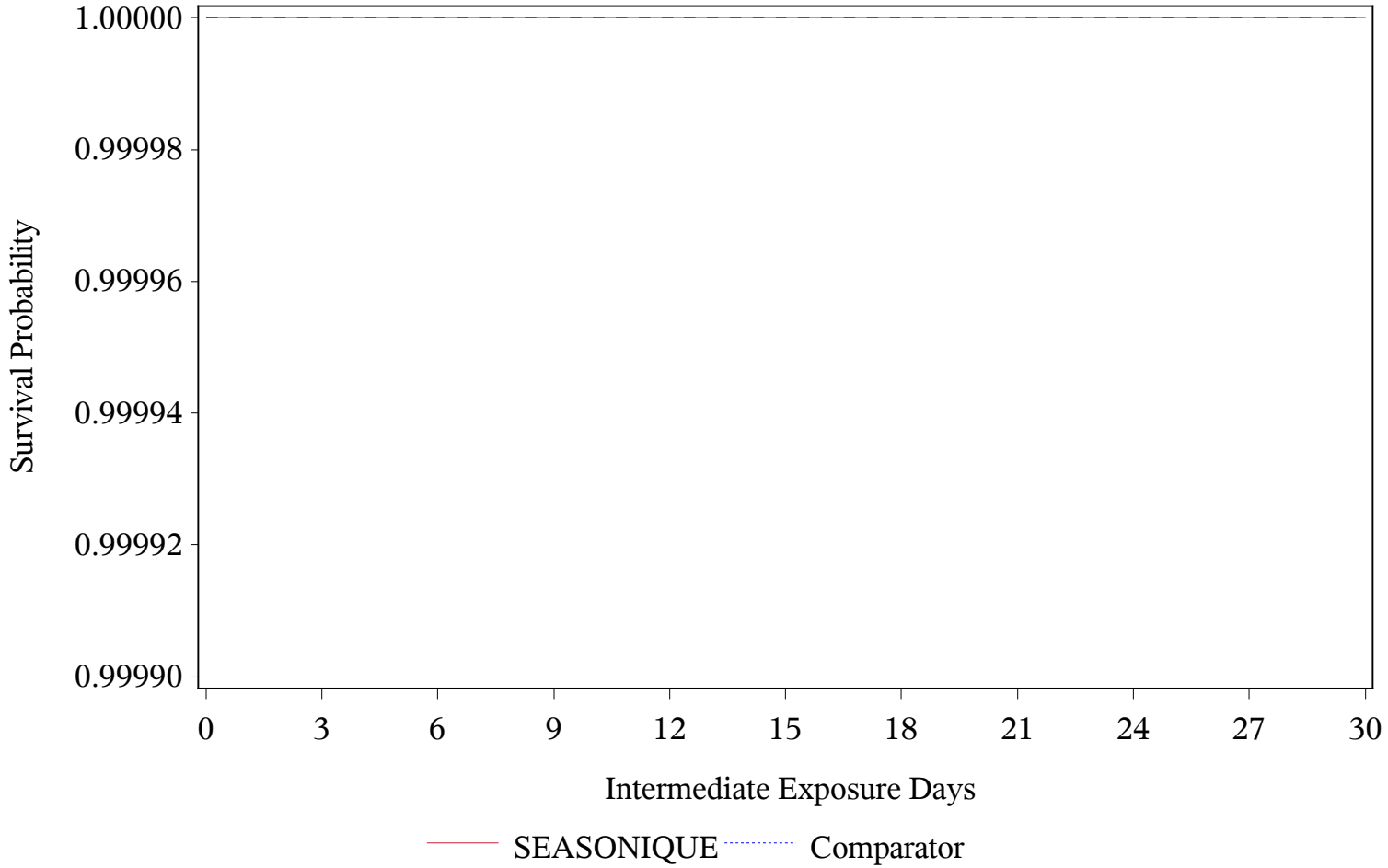


Figure 7g. Log-log Survival Curves, Endometrial Cancer, Remote Exposure

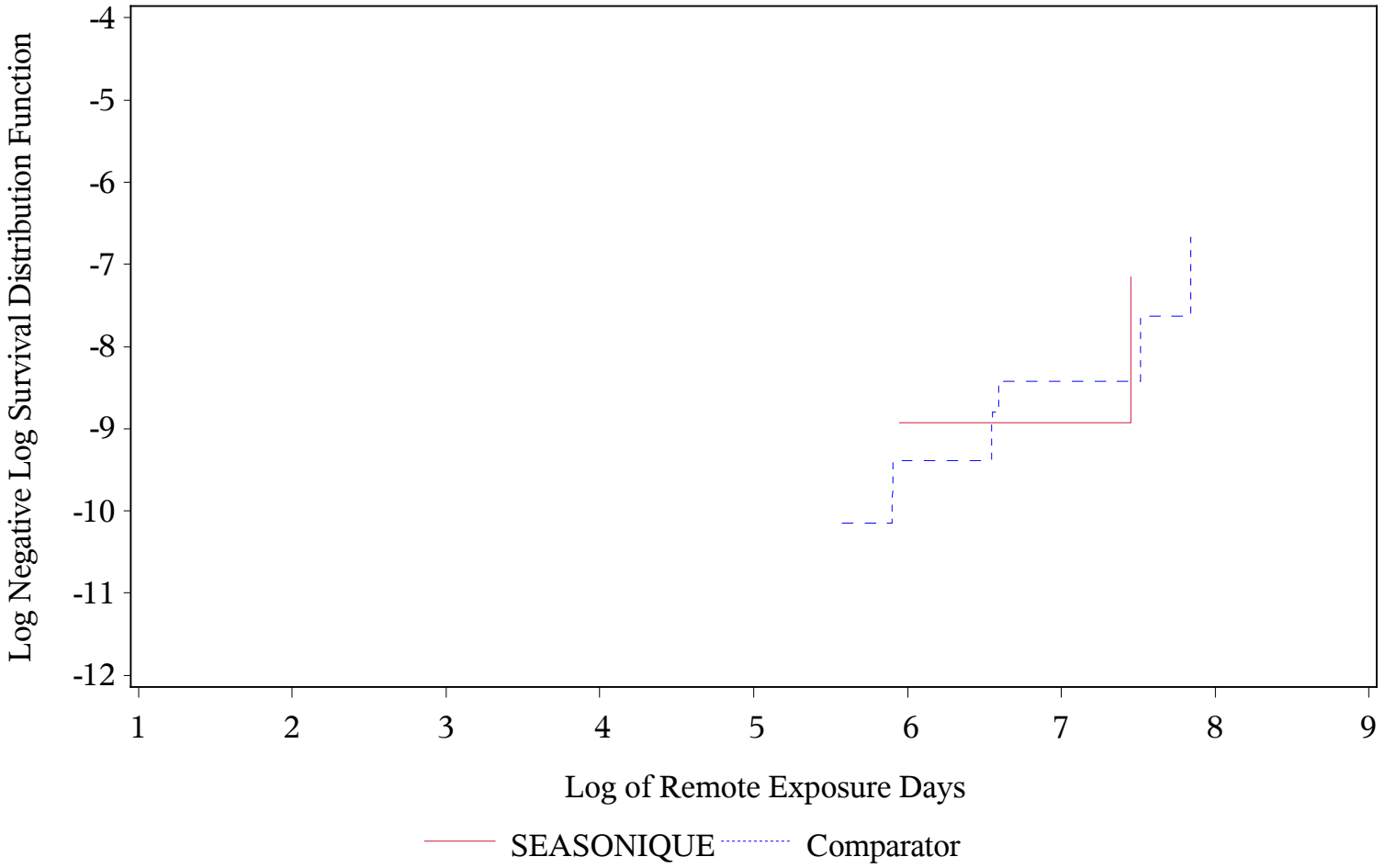


Figure 7h. Survival Curves, Endometrial Cancer, Remote Exposure

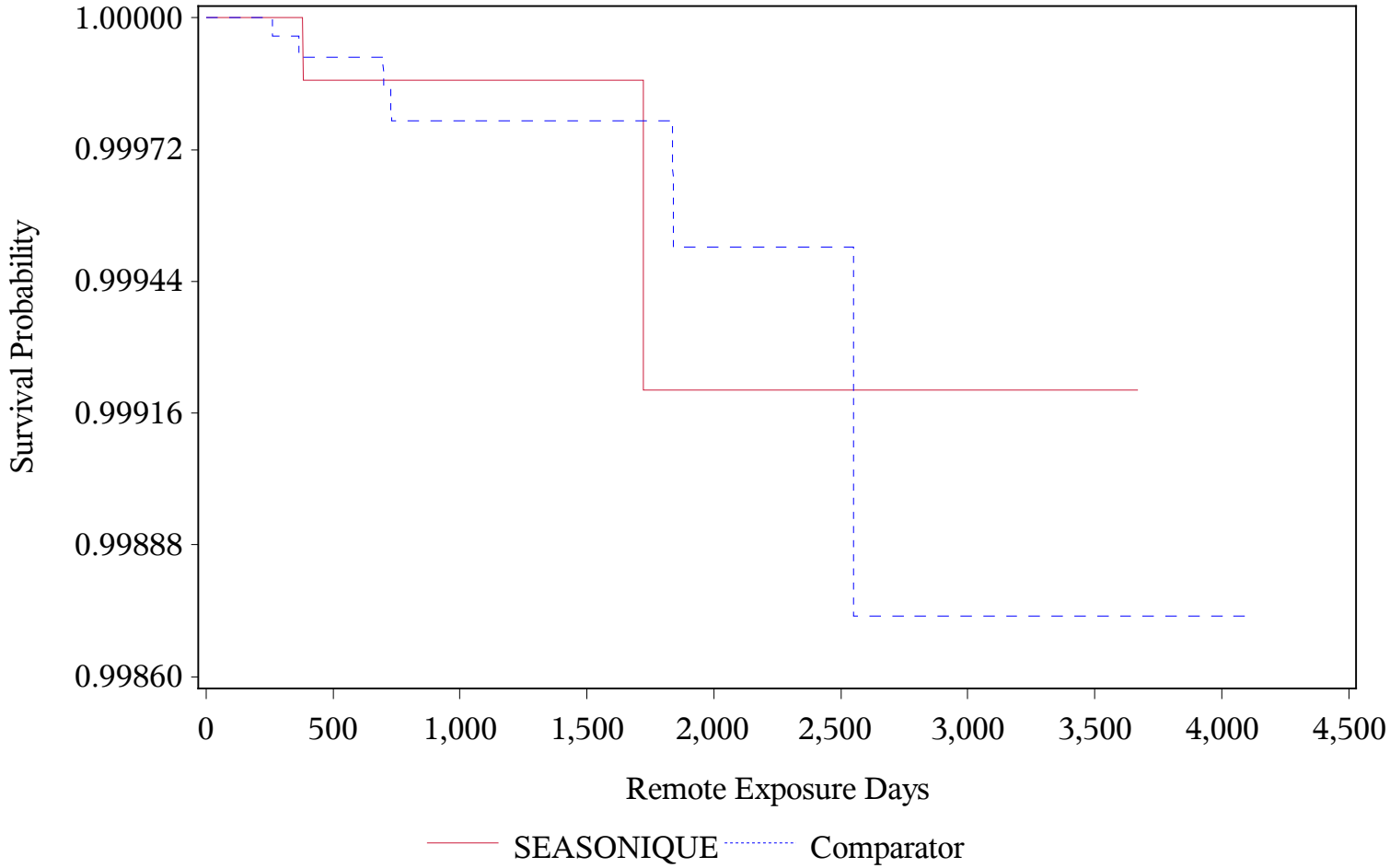


Figure 8a. Log-log Survival Curves, Ovarian Cancer, Current Exposure

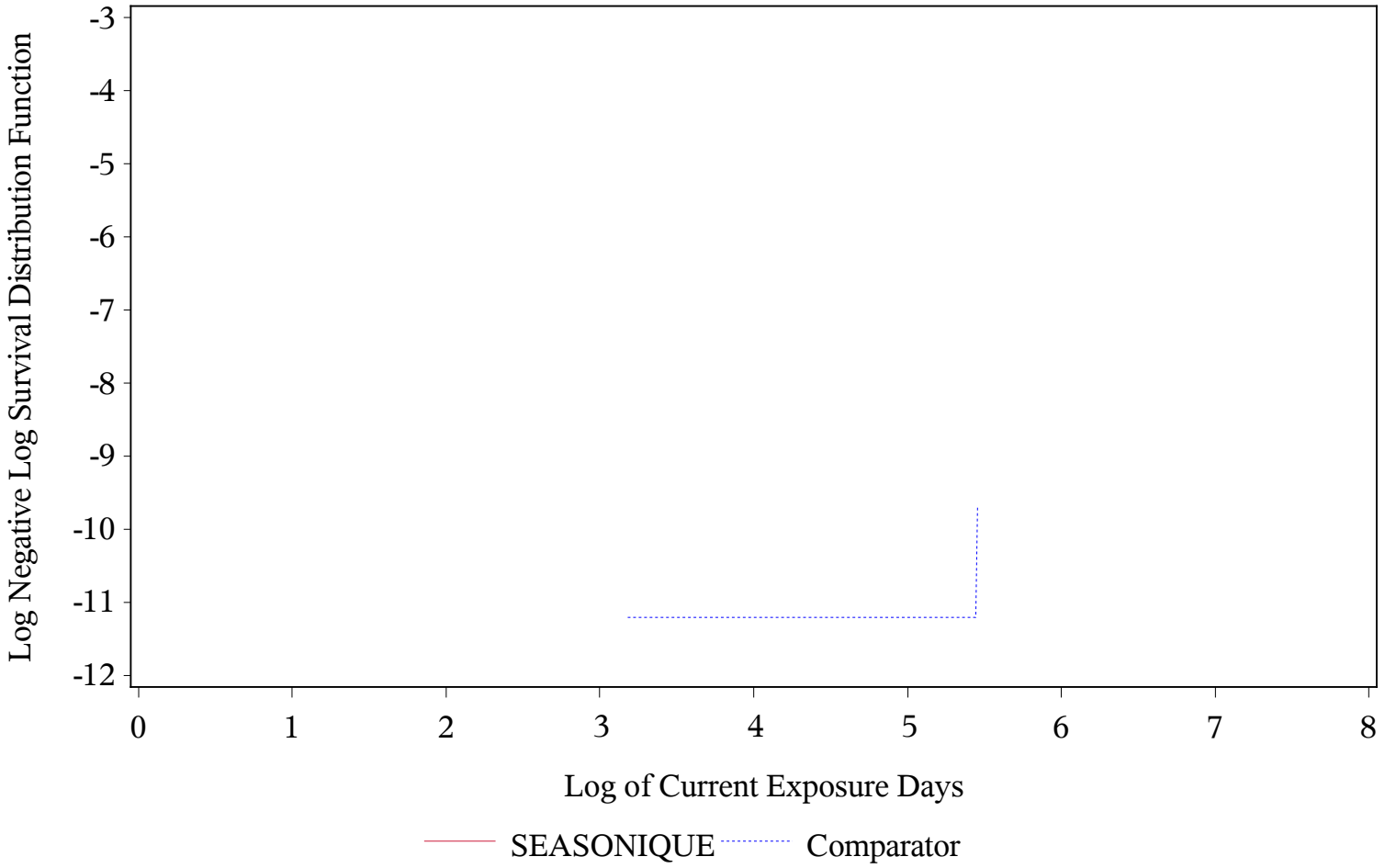


Figure 8b. Survival Curves, Ovarian Cancer, Current Exposure

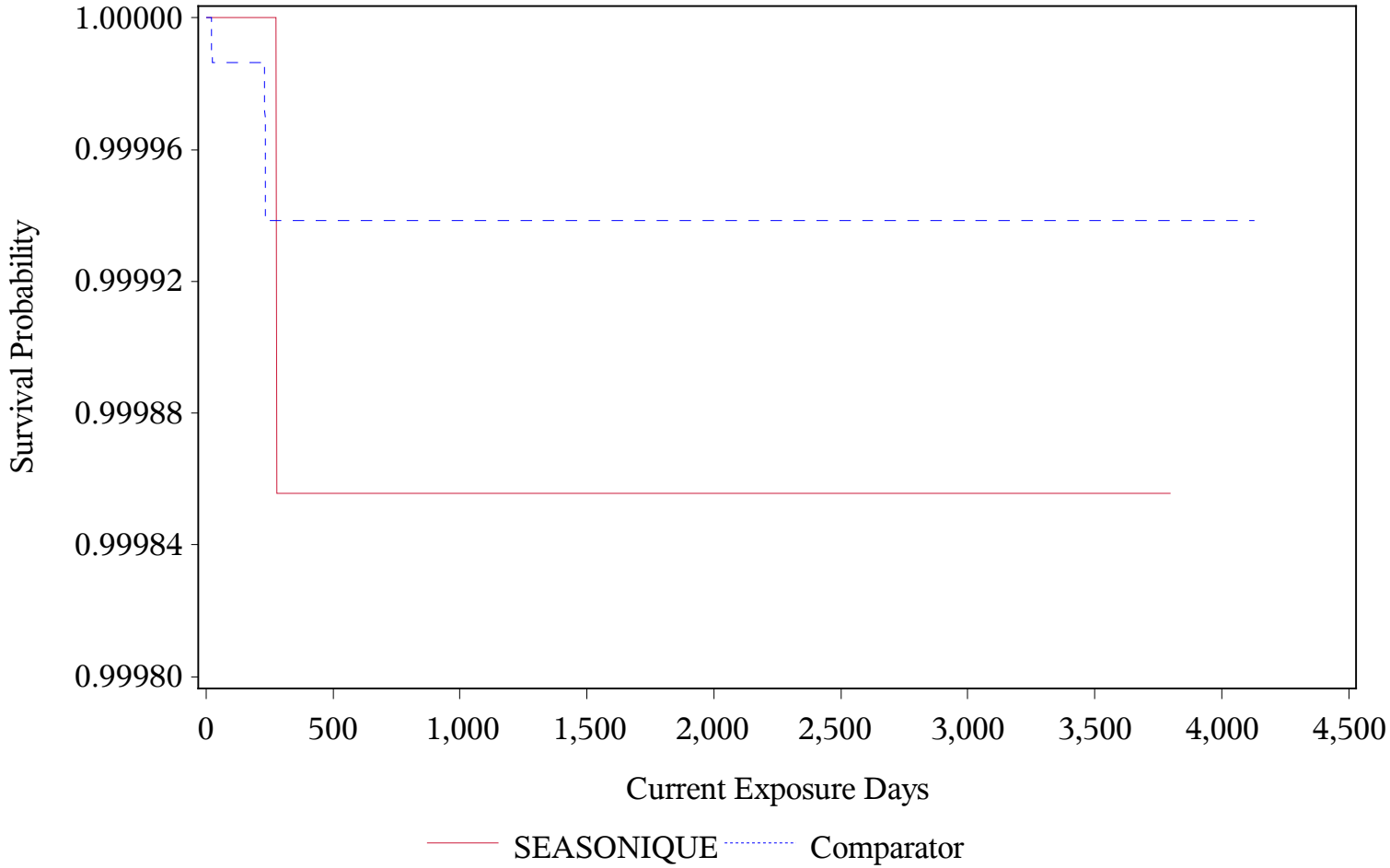


Figure 8c. Log-log Survival Curves, Ovarian Cancer, Recent Exposure

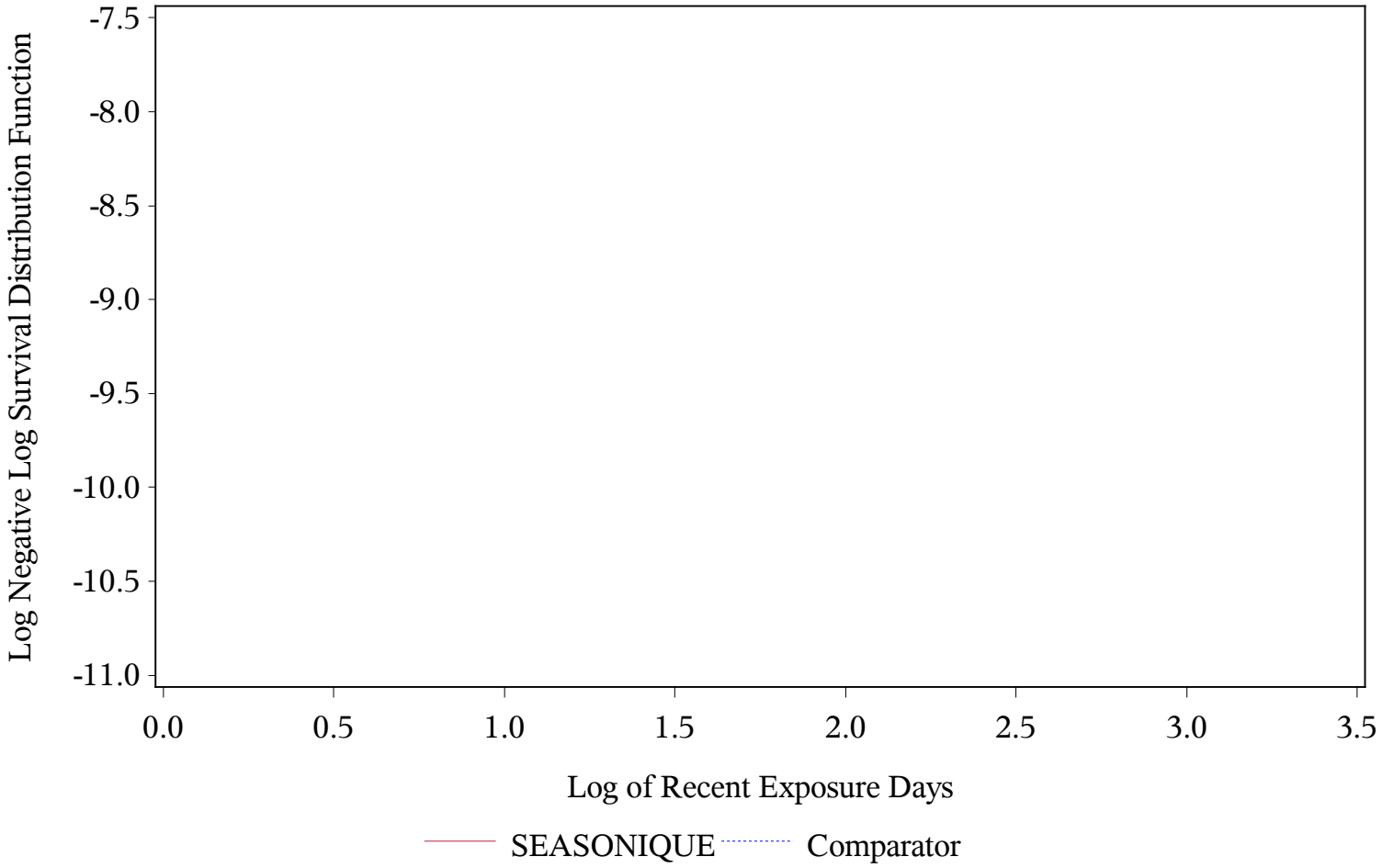


Figure 8d. Survival Curves, Ovarian Cancer, Recent Exposure

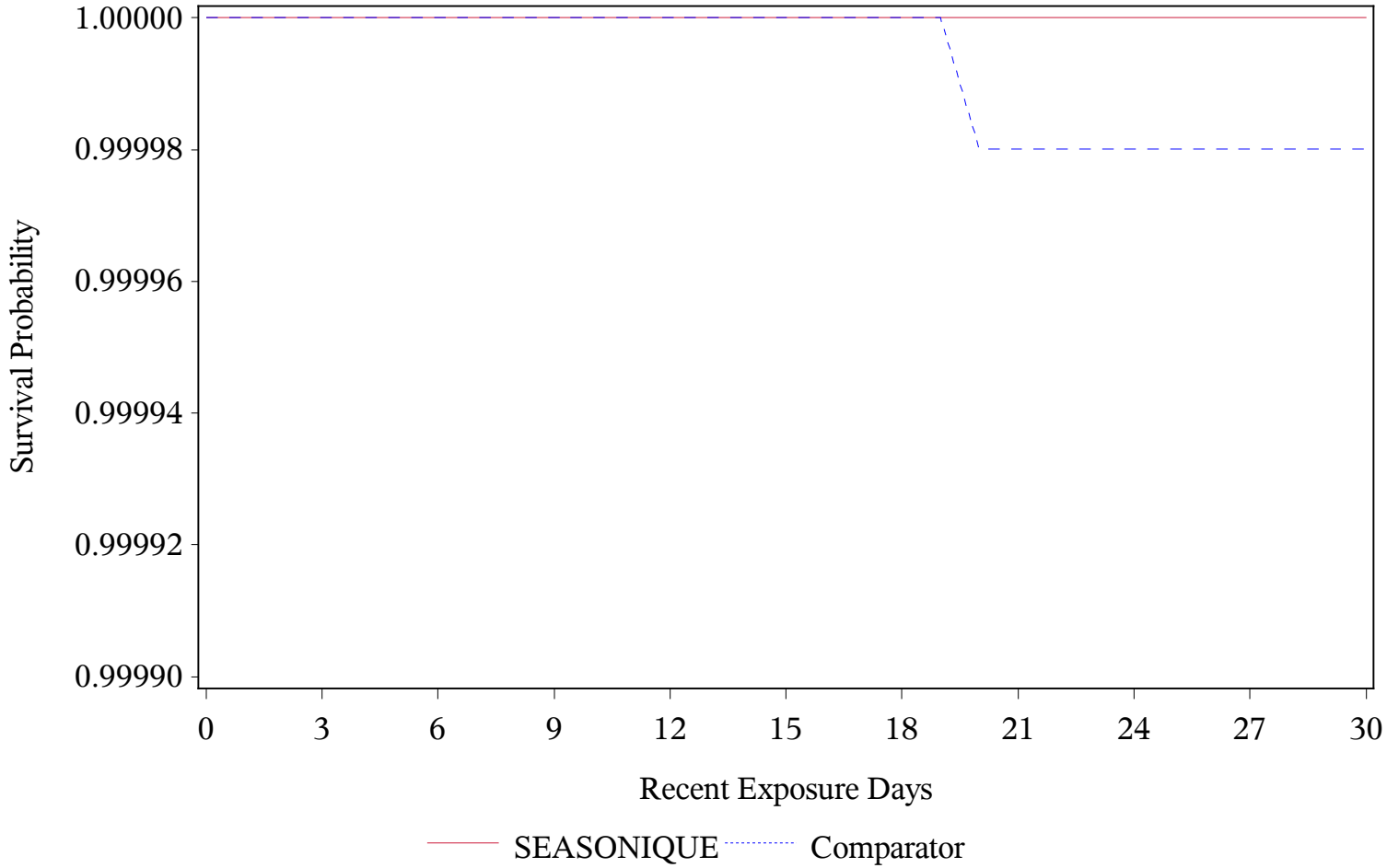


Figure 8e. Log-log Survival Curves, Ovarian Cancer, Intermediate Exposure

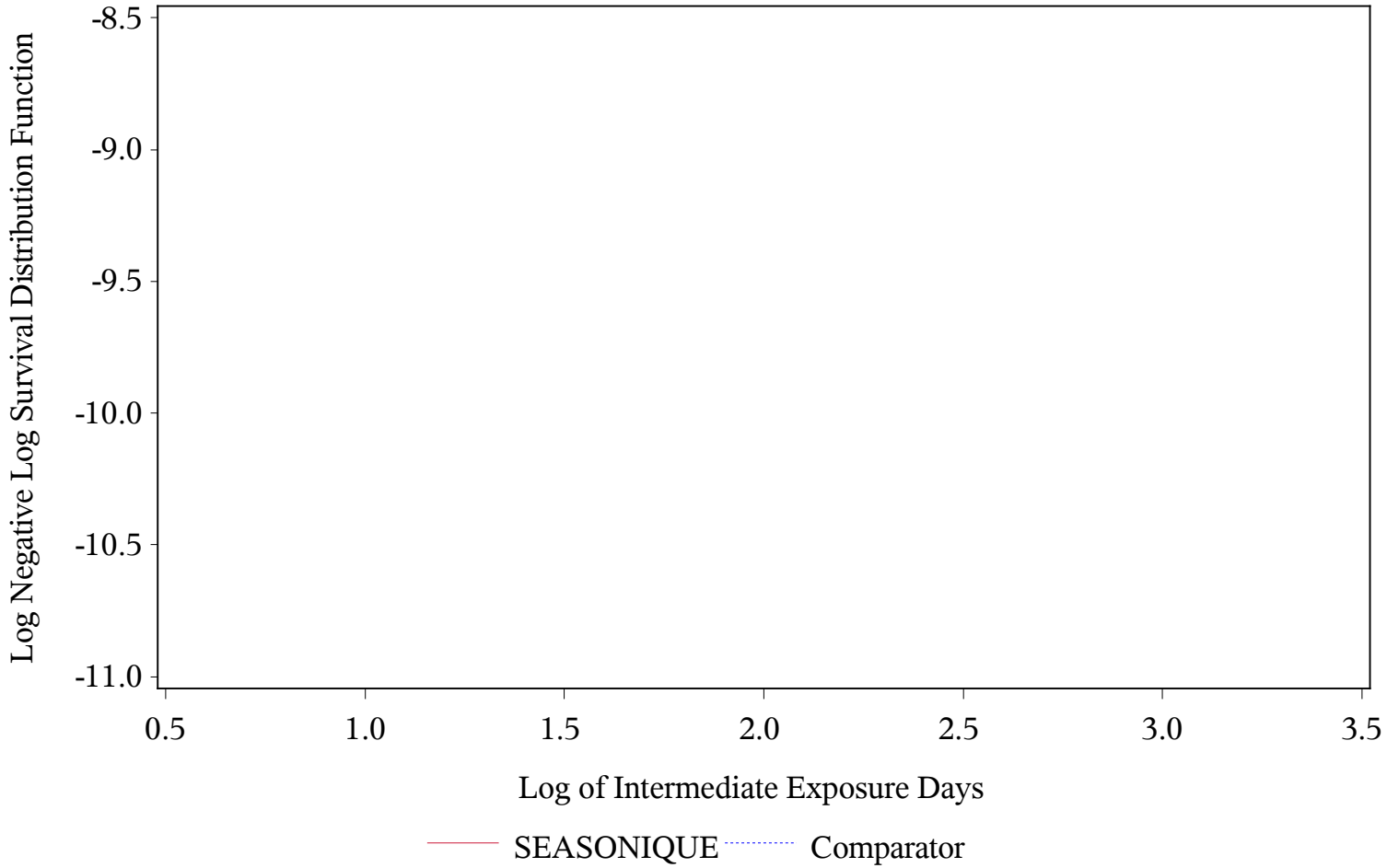


Figure 8f. Survival Curves, Ovarian Cancer, Intermediate Exposure

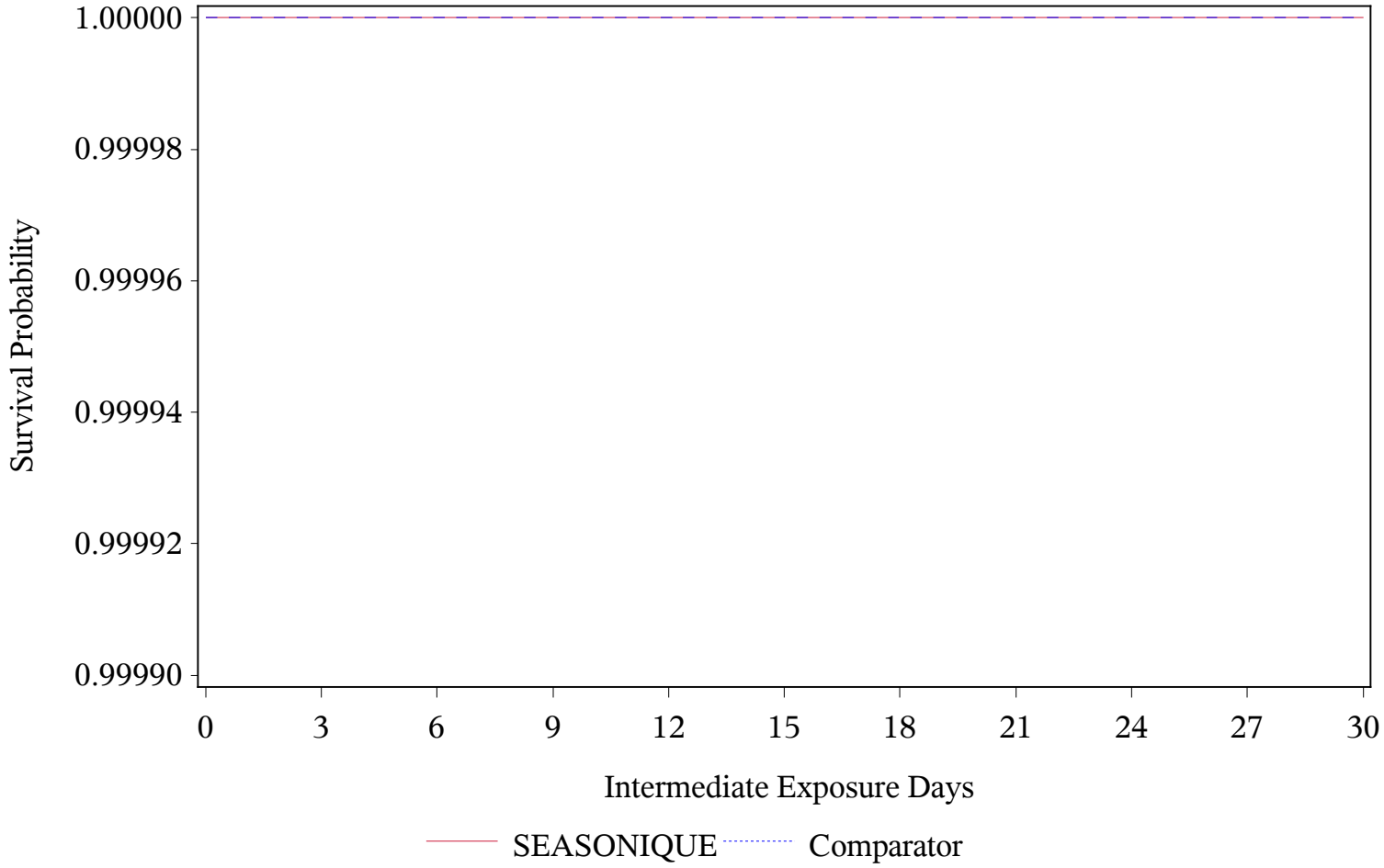


Figure 8g. Log-log Survival Curves, Ovarian Cancer, Remote Exposure

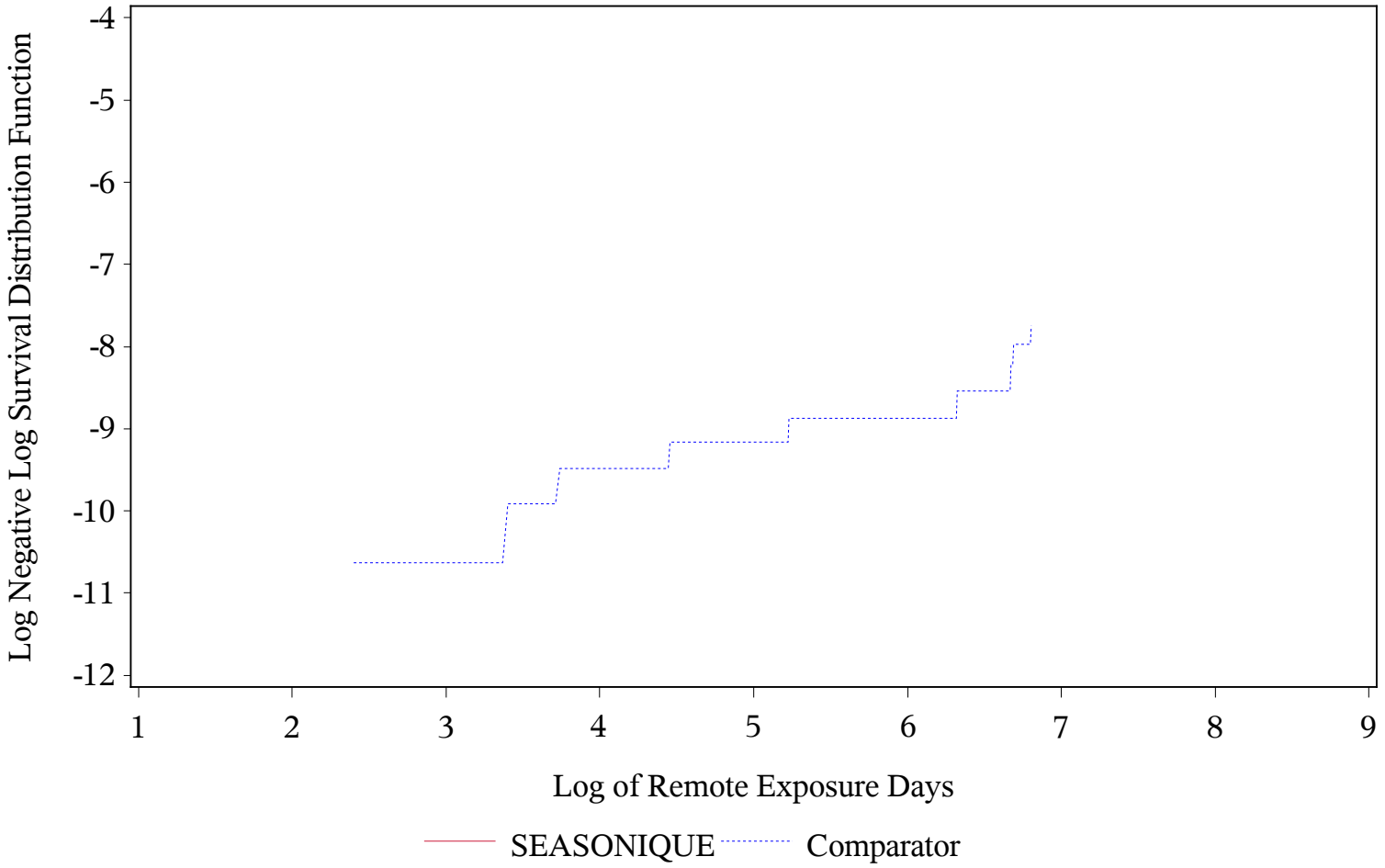
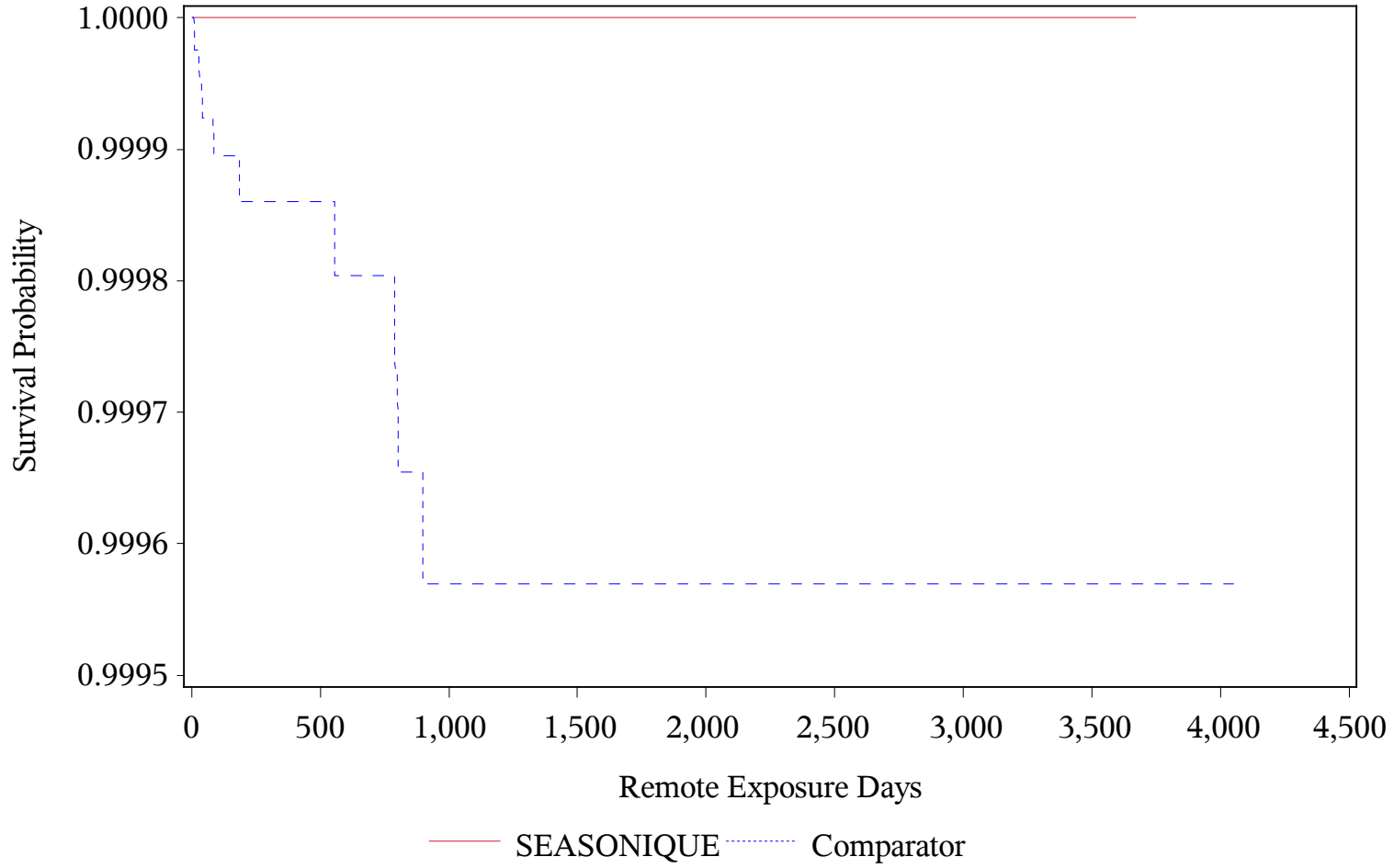


Figure 8h. Survival Curves, Ovarian Cancer, Remote Exposure



Annex 4. Codes to Define Outcomes and Censoring

The ICD code lists below contain only billable codes and do not contain wildcards. The code lists include all codes which were used in the identification of the outcomes (even if they were not observed in the database). The code lists originally summarized in the protocol by Teva were further reviewed by the Optum team, Teva, and a Teva clinician for refinement. The VTE code list was informed by previously validated claims-based VTE algorithms (12). There were some differences between ICD-9 and -10 code lists for DVT: for example, the ICD-9 code list included thrombophlebitis migrans and the ICD-10 code list included some codes for chronic DVT.

VTE

PE

Code	Description
ICD-9	
415.11	Iatrogenic pulmonary embolism and infarction
415.19	Other pulmonary embolism and infarction
ICD-10	
I26.99	Other pulmonary embolism without acute cor pulmonale

DVT

Code	Description
ICD-9	
451.11	Phlebitis and thrombophlebitis of femoral vein (deep) (superficial)
451.19	Phlebitis and thrombophlebitis of deep veins of lower extremities, other
451.2	Phlebitis and thrombophlebitis of lower extremities, unspecified
451.81	Phlebitis and thrombophlebitis of iliac vein
451.83	Phlebitis and thrombophlebitis of deep veins of upper extremities
451.84	Phlebitis and thrombophlebitis of upper extremities, unspecified
451.89	Phlebitis and thrombophlebitis of other sites
453.1	Thrombophlebitis migrans
453.2	Other venous embolism and thrombosis of inferior vena cava
453.40	Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.41	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
453.42	Acute venous embolism and thrombosis of deep vessels of distal lower extremity
453.81	Acute venous embolism and thrombosis of superficial veins of upper extremity
453.82	Acute venous embolism and thrombosis of deep veins of upper extremity
453.83	Acute venous embolism and thrombosis of upper extremity, unspecified
453.84	Acute venous embolism and thrombosis of axillary veins
453.85	Acute venous embolism and thrombosis of subclavian veins
453.86	Acute venous embolism and thrombosis of internal jugular veins
453.87	Acute venous embolism and thrombosis of other thoracic veins
453.89	Acute venous embolism and thrombosis of other specified veins

453.9	Other venous embolism and thrombosis of unspecified site
ICD-10	
I80.10	Phlebitis and thrombophlebitis of unspecified femoral vein
I80.11	Phlebitis and thrombophlebitis of right femoral vein
I80.12	Phlebitis and thrombophlebitis of left femoral vein
I80.13	Phlebitis and thrombophlebitis of bilateral femoral veins
I80.201	Phlebitis and thrombophlebitis of unspecified deep vessels of right lower extremity
I80.202	Phlebitis and thrombophlebitis of unspecified deep vessels of left lower extremity
I80.203	Phlebitis and thrombophlebitis of unspecified deep vessels of bilateral lower extremities
I80.209	Phlebitis and thrombophlebitis of unspecified deep vessels of unspecified lower extremity
I80.211	Phlebitis and thrombophlebitis of right iliac vein
I80.212	Phlebitis and thrombophlebitis of left iliac vein
I80.213	Phlebitis and thrombophlebitis of bilateral iliac veins
I80.219	Phlebitis and thrombophlebitis of unspecified iliac vein
I80.221	Phlebitis and thrombophlebitis of right popliteal vein
I80.222	Phlebitis and thrombophlebitis of left popliteal vein
I80.223	Phlebitis and thrombophlebitis of bilateral popliteal veins
I80.229	Phlebitis and thrombophlebitis of unspecified popliteal vein
I80.231	Phlebitis and thrombophlebitis of right tibial vein
I80.232	Phlebitis and thrombophlebitis of left tibial vein
I80.233	Phlebitis and thrombophlebitis of bilateral tibial veins
I80.239	Phlebitis and thrombophlebitis of unspecified tibial vein
I80.291	Phlebitis and thrombophlebitis of other deep vessels of right lower extremity
I80.292	Phlebitis and thrombophlebitis of other deep vessels of left lower extremity
I80.293	Phlebitis and thrombophlebitis of other deep vessels of bilateral lower extremities
I80.299	Phlebitis and thrombophlebitis of other deep vessels of unspecified lower extremity
I80.3	Phlebitis and thrombophlebitis of lower extremities, unspecified
I82.210	Acute embolism and thrombosis of superior vena cava
I82.211	Chronic embolism and thrombosis of superior vena cava
I82.220	Acute embolism and thrombosis of inferior vena cava
I82.221	Chronic embolism and thrombosis of inferior vena cava
I82.290	Acute embolism and thrombosis of other thoracic veins
I82.291	Chronic embolism and thrombosis of other thoracic veins
I82.811	Embolism and thrombosis of superficial veins of right lower extremities
I82.812	Embolism and thrombosis of superficial veins of left lower extremities
I82.813	Embolism and thrombosis of superficial veins of bilateral lower extremities
I82.819	Embolism and thrombosis of superficial veins of unspecified lower extremities
I82.890	Acute embolism and thrombosis of other specified veins
I82.891	Chronic embolism and thrombosis of other specified veins

I82.90	Acute embolism and thrombosis of unspecified vein
I82.91	Chronic embolism and thrombosis of unspecified vein

ATE

CVA

Code	Description
ICD-9	
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
434.01	Cerebral thrombosis with cerebral infarction
434.11	Cerebral embolism with cerebral infarction
434.91	Cerebral artery occlusion, unspecified with cerebral infarction
436	Acute, but ill-defined, cerebrovascular disease
ICD-10	
I60.00	Nontraumatic subarachnoid hemorrhage from unspecified carotid siphon and bifurcation
I60.01	Nontraumatic subarachnoid hemorrhage from right carotid siphon and bifurcation
I60.02	Nontraumatic subarachnoid hemorrhage from left carotid siphon and bifurcation
I60.10	Nontraumatic subarachnoid hemorrhage from unspecified middle cerebral artery
I60.11	Nontraumatic subarachnoid hemorrhage from right middle cerebral artery
I60.12	Nontraumatic subarachnoid hemorrhage from left middle cerebral artery
I60.2	Nontraumatic subarachnoid hemorrhage from anterior communicating artery
I60.30	Nontraumatic subarachnoid hemorrhage from unspecified posterior communicating artery
I60.31	Nontraumatic subarachnoid hemorrhage from right posterior communicating artery
I60.32	Nontraumatic subarachnoid hemorrhage from left posterior communicating artery
I60.4	Nontraumatic subarachnoid hemorrhage from basilar artery
I60.50	Nontraumatic subarachnoid hemorrhage from unspecified vertebral artery
I60.51	Nontraumatic subarachnoid hemorrhage from right vertebral artery
I60.52	Nontraumatic subarachnoid hemorrhage from left vertebral artery
I60.6	Nontraumatic subarachnoid hemorrhage from other intracranial arteries
I60.7	Nontraumatic subarachnoid hemorrhage from unspecified intracranial arteries
I60.8	Other nontraumatic subarachnoid hemorrhage
I60.9	Nontraumatic subarachnoid hemorrhage, unspecified
I61.0	Nontraumatic intracerebral hemorrhage in hemisphere, subcortical
I61.1	Nontraumatic intracerebral hemorrhage in hemisphere, cortical

I61.2	Nontraumatic intracerebral hemorrhage in hemisphere, unspecified
I61.3	Nontraumatic intracerebral hemorrhage in brain stem
I61.4	Nontraumatic intracerebral hemorrhage in cerebellum
I61.5	Nontraumatic intracerebral hemorrhage, intraventricular
I61.6	Nontraumatic intracerebral hemorrhage, multiple localized
I61.8	Other nontraumatic intracerebral hemorrhage
I61.9	Nontraumatic intracerebral hemorrhage, unspecified
I63.00	Cerebral infarction due to thrombosis of unspecified precerebral artery
I63.011	Cerebral infarction due to thrombosis of right vertebral artery
I63.012	Cerebral infarction due to thrombosis of left vertebral artery
I63.013	Cerebral infarction due to thrombosis of bilateral vertebral arteries
I63.019	Cerebral infarction due to thrombosis of unspecified vertebral artery
I63.02	Cerebral infarction due to thrombosis of basilar artery
I63.031	Cerebral infarction due to thrombosis of right carotid artery
I63.032	Cerebral infarction due to thrombosis of left carotid artery
I63.033	Cerebral infarction due to thrombosis of bilateral carotid arteries
I63.039	Cerebral infarction due to thrombosis of unspecified carotid artery
I63.09	Cerebral infarction due to thrombosis of other precerebral artery
I63.10	Cerebral infarction due to embolism of unspecified precerebral artery
I63.111	Cerebral infarction due to embolism of right vertebral artery
I63.112	Cerebral infarction due to embolism of left vertebral artery
I63.113	Cerebral infarction due to embolism of bilateral vertebral arteries
I63.119	Cerebral infarction due to embolism of unspecified vertebral artery
I63.12	Cerebral infarction due to embolism of basilar artery
I63.131	Cerebral infarction due to embolism of right carotid artery
I63.132	Cerebral infarction due to embolism of left carotid artery
I63.133	Cerebral infarction due to embolism of bilateral carotid arteries
I63.139	Cerebral infarction due to embolism of unspecified carotid artery
I63.19	Cerebral infarction due to embolism of other precerebral artery
I63.20	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries
I63.211	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral arteries
I63.212	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral arteries
I63.213	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries
I63.219	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral arteries
I63.22	Cerebral infarction due to unspecified occlusion or stenosis of basilar arteries
I63.231	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries
I63.232	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries
I63.233	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries
I63.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries

I63.29	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries
I63.30	Cerebral infarction due to thrombosis of unspecified cerebral artery
I63.311	Cerebral infarction due to thrombosis of right middle cerebral artery
I63.312	Cerebral infarction due to thrombosis of left middle cerebral artery
I63.313	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
I63.319	Cerebral infarction due to thrombosis of unspecified middle cerebral artery
I63.321	Cerebral infarction due to thrombosis of right anterior cerebral artery
I63.322	Cerebral infarction due to thrombosis of left anterior cerebral artery
I63.323	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries
I63.329	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
I63.331	Cerebral infarction due to thrombosis of right posterior cerebral artery
I63.332	Cerebral infarction due to thrombosis of left posterior cerebral artery
I63.333	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries
I63.339	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
I63.341	Cerebral infarction due to thrombosis of right cerebellar artery
I63.342	Cerebral infarction due to thrombosis of left cerebellar artery
I63.343	Cerebral infarction due to thrombosis of bilateral cerebellar arteries
I63.349	Cerebral infarction due to thrombosis of unspecified cerebellar artery
I63.39	Cerebral infarction due to thrombosis of other cerebral artery
I63.40	Cerebral infarction due to embolism of unspecified cerebral artery
I63.411	Cerebral infarction due to embolism of right middle cerebral artery
I63.412	Cerebral infarction due to embolism of left middle cerebral artery
I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries
I63.419	Cerebral infarction due to embolism of unspecified middle cerebral artery
I63.421	Cerebral infarction due to embolism of right anterior cerebral artery
I63.422	Cerebral infarction due to embolism of left anterior cerebral artery
I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries
I63.429	Cerebral infarction due to embolism of unspecified anterior cerebral artery
I63.431	Cerebral infarction due to embolism of right posterior cerebral artery
I63.432	Cerebral infarction due to embolism of left posterior cerebral artery
I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries
I63.439	Cerebral infarction due to embolism of unspecified posterior cerebral artery
I63.441	Cerebral infarction due to embolism of right cerebellar artery
I63.442	Cerebral infarction due to embolism of left cerebellar artery
I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries
I63.449	Cerebral infarction due to embolism of unspecified cerebellar artery
I63.49	Cerebral infarction due to embolism of other cerebral artery
I63.50	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery

I63.513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries
I63.519	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries
I63.529	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery
I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries
I63.539	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery
I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
I63.549	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
	* code I64 (Stroke, not specified as haemorrhage or infarction) was omitted as the US ICD-10 version does not contain this code

AMI

Code	Description
ICD-9	
410.00	Acute myocardial infarction of anterolateral wall, episode of care unspecified
410.01	Acute myocardial infarction of anterolateral wall, initial episode of care
410.02	Acute myocardial infarction of anterolateral wall, subsequent episode of care
410.10	Acute myocardial infarction of other anterior wall, episode of care unspecified
410.11	Acute myocardial infarction of other anterior wall, initial episode of care
410.12	Acute myocardial infarction of other anterior wall, subsequent episode of care
410.20	Acute myocardial infarction of inferolateral wall, episode of care unspecified
410.21	Acute myocardial infarction of inferolateral wall, initial episode of care
410.22	Acute myocardial infarction of inferolateral wall, subsequent episode of care
410.30	Acute myocardial infarction of inferoposterior wall, episode of care unspecified
410.31	Acute myocardial infarction of inferoposterior wall, initial episode of care
410.32	Acute myocardial infarction of inferoposterior wall, subsequent episode of care

410.40	Acute myocardial infarction of other inferior wall, episode of care unspecified
410.41	Acute myocardial infarction of other inferior wall, initial episode of care
410.42	Acute myocardial infarction of other inferior wall, subsequent episode of care
410.50	Acute myocardial infarction of other lateral wall, episode of care unspecified
410.51	Acute myocardial infarction of other lateral wall, initial episode of care
410.52	Acute myocardial infarction of other lateral wall, subsequent episode of care
410.60	True posterior wall infarction, episode of care unspecified
410.61	True posterior wall infarction, initial episode of care
410.62	True posterior wall infarction, subsequent episode of care
410.70	Subendocardial infarction, episode of care unspecified
410.71	Subendocardial infarction, initial episode of care
410.72	Subendocardial infarction, subsequent episode of care
410.80	Acute myocardial infarction of other specified sites, episode of care unspecified
410.81	Acute myocardial infarction of other specified sites, initial episode of care
410.82	Acute myocardial infarction of other specified sites, subsequent episode of care
410.90	Acute myocardial infarction of unspecified site, episode of care unspecified
410.91	Acute myocardial infarction of other unspecified site, initial episode of care
410.92	Acute myocardial infarction of other unspecified site, subsequent episode of care
ICD-10	
I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery
I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery
I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall
I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
I21.19	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall
I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery
I21.29	ST elevation (STEMI) myocardial infarction involving other sites
I21.3	ST elevation (STEMI) myocardial infarction of unspecified site
I21.4	Non-ST elevation (NSTEMI) myocardial infarction

Pregnancy

Delivery

Code	Description
ICD-9 diagnosis codes	
V27.0	Outcome of delivery, single liveborn
V27.1	Outcome of delivery, single stillborn
V27.2	Outcome of delivery, twins, both liveborn
V27.3	Outcome of delivery, twins, one liveborn and one stillborn
V27.4	Outcome of delivery, twins, both stillborn

V27.5	Outcome of delivery, other multiple birth, all liveborn
V27.6	Outcome of delivery, other multiple birth, some liveborn
V27.7	Outcome of delivery, other multiple birth, all stillborn
V27.9	Outcome of delivery, unspecified outcome of delivery
645.11	Post term pregnancy, delivered, with or without mention of antepartum condition
645.21	Prolonged pregnancy, delivered, with or without mention of antepartum condition
650	Normal delivery
651.00	Twin pregnancy, unspecified as to episode of care or not applicable
651.01	Twin pregnancy, delivered, with or without mention of antepartum condition
651.03	Twin pregnancy, antepartum condition or complication
651.10	Triplet pregnancy, unspecified as to episode of care or not applicable
651.11	Triplet pregnancy, delivered, with or without mention of antepartum condition
651.13	Triplet pregnancy, antepartum condition or complication
651.20	Quadruplet pregnancy, unspecified as to episode of care or not applicable
651.21	Quadruplet pregnancy, delivered, with or without mention of antepartum condition
651.23	Quadruplet pregnancy, antepartum condition or complication
651.30	Twin pregnancy with fetal loss and retention of one fetus, unspecified as to episode of care or not applicable
651.31	Twin pregnancy with fetal loss and retention of one fetus, delivered, with or without mention of antepartum condition
651.33	Twin pregnancy with fetal loss and retention of one fetus, antepartum condition or complication
651.40	Triplet pregnancy with fetal loss and retention of one or more fetus(es), unspecified as to episode of care or not applicable
651.41	Triplet pregnancy with fetal loss and retention of one or more fetus(es), delivered, with or without mention of antepartum condition
651.43	Triplet pregnancy with fetal loss and retention of one or more fetus(es), antepartum condition or complication
651.50	Quadruplet pregnancy with fetal loss and retention of one or more fetus(es), unspecified as to episode of care or not applicable
651.51	Quadruplet pregnancy with fetal loss and retention of one or more fetus(es), delivered, with or without mention of antepartum condition
651.53	Quadruplet pregnancy with fetal loss and retention of one or more fetus(es), antepartum condition or complication
651.60	Other multiple pregnancy with fetal loss and retention of one or more fetus(es), unspecified as to episode of care or not applicable
651.61	Other multiple pregnancy with fetal loss and retention of one or more fetus(es), delivered, with or without mention of antepartum condition
651.63	Other multiple pregnancy with fetal loss and retention of one or more fetus(es), antepartum condition or complication

651.70	Multiple gestation following (elective) feta reduction, unspecified as to episode of care or not applicable
651.71	Multiple gestation following (elective) feta reduction, delivered, with or without mention of antepartum condition
651.73	Multiple gestation following (elective) feta reduction, antepartum condition or complication
651.80	Other specified multiple gestation, unspecified as to episode of care or not applicable
651.81	Other specified multiple gestation, delivered, with or without mention of antepartum condition
651.83	Other specified multiple gestation, antepartum condition or complication
651.90	Unspecified multiple gestation, unspecified as to episode of care or not applicable
651.91	Unspecified multiple gestation, delivered, with or without mention of antepartum condition
651.93	Unspecified multiple gestation, antepartum condition or complication
ICD-9 procedure codes	
72.0	Low forceps operation
72.1	Low forceps operation with episiotomy
72.21	Mid forceps operation with episiotomy
72.29	Other mid forceps operation
72.31	High forceps operation with episiotomy
72.39	Other high forceps operation
72.4	Forceps rotation of fetal head
72.51	Partial breech extraction with forceps to aftercoming head
72.52	Other partial breech extraction
72.53	Total breech extraction with forceps to aftercoming head
72.54	Other total breech extraction
72.6	Forceps application to aftercoming head
72.71	Vacuum extraction with episiotomy
72.79	Other vacuum extraction
72.8	Other specified instrumental delivery
72.9	Unspecified instrumental delivery
73.01	Induction of labor by artificial rupture of membranes
73.09	Other artificial rupture of membranes
73.1	Other surgical induction of labor
73.21	Internal and combined version without extraction
73.22	internal and combined version with extraction
73.3	Failed forceps
73.4	Medical induction of labor
73.51	Manual rotation of fetal head
73.59	Other manually assisted delivery

73.6	Episiotomy
73.8	Operations on fetus to facilitate delivery
73.91	External version
73.92	Replacement of prolapsed umbilical cord
73.93	Incision of cervix to assist delivery
73.94	Pubiotomy to assist delivery
73.99	Other operations assisting delivery
74.0	Classical cesarean section
74.1	Low cervical cesarean section
74.2	Extraperitoneal cesarean section
74.4	Cesarean section of other specified type
74.91	Hysterotomy to terminate pregnancy
74.99	Other cesarean section of unspecified type
CPT codes	
59409	Vaginal delivery only (with or without episiotomy and/or forceps)
59410	Vaginal delivery only (with or without episiotomy and/or forceps); including postpartum care
59514	Cesarean delivery only
59515	Cesarean delivery only; including postpartum care
59612	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy, and/or forceps)
59614	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy, and/or forceps); including postpartum care
59620	Cesarean delivery only, following attempted vaginal delivery after previous cesarean delivery
59622	Cesarean delivery only, following attempted vaginal delivery after previous cesarean delivery; including postpartum care
ICD-10 diagnosis codes	
O80	Encounter for full-term uncomplicated delivery
O82	Encounter for cesarean delivery without indication
	* Codes O83, O84 were omitted as the US ICD-10 version does not contain these codes

Pregnancy with abortive outcome

Code	Description
ICD-9 diagnosis codes	
634.00	Spontaneous abortion, complicated by genital tract and pelvic infection, unspecified
634.01	Spontaneous abortion, complicated by genital tract and pelvic infection, incomplete
634.02	Spontaneous abortion, complicated by genital tract and pelvic infection, complete
634.10	Spontaneous abortion, complicated by delayed or excessive hemorrhage, unspecified
634.11	Spontaneous abortion, complicated by delayed or excessive hemorrhage, incomplete
634.12	Spontaneous abortion, complicated by delayed or excessive hemorrhage, complete

634.20	Spontaneous abortion, complicated by damage to pelvic organs or tissues, unspecified
634.21	Spontaneous abortion, complicated by damage to pelvic organs or tissues, incomplete
634.22	Spontaneous abortion, complicated by damage to pelvic organs or tissues, complete
634.30	Spontaneous abortion, complicated by renal failure, unspecified
634.31	Spontaneous abortion, complicated by renal failure, incomplete
634.32	Spontaneous abortion, complicated by renal failure, complete
634.40	Spontaneous abortion, complicated by metabolic disorder, unspecified
634.41	Spontaneous abortion, complicated by metabolic disorder, incomplete
634.42	Spontaneous abortion, complicated by metabolic disorder, complete
634.50	Spontaneous abortion, complicated by shock, unspecified
634.51	Spontaneous abortion, complicated by shock, incomplete
634.52	Spontaneous abortion, complicated by shock, complete
634.60	Spontaneous abortion, complicated by embolism, unspecified
634.61	Spontaneous abortion, complicated by embolism, incomplete
634.62	Spontaneous abortion, complicated by embolism, complete
634.70	Spontaneous abortion, with other specified complications, unspecified
634.71	Spontaneous abortion, with other specified complications, incomplete
634.72	Spontaneous abortion, with other specified complications, complete
634.80	Spontaneous abortion, with unspecified complication, unspecified
634.81	Spontaneous abortion, with unspecified complication, incomplete
634.82	Spontaneous abortion, with unspecified complication, complete
634.90	Spontaneous abortion, without mention of complication, unspecified
634.91	Spontaneous abortion, without mention of complication, incomplete
634.92	Spontaneous abortion, without mention of complication, complete
635.00	Legally induced abortion, complicated by genital tract and pelvic infection, unspecified
635.01	Legally induced abortion, complicated by genital tract and pelvic infection, incomplete
635.02	Legally induced abortion, complicated by genital tract and pelvic infection, complete
635.10	Legally induced abortion, complicated by delayed or excessive hemorrhage, unspecified
635.11	Legally induced abortion, complicated by delayed or excessive hemorrhage, incomplete
635.12	Legally induced abortion, complicated by delayed or excessive hemorrhage, complete
635.20	Legally induced abortion, complicated by damage to pelvic organs or tissues, unspecified
635.21	Legally induced abortion, complicated by damage to pelvic organs or tissues, incomplete
635.22	Legally induced abortion, complicated by damage to pelvic organs or tissues, complete
635.30	Legally induced abortion, complicated by renal failure, unspecified
635.31	Legally induced abortion, complicated by renal failure, incomplete
635.32	Legally induced abortion, complicated by renal failure, complete
635.40	Legally induced abortion, complicated by metabolic disorder, unspecified
635.41	Legally induced abortion, complicated by metabolic disorder, incomplete
635.42	Legally induced abortion, complicated by metabolic disorder, complete

635.50	Legally induced abortion, complicated by shock, unspecified
635.51	Legally induced abortion, complicated by shock, incomplete
635.52	Legally induced abortion, complicated by shock, complete
635.60	Legally induced abortion, complicated by embolism, unspecified
635.61	Legally induced abortion, complicated by embolism, incomplete
635.62	Legally induced abortion, complicated by embolism, complete
635.70	Legally induced abortion, with other specified complications, unspecified
635.71	Legally induced abortion, with other specified complications, incomplete
635.72	Legally induced abortion, with other specified complications, complete
635.80	Legally induced abortion, with unspecified complication, unspecified
635.81	Legally induced abortion, with unspecified complication, incomplete
635.82	Legally induced abortion, with unspecified complication, complete
635.90	Legally induced abortion, without mention of complication, unspecified
635.91	Legally induced abortion, without mention of complication, incomplete
635.92	Legally induced abortion, without mention of complication, complete
636.00	Illegally induced abortion, complicated by genital tract and pelvic infection, unspecified
636.01	Illegally induced abortion, complicated by genital tract and pelvic infection, incomplete
636.02	Illegally induced abortion, complicated by genital tract and pelvic infection, complete
636.10	Illegally induced abortion, complicated by delayed or excessive hemorrhage, unspecified
636.11	Illegally induced abortion, complicated by delayed or excessive hemorrhage, incomplete
636.12	Illegally induced abortion, complicated by delayed or excessive hemorrhage, complete
636.20	Illegally induced abortion, complicated by damage to pelvic organs or tissues, unspecified
636.21	Illegally induced abortion, complicated by damage to pelvic organs or tissues, incomplete
636.22	Illegally induced abortion, complicated by damage to pelvic organs or tissues, complete
636.30	Illegally induced abortion, complicated by renal failure, unspecified
636.31	Illegally induced abortion, complicated by renal failure, incomplete
636.32	Illegally induced abortion, complicated by renal failure, complete
636.40	Illegally induced abortion, complicated by metabolic disorder, unspecified
636.41	Illegally induced abortion, complicated by metabolic disorder, incomplete
636.42	Illegally induced abortion, complicated by metabolic disorder, complete
636.50	Illegally induced abortion, complicated by shock, unspecified
636.51	Illegally induced abortion, complicated by shock, incomplete
636.52	Illegally induced abortion, complicated by shock, complete
636.60	Illegally induced abortion, complicated by embolism, unspecified
636.61	Illegally induced abortion, complicated by embolism, incomplete
636.62	Illegally induced abortion, complicated by embolism, complete
636.70	Illegally induced abortion, with other specified complications, unspecified
636.71	Illegally induced abortion, with other specified complications, incomplete
636.72	Illegally induced abortion, with other specified complications, complete

636.80	Illegally induced abortion, with unspecified complication, unspecified
636.81	Illegally induced abortion, with unspecified complication, incomplete
636.82	Illegally induced abortion, with unspecified complication, complete
636.90	Illegally induced abortion, without mention of complication, unspecified
636.91	Illegally induced abortion, without mention of complication, incomplete
636.92	Illegally induced abortion, without mention of complication, complete
637.00	Unspecified abortion, complicated by genital tract and pelvic infection, unspecified
637.01	Unspecified abortion, complicated by genital tract and pelvic infection, incomplete
637.02	Unspecified abortion, complicated by genital tract and pelvic infection, complete
637.10	Unspecified abortion, complicated by delayed or excessive hemorrhage, unspecified
637.11	Unspecified abortion, complicated by delayed or excessive hemorrhage, incomplete
637.12	Unspecified abortion, complicated by delayed or excessive hemorrhage, complete
637.20	Unspecified abortion, complicated by damage to pelvic organs or tissues, unspecified
637.21	Unspecified abortion, complicated by damage to pelvic organs or tissues, incomplete
637.22	Unspecified abortion, complicated by damage to pelvic organs or tissues, complete
637.30	Unspecified abortion, complicated by renal failure, unspecified
637.31	Unspecified abortion, complicated by renal failure, incomplete
637.32	Unspecified abortion, complicated by renal failure, complete
637.40	Unspecified abortion, complicated by metabolic disorder, unspecified
637.41	Unspecified abortion, complicated by metabolic disorder, incomplete
637.42	Unspecified abortion, complicated by metabolic disorder, complete
637.50	Unspecified abortion, complicated by shock, unspecified
637.51	Unspecified abortion, complicated by shock, incomplete
637.52	Unspecified abortion, complicated by shock, complete
637.60	Unspecified abortion, complicated by embolism, unspecified
637.61	Unspecified abortion, complicated by embolism, incomplete
637.62	Unspecified abortion, complicated by embolism, complete
637.70	Unspecified abortion, with other specified complications, unspecified
637.71	Unspecified abortion, with other specified complications, incomplete
637.72	Unspecified abortion, with other specified complications, complete
637.80	Unspecified abortion, with unspecified complication, unspecified
637.81	Unspecified abortion, with unspecified complication, incomplete
637.82	Unspecified abortion, with unspecified complication, complete
637.90	Unspecified abortion, without mention of complication, unspecified
637.91	Unspecified abortion, without mention of complication, incomplete
637.92	Unspecified abortion, without mention of complication, complete
638.0	Failed attempted abortion complicated by genital tract and pelvic infection
638.1	Failed attempted abortion complicated by delayed or excessive hemorrhage
638.2	Failed attempted abortion complicated by damage to pelvic organs or tissues
638.3	Failed attempted abortion complicated by renal failure

638.4	Failed attempted abortion complicated by metabolic disorder
638.5	Failed attempted abortion complicated by shock
638.6	Failed attempted abortion complicated by embolism
638.7	Failed attempted abortion with other specified complications
638.8	Failed attempted abortion with unspecified complication
638.9	Failed attempted abortion without mention of complication
639.0	Genital tract and pelvic infection following abortion or ectopic and molar pregnancies
639.1	Delayed or excessive hemorrhage following abortion or ectopic and molar pregnancies
639.2	Damage to pelvic organs following abortion or ectopic and molar pregnancies
639.3	Kidney failure following abortion or ectopic and molar pregnancies
639.4	Metabolic disorders following abortion or ectopic and molar pregnancies
639.5	Shock following abortion or ectopic and molar pregnancies
639.6	Embolism following abortion or ectopic and molar pregnancies
639.8	Other specified complications following abortion or ectopic and molar pregnancies
639.9	Unspecified complication following abortion or ectopic and molar pregnancies
ICD-9 procedure codes	
69.01	Dilation and curettage for termination of pregnancy
69.51	Aspiration curettage of uterus for termination of pregnancy
74.3	Removal of extratubal ectopic pregnancy
ICD-10 diagnosis codes	
O00.00	Abdominal pregnancy without intrauterine pregnancy
O00.01	Abdominal pregnancy with intrauterine pregnancy
O00.101	Right tubal pregnancy without intrauterine pregnancy
O00.102	Left tubal pregnancy without intrauterine pregnancy
O00.111	Right tubal pregnancy with intrauterine pregnancy
O00.112	Left tubal pregnancy with intrauterine pregnancy
O00.201	Right ovarian pregnancy without intrauterine pregnancy
O00.202	Left ovarian pregnancy without intrauterine pregnancy
O00.211	Right ovarian pregnancy with intrauterine pregnancy
O00.212	Left ovarian pregnancy with intrauterine pregnancy
O00.80	Other ectopic pregnancy without intrauterine pregnancy
O00.81	Other ectopic pregnancy with intrauterine pregnancy
O00.90	Unspecified ectopic pregnancy without intrauterine pregnancy
O00.91	Unspecified ectopic pregnancy with intrauterine pregnancy
O01.0	Classical hydatidiform mole
O01.1	Incomplete and partial hydatidiform mole
O01.9	Hydatidiform mole, unspecified
O02.0	Blighted ovum and nonhydatidiform mole
O02.1	Missed abortion

O02.81	Inappropriate change in quantitative human chorionic gonadotropin (hCG) in early pregnancy
O02.89	Other abnormal products of conception
O02.9	Abnormal product of conception, unspecified
O03.0	Genital tract and pelvic infection following incomplete spontaneous abortion
O03.1	Delayed or excessive hemorrhage following incomplete spontaneous abortion
O03.2	Embolism following incomplete spontaneous abortion
O03.30	Unspecified complication following incomplete spontaneous abortion
O03.31	Shock following incomplete spontaneous abortion
O03.32	Renal failure following incomplete spontaneous abortion
O03.33	Metabolic disorder following incomplete spontaneous abortion
O03.34	Damage to pelvic organs following incomplete spontaneous abortion
O03.35	Other venous complications following incomplete spontaneous abortion
O03.36	Cardiac arrest following incomplete spontaneous abortion
O03.37	Sepsis following incomplete spontaneous abortion
O03.38	Urinary tract infection following incomplete spontaneous abortion
O03.39	Incomplete spontaneous abortion with other complications
O03.4	Incomplete spontaneous abortion without complication
O03.5	Genital tract and pelvic infection following complete or unspecified spontaneous abortion
O03.6	Delayed or excessive hemorrhage following complete or unspecified spontaneous abortion
O03.7	Embolism following complete or unspecified spontaneous abortion
O03.80	Unspecified complication following complete or unspecified spontaneous abortion
O03.81	Shock following complete or unspecified spontaneous abortion
O03.82	Renal failure following complete or unspecified spontaneous abortion
O03.83	Metabolic disorder following complete or unspecified spontaneous abortion
O03.84	Damage to pelvic organs following complete or unspecified spontaneous abortion
O03.85	Other venous complications following complete or unspecified spontaneous abortion
O03.86	Cardiac arrest following complete or unspecified spontaneous abortion
O03.87	Sepsis following complete or unspecified spontaneous abortion
O03.88	Urinary tract infection following complete or unspecified spontaneous abortion
O03.89	Complete or unspecified spontaneous abortion with other complications
O03.9	Complete or unspecified spontaneous abortion without complication
O04.5	Genital tract and pelvic infection following (induced) termination of pregnancy
O04.6	Delayed or excessive hemorrhage following (induced) termination of pregnancy
O04.7	Embolism following (induced) termination of pregnancy
O04.80	(Induced) termination of pregnancy with unspecified complications
O04.81	Shock following (induced) termination of pregnancy
O04.82	Renal failure following (induced) termination of pregnancy
O04.83	Metabolic disorder following (induced) termination of pregnancy

O04.84	Damage to pelvic organs following (induced) termination of pregnancy
O04.85	Other venous complications following (induced) termination of pregnancy
O04.86	Cardiac arrest following (induced) termination of pregnancy
O04.87	Sepsis following (induced) termination of pregnancy
O04.88	Urinary tract infection following (induced) termination of pregnancy
O04.89	(Induced) termination of pregnancy with other complications
O07.0	Genital tract and pelvic infection following failed attempted termination of pregnancy
O07.1	Delayed or excessive hemorrhage following failed attempted termination of pregnancy
O07.2	Embolism following failed attempted termination of pregnancy
O07.30	Failed attempted termination of pregnancy with unspecified complications
O07.31	Shock following failed attempted termination of pregnancy
O07.32	Renal failure following failed attempted termination of pregnancy
O07.33	Metabolic disorder following failed attempted termination of pregnancy
O07.34	Damage to pelvic organs following failed attempted termination of pregnancy
O07.35	Other venous complications following failed attempted termination of pregnancy
O07.36	Cardiac arrest following failed attempted termination of pregnancy
O07.37	Sepsis following failed attempted termination of pregnancy
O07.38	Urinary tract infection following failed attempted termination of pregnancy
O07.39	Failed attempted termination of pregnancy with other complications
O07.4	Failed attempted termination of pregnancy without complication
O08.0	Genital tract and pelvic infection following ectopic and molar pregnancy
O08.1	Delayed or excessive hemorrhage following ectopic and molar pregnancy
O08.2	Embolism following ectopic and molar pregnancy
O08.3	Shock following ectopic and molar pregnancy
O08.4	Renal failure following ectopic and molar pregnancy
O08.5	Metabolic disorder following ectopic and molar pregnancy
O08.6	Damage to pelvic organs following ectopic and molar pregnancy
O08.7	Other venous complications following ectopic and molar pregnancy
O08.81	Cardiac arrest following ectopic and molar pregnancy
O08.82	Sepsis following ectopic and molar pregnancy
O08.83	Urinary tract infection ectopic and molar pregnancy
O08.89	Other complications following ectopic and molar pregnancy
O08.9	Unspecified complication following ectopic and molar pregnancy
	Codes O05 and O06 were omitted as the US ICD-10 version does not contain these codes
CPT codes	
59120	Surgical treatment of ectopic pregnancy; tubal or ovarian, requiring salpingectomy and/or oophorectomy, abdominal or vaginal approach
59121	Surgical treatment of ectopic pregnancy; tubal or ovarian, without salpingectomy and/or oophorectomy
59130	Surgical treatment of ectopic pregnancy; abdominal pregnancy

59135	Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy requiring total hysterectomy
59136	Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy with partial resection of uterus
59140	Surgical treatment of ectopic pregnancy; cervical, with evacuation
59150	Laparoscopic treatment of ectopic pregnancy; without salpingectomy and/or oophorectomy
59151	Laparoscopic treatment of ectopic pregnancy; with salpingectomy and/or oophorectomy
59840	Induced abortion, by dilation and curettage
59841	Induced abortion, by dilation and evacuation
59850	Induced abortion, by one or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines
59851	Induced abortion, by one or more intra-amniotic injections (amniocentesis injections), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation
59852	Induced abortion, by one or more intra-amniotic injections (amniocentesis injections), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed intra-amniotic injection)
59855	Induced abortion, by one or more vaginal suppositories (i.e., prostaglandin) with or without cervical dilation (i.e., laminaria), including hospital admission and visits, delivery of fetus and secundines
59856	Induced abortion, by one or more vaginal suppositories (i.e., prostaglandin) with or without cervical dilation (i.e., laminaria), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation
59857	Induced abortion, by one or more vaginal suppositories (i.e., prostaglandin) with or without cervical dilation (i.e., laminaria), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed medical evacuation)
59866	Multifetal pregnancy reduction(s) (MPR)
59812	Treatment of incomplete abortion, any trimester, completed surgically
59820	Treatment of missed abortion, completed surgically; first trimester
59821	Treatment of missed abortion, completed surgically; second trimester
59830	Treatment of septic abortion, completed surgically

Prenatal Care

Code	Description
ICD-9 diagnosis codes	
640.xx	Hemorrhage in early pregnancy
641.xx	Antepartum hemorrhage, abruptio placentae, and placenta previa
642.xx	Hypertension complicating pregnancy, childbirth, and the puerperium
643.xx	Excessive vomiting in pregnancy
644.xx	Early or threatened labor
645.xx	Late pregnancy
646.xx	Other complications of pregnancy, not elsewhere classified
647.xx	Infectious and parasitic conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium
648.xx	Other current conditions in the mother classifiable elsewhere, but Complicating pregnancy, childbirth, or the puerperium

649.xx	Other conditions or status of the mother complicating pregnancy, childbirth, or puerperium
651.xx	Multiple gestation
652.xx	Malposition or malpresentation of fetus
653.xx	Disproportion
654.xx	Abnormality of organs and soft tissues of pelvis
655.xx	Known or suspected fetal abnormality affecting management of mother
656.xx	Other known or suspected fetal and placental problems affecting management of mother
657.xx	Polyhydramnios
658.xx	Other problems associated with amniotic cavity and membranes
659.xx	Other indications for care or intervention related to labor and delivery, not elsewhere classified
665.xx	Other obstetrical trauma
V22.x	Normal pregnancy
V23.xx	Supervision of high risk pregnancy
V28.xx	Encounter for antenatal screening of mother
V72.4x	Pregnancy examination or test
ICD-9 procedure codes	
75.xx	Other obstetric operations
ICD-10 diagnosis codes	
O09.xxx	Supervision of high risk pregnancy
O10.xxx	Pre-existing hypertension complicating pregnancy, childbirth, and the puerperium
O11.x	Pre-existing hypertension with pre-eclampsia
O12.xx	Gestational [pregnancy-induced] edema and proteinuria without hypertension
O13.x	Gestational [pregnancy-induced] hypertension without significant proteinuria
O14.xx	Pre-eclampsia
O16.x	Unspecified maternal hypertension
O20.x	Hemorrhage in early pregnancy
O21.x	Excessive vomiting in pregnancy
O22.xxx	Venous complications and hemorrhoids in pregnancy
O23.xxx	Infections of genitourinary tract in pregnancy
O24.xxx	Diabetes mellitus in pregnancy, childbirth, and the puerperium
025.xx	Malnutrition in pregnancy, childbirth and the puerperium
O26.xxx	Maternal care for other conditions predominantly related to pregnancy
O28.x	Abnormal findings on antenatal screening of mother
O29.xxx	Complications of anesthesia during pregnancy
O30.xxx	Multiple gestation
O31.xxxx	Complications specific to multiple gestation
O32.xxxx	Maternal care for malpresentation of fetus
O33.xxxx	Maternal care for disproportion

O34.xxx	Maternal care for abnormality of pelvic organs
O35.xxxx	Maternal care for known or suspected fetal abnormality and damage
O36.xxxx	Maternal care for other fetal problems
O40.xxxx	Polyhydramnios
O41.xxxx	Other disorders of amniotic fluid and membranes
O42.xxx	Premature rupture of membranes
O43.xxx	Placental disorders
O44.xx	Placenta previa
O45.xxx	Premature separation of placenta [abruptio placentae]
O46.xxx	Antepartum hemorrhage, not elsewhere classified
O47.xx	False labor
O48.x	Late pregnancy
O60.xxxx	Preterm labor
O61.x	Failed induction of labor
O62.x	Abnormalities of forces of labor
O63.x	Long labor
O88.xxx	Obstetric embolism
O91.xxx	Infections of the breast associated with pregnancy, the puerperium and lactation
O92.xxx	Other disorders of breast and disorders of lactation associated with pregnancy and the puerperium
O98.xxx	Maternal infectious and parasitic diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium
O99.xxx	Other maternal diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium
Z32.xx	Encounter for pregnancy test and childbirth and childcare instruction
Z33.x	Pregnant state
Z34.xx	Encounter for supervision of normal pregnancy
Z36.xx	Encounter for antenatal screening of mother
Z76.81	Expectant parent(s) prebirth pediatrician visit
ICD-10 procedure codes	
0UVC0CZ	Restriction of Cervix with Extralum Dev, Open Approach
0UVC0DZ	Restriction of Cervix with Intralum Dev, Open Approach
0UVC0ZZ	Restriction of Cervix, Open Approach
0UVC3CZ	Restriction of Cervix with Extralum Dev, Perc Approach
0UVC3DZ	Restriction of Cervix with Intralum Dev, Perc Approach
0UVC3ZZ	Restriction of Cervix, Percutaneous Approach
0UVC4CZ	Restriction of Cervix with Extralum Dev, Perc Endo Approach
0UVC4DZ	Restriction of Cervix with Intralum Dev, Perc Endo Approach
0UVC4ZZ	Restriction of Cervix, Percutaneous Endoscopic Approach
0UVC7DZ	Restriction of Cervix with Intraluminal Device, Via Opening
0UVC7ZZ	Restriction of Cervix, Via Natural or Artificial Opening

0UVC8DZ	Restriction of Cervix with Intraluminal Device, Endo
0UVC8ZZ	Restriction of Cervix, Endo
HCPCS codes	
H1001	Prenatal care, at-risk enhanced service; antepartum management
H1000	Prenatal care, at-risk assessment
H1002	Prenatal care, at risk enhanced service; care coordination
H1003	Prenatal care, at-risk enhanced service; education
H1005	Prenatal care, at-risk enhanced service package (includes H1001-H1004)
H1004	Prenatal care, at-risk enhanced service; follow-up home visit
CPT codes	
0500F	Initial prenatal care visit (report at first prenatal encounter with health care professional providing obstetrical care. Report also date of visit and, in a separate field, the date of the last menstrual period [LMP]) (Prenatal)
0501F	Prenatal flow sheet documented in medical record by first prenatal visit (documentation includes at minimum blood pressure, weight, urine protein, uterine size, fetal heart tones, and estimated date of delivery)
0502F	Subsequent prenatal care visit (Prenatal) [Excludes: patients who are seen for a condition unrelated to pregnancy or prenatal care (e.g., an upper respiratory infection; patients seen for consultation only, not for continuing care)]
4178F	Anti-D immune globulin received between 26 and 30 weeks gestation (Pre-Cf)
59000	Amniocentesis; diagnostic
59015	Chorionic villus sampling, any method
59025	Fetal non-stress test
59030	Fetal scalp blood sampling
59070	Transabdominal amnioinfusion, including ultrasound guidance
59072	Fetal umbilical cord occlusion, including ultrasound guidance
59074	Fetal fluid drainage (e.g., vesicocentesis, thoracocentesis, paracentesis), including ultrasound guidance
59076	Fetal shunt placement, including ultrasound guidance
59320	Cerclage of cervix, during pregnancy; vaginal
59425	Antepartum care only; 4-6 visits
59426	Antepartum care only; 7 or more visits
59897	Unlisted fetal invasie procedure, including ultrasound guidance, when performed
59898	Unlisted laparoscopy procedure, maternity care and delivery
59899	Unlisted procedure, maternity care and delivery
76801	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, first trimester (< 14 weeks 0 days), transabdominal approach; single or first gestation
76802	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, first trimester (< 14 weeks 0 days), transabdominal approach; each additional gestation (List separately in addition to code for primary procedure)

76805	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; single or first gestation
76810	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; each additional gestation (List separately in addition to code for primary procedure)
76811	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation plus detailed fetal anatomic examination, transabdominal approach; single or first gestation
76813	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation
76815	Ultrasound, pregnant uterus, real time with image documentation, limited (e.g., fetal heartbeat, placental location, fetal position and/or qualitative amniotic fluid volume), 1 or more fetuses
76816	Ultrasound, pregnant uterus, real time with image documentation, follow-up (e.g., re-evaluation of fetal size by measuring standard growth parameters and amniotic fluid volume, re-evaluation of organ system(s) suspected or confirmed to be abnormal on a previous scan), transabdominal approach, per fetus
76817	Ultrasound, pregnant uterus, real time with image documentation, transvaginal
76818	Fetal biophysical profile; with non-stress testing
76819	Fetal biophysical profile; without non-stress testing
76820	Doppler velocimetry, fetal; umbilical artery
76821	Doppler velocimetry, fetal; middle cerebral artery
76825	Echocardiography, fetal, cardiovascular system, real time with image documentation (2D), with or without M-mode recording
76826	Echocardiography, fetal, cardiovascular system, real time with image documentation (2D), with or without M-mode recording; follow-up or repeat study
76827	Doppler echocardiography, fetal, pulsed wave and/or continuous wave with spectral display; complete
76828	Doppler echocardiography, fetal, pulsed wave and/or continuous wave with spectral display; follow-up or repeat study
76831	Saline infusion sonohysterography (SIS), including color flow Doppler, when performed
76941	Ultrasonic guidance for intrauterine fetal transfusion or cordocentesis, imaging supervision and interpretation
76945	Ultrasonic guidance for chorionic villus sampling, imaging supervision and interpretation
76946	Ultrasonic guidance for amniocentesis, imaging supervision and interpretation
80055	Obstetric panel This panel must include the following: Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Hepatitis B surface antigen (HBsAg) (87340) Antibody, rubella (86762) Syphilis test, non-treponemal antibody; qualitative (e.g., VDRL, RPR, ART) (86592) Antibody screen, RBC, each serum technique (86850) Blood typing, ABO (86900) AND Blood typing, Rh (D) (86901)

81025	Urine pregnancy test, by visual color comparison methods
82106	Alpha-fetoprotein (AFP); amniotic fluid
82677	Estriol
82731	Fetal fibronectin, cervicovaginal secretions, semi-quantitative
83632	Lactogen, human placental (HPL) human chorionic somatomammotropin
83661	Fetal lung maturity assessment; lecithin sphingomyelin (L/S) ratio
83662	Fetal lung maturity assessment; foam stability test
83663	Fetal lung maturity assessment; fluorescence polarization
84081	Phosphatidylglycerol
88235	Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells

Breast Cancer and Other Gynaecological Cancers

Breast cancer

Code	Description
ICD-9	
174.0	Malignant neoplasm of nipple and areola of female breast
174.1	Malignant neoplasm of central portion of female breast
174.2	Malignant neoplasm of upper-inner quadrant of female breast
174.3	Malignant neoplasm of lower-inner quadrant of female breast
174.4	Malignant neoplasm of upper-outer quadrant of female breast
174.5	Malignant neoplasm of lower-outer quadrant of female breast
174.6	Malignant neoplasm of axillary tail of female breast
174.8	Malignant neoplasm of other specified sites of female breast
174.9	Malignant neoplasm of breast (female), unspecified
ICD-10	
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast

C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast

Cervical cancer

Code	Description
ICD-9	
180.0	Malignant neoplasm of endocervix
180.1	Malignant neoplasm of exocervix
180.8	Malignant neoplasm of other specified sites of cervix
180.9	Malignant neoplasm of cervix uteri, unspecified site
ICD-10	
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C53.8	Malignant neoplasm of overlapping sites of cervix uteri
C53.9	Malignant neoplasm of cervix uteri, unspecified

Endometrial cancer

Code	Description
ICD-9	
182.0	Malignant neoplasm of corpus uteri, except isthmus
ICD-10	
C54.1	Malignant neoplasm of endometrium

Ovarian cancer

Code	Description
ICD-9	
183.0	Malignant neoplasm of ovary
ICD-10	
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary

Malignancies

Code	Description
ICD-9	
140.0	Malignant neoplasm of upper lip, vermilion border
140.1	Malignant neoplasm of lower lip, vermilion border
140.3	Malignant neoplasm of upper lip, inner aspect
140.4	Malignant neoplasm of lower lip, inner aspect
140.5	Malignant neoplasm of lip, unspecified, inner aspect
140.6	Malignant neoplasm of commissure of lip
140.8	Malignant neoplasm of other sites of lip
140.9	Malignant neoplasm of lip, unspecified, vermilion border
141.0	Malignant neoplasm of base of tongue
141.1	Malignant neoplasm of dorsal surface of tongue
141.2	Malignant neoplasm of tip and lateral border of tongue
141.3	Malignant neoplasm of tip of ventral surface of tongue
141.4	Malignant neoplasm of anterior two-thirds of tongue, part unspecified
141.5	Malignant neoplasm of junctional zone of tongue
141.6	Malignant neoplasm of lingual tonsil
141.8	Malignant neoplasm of other sites of tongue
141.9	Malignant neoplasm of tongue, unspecified
142.0	Malignant neoplasm of parotid gland
142.1	Malignant neoplasm of submandibular gland
142.2	Malignant neoplasm of sublingual gland
142.8	Malignant neoplasm of other major salivary glands
142.9	Malignant neoplasm of salivary gland, unspecified
143.0	Malignant neoplasm of upper gum
143.1	Malignant neoplasm of lower gum
143.8	Malignant neoplasm of other sites of gum
143.9	Malignant neoplasm of gum, unspecified
144.0	Malignant neoplasm of anterior portion of floor of mouth
144.1	Malignant neoplasm of lateral portion of floor of mouth
144.8	Malignant neoplasm of other sites of floor of mouth
144.9	Malignant neoplasm of floor of mouth, part unspecified
145.0	Malignant neoplasm of cheek mucosa
145.1	Malignant neoplasm of vestibule of mouth
145.2	Malignant neoplasm of hard palate
145.3	Malignant neoplasm of soft palate
145.4	Malignant neoplasm of uvula
145.5	Malignant neoplasm of palate, unspecified
145.6	Malignant neoplasm of retromolar area

145.8	Malignant neoplasm of other specified parts of mouth
145.9	Malignant neoplasm of mouth, unspecified
146.0	Malignant neoplasm of tonsil
146.1	Malignant neoplasm of tonsillar fossa
146.2	Malignant neoplasm of tonsillar pillars (anterior) (posterior)
146.3	Malignant neoplasm of vallecular epiglottica
146.4	Malignant neoplasm of anterior aspect of epiglottis
146.5	Malignant neoplasm of junctional region of oropharynx
146.6	Malignant neoplasm of lateral wall of oropharynx
146.7	Malignant neoplasm of posterior wall of oropharynx
146.8	Malignant neoplasm of other specified sites of oropharynx
146.9	Malignant neoplasm of oropharynx, unspecified site
147.0	Malignant neoplasm of superior wall of nasopharynx
147.1	Malignant neoplasm of posterior wall of nasopharynx
147.2	Malignant neoplasm of lateral wall of nasopharynx
147.3	Malignant neoplasm of anterior wall of nasopharynx
147.8	Malignant neoplasm of other specified sites of nasopharynx
147.9	Malignant neoplasm of nasopharynx, unspecified site
148.0	Malignant neoplasm of postcricoid region of hypopharynx
148.1	Malignant neoplasm of pyriform sinus
148.2	Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
148.3	Malignant neoplasm of posterior hypopharyngeal wall
148.8	Malignant neoplasm of other specified sites of hypopharynx
148.9	Malignant neoplasm of hypopharynx, unspecified site
149.0	Malignant neoplasm of pharynx, unspecified
149.1	Malignant neoplasm of waldeyer’s ring
149.8	Malignant neoplasm of other sites within the lip and oral cavity
149.9	Malignant neoplasm of ill-defined sites within the lip and oral cavity
150.0	Malignant neoplasm of cervical esophagus
150.1	Malignant neoplasm of thoracic esophagus
150.2	Malignant neoplasm of abdominal esophagus
150.3	Malignant neoplasm of upper third of esophagus
150.4	Malignant neoplasm of middle third of esophagus
150.5	Malignant neoplasm of lower third of esophagus
150.8	Malignant neoplasm of other specified part of esophagus
150.9	Malignant neoplasm of esophagus, unspecified site
151.0	Malignant neoplasm of cardia
151.1	Malignant neoplasm of pylorus
151.2	Malignant neoplasm of pyloric antrum
151.3	Malignant neoplasm of fundus of stomach

151.4	Malignant neoplasm of body of stomach
151.5	Malignant neoplasm of lesser curvature of stomach, unspecified
151.6	Malignant neoplasm of greater curvature of stomach, unspecified
151.8	Malignant neoplasm of other specified sites of stomach
151.9	Malignant neoplasm of stomach, unspecified site
152.0	Malignant neoplasm of duodenum
152.1	Malignant neoplasm of jejunum
152.2	Malignant neoplasm of ileum
152.3	Malignant neoplasm of Meckel's diverticulum
152.8	Malignant neoplasm of other specified sites of small intestine
152.9	Malignant neoplasm of small intestine, unspecified site
153.0	Malignant neoplasm of hepatic flexure
153.1	Malignant neoplasm of transverse colon
153.2	Malignant neoplasm of descending colon
153.3	Malignant neoplasm of sigmoid colon
153.4	Malignant neoplasm of cecum
153.5	Malignant neoplasm of appendix vermiformis
153.6	Malignant neoplasm of ascending colon
153.7	Malignant neoplasm of splenic flexure
153.8	Malignant neoplasm of other specified sites of large intestine
153.9	Malignant neoplasm of colon, unspecified site
154.0	Malignant neoplasm of rectosigmoid junction
154.1	Malignant neoplasm of rectum
154.2	Malignant neoplasm of anal canal
154.3	Malignant neoplasm of anus, unspecified site
154.8	Malignant neoplasm of other sites of rectum, rectosigmoid junction, and anus
155.0	Malignant neoplasm of liver, primary
155.1	Malignant neoplasm of intrahepatic bile duct
155.2	Malignant neoplasm of liver, not specified as primary or secondary
156.0	Malignant neoplasm of gallbladder
156.1	Malignant neoplasm of extrahepatic bile ducts
156.2	Malignant neoplasm of ampulla of vater
156.8	Malignant neoplasm of other specified sites of gallbladder and extrahepatic bile ducts
156.9	Malignant neoplasm of biliary tract, part unspecified site
157.0	Malignant neoplasm of head of pancreas
157.1	Malignant neoplasm of body of pancreas
157.2	Malignant neoplasm of tail of pancreas
157.3	Malignant neoplasm of pancreatic duct
157.4	Malignant neoplasm of islets of Langerhans
157.8	Malignant neoplasm of other specified sites of pancreas

157.9	Malignant neoplasm of pancreas, part unspecified
158.0	Malignant neoplasm of retroperitoneum
158.8	Malignant neoplasm of specified parts of peritoneum
158.9	Malignant neoplasm of peritoneum, unspecified
159.0	Malignant neoplasm of intestinal tract, part unspecified
159.1	Malignant neoplasm of spleen, not elsewhere classified
159.8	Malignant neoplasm of other sites of digestive system and intra-abdominal organs
159.9	Malignant neoplasm of ill-defined sites within the digestive organs and peritoneum
160.0	Malignant neoplasm of nasal cavities
160.1	Malignant neoplasm of auditory tube, middle ear, and mastoid air cells
160.2	Malignant neoplasm of maxillary sinus
160.3	Malignant neoplasm of ethmoidal sinus
160.4	Malignant neoplasm of frontal sinus
160.5	Malignant neoplasm of sphenoidal sinus
160.8	Malignant neoplasm of other accessory sinuses
160.9	Malignant neoplasm of accessory sinus, unspecified
161.0	Malignant neoplasm of glottis
161.1	Malignant neoplasm of supraglottis
161.2	Malignant neoplasm of subglotitis
161.3	Malignant neoplasm of laryngeal cartilages
161.8	Malignant neoplasm of other specified sites of larynx
161.9	Malignant neoplasm of larynx, unspecified
162.0	Malignant neoplasm of trachea
162.2	Malignant neoplasm of main bronchus
162.3	Malignant neoplasm of upper lobe, bronchus or lung
162.4	Malignant neoplasm of middle lobe, bronchus or lung
162.5	Malignant neoplasm of lower lobe, bronchus or lung
162.8	Malignant neoplasm of other parts of bronchus or lung
162.9	Malignant neoplasm of bronchus long, unspecified
163.0	Malignant neoplasm of parietal pleura
163.1	Malignant neoplasm of visceral pleura
163.8	Malignant neoplasm of other specified sites of pleura
163.9	Malignant neoplasm of pleura, unspecified
164.0	Malignant neoplasm of thymus
164.1	Malignant neoplasm of heart
164.2	Malignant neoplasm of anterior mediastinum
164.3	Malignant neoplasm of posterior mediastinum
164.8	Malignant neoplasm of other parts of mediastinum
164.9	Malignant neoplasm of mediastinum, part unspecified
165.0	Malignant neoplasm of upper respiratory tract, part unspecified

165.8	Malignant neoplasm of other sites within the respiratory system and intrathoracic organs
165.9	Malignant neoplasm of ill-defined sites within the respiratory system
170.0	Malignant neoplasm of bones of skull and face, except mandible
170.1	Malignant neoplasm of mandible
170.2	Malignant neoplasm of vertebral column, excluding sacrum and coccyx
170.3	Malignant neoplasm of ribs, sternum, and clavicle
170.4	Malignant neoplasm of scapula and long bones of upper limb
170.5	Malignant neoplasm of short bones of upper limb
170.6	Malignant neoplasm of pelvic bones, sacrum, and coccyx
170.7	Malignant neoplasm of long bones of lower limb
170.8	Malignant neoplasm of short bones of lower limb
170.9	Malignant neoplasm of bone and articular cartilage, site unspecified
171.0	Malignant neoplasm of connective and other soft tissue of head, face, and neck
171.2	Malignant neoplasm of connective and other soft tissue of upper limb, including shoulder
171.3	Malignant neoplasm of connective and other soft tissue of lower limb, including hip
171.4	Malignant neoplasm of connective and other soft tissue of thorax
171.5	Malignant neoplasm of connective and other soft tissue of abdomen
171.6	Malignant neoplasm of connective and other soft tissue of pelvis
171.7	Malignant neoplasm of connective and other soft tissue of trunk, unspecified
171.8	Malignant neoplasm of other specified sites of connective and other soft tissue
171.9	Malignant neoplasm of connective and other soft tissue, site unspecified
172.0	Malignant melanoma of skin of lip
172.1	Malignant melanoma of skin of eyelid, including canthus
172.2	Malignant melanoma of skin of ear and external auditory canal
172.3	Malignant melanoma of skin of other and unspecified parts of face
172.4	Malignant melanoma of skin of scalp and neck
172.5	Malignant melanoma of skin of trunk, except scrotum
172.6	Malignant melanoma of skin of upper limb, including shoulder
172.7	Malignant melanoma of skin of lower limb, including hip
172.8	Malignant melanoma of other specified sites of skin
172.9	Malignant melanoma of skin, site unspecified
173.00	Unspecified malignant neoplasm of skin of lip
173.01	Basal cell carcinoma of skin of lip
173.02	Squamous cell carcinoma of skin of lip
173.09	Other specified malignant neoplasm of skin of lip
173.10	Unspecified malignant neoplasm of eyelid, including canthus
173.11	Basal cell carcinoma of eyelid, including canthus
173.12	Squamous cell carcinoma of eyelid, including canthus
173.19	Other specified malignant neoplasm of eyelid, including canthus
173.20	Unspecified malignant neoplasm of skin of ear and external auditory canal

173.21	Basal cell carcinoma of skin of ear and external auditory canal
173.22	Squamous cell carcinoma of skin of ear and external auditory canal
173.29	Other specified malignant neoplasm of skin of ear and external auditory canal
173.30	Unspecified malignant neoplasm of skin of other and unspecified parts of face
173.31	Basal cell carcinoma of skin of other and unspecified parts of face
173.32	Squamous cell carcinoma of skin of other and unspecified parts of face
173.39	Other specified malignant neoplasm of skin of lip other and unspecified parts of face
173.40	Unspecified malignant neoplasm of scalp and skin of neck
173.41	Basal cell carcinoma of scalp and skin of neck
173.42	Squamous cell carcinoma of scalp and skin of neck
173.49	Other specified malignant neoplasm of scalp and skin of neck
173.50	Unspecified malignant neoplasm of skin of trunk, except scrotum
173.51	Basal cell carcinoma of skin of trunk, except scrotum
173.52	Squamous cell carcinoma of skin of trunk, except scrotum
173.59	Other specified malignant neoplasm of skin of trunk, except scrotum
173.60	Unspecified malignant neoplasm of skin of upper limb, including shoulder
173.61	Basal cell carcinoma of skin of upper limb, including shoulder
173.62	Squamous cell carcinoma of skin of upper limb, including shoulder
173.69	Other specified malignant neoplasm of skin of upper limb, including shoulder
173.70	Unspecified malignant neoplasm of skin of lower limb, including hip
173.71	Basal cell carcinoma of skin of lower limb, including hip
173.72	Squamous cell carcinoma of skin of lower limb, including hip
173.79	Other specified malignant neoplasm of skin of lower limb, including hip
173.80	Unspecified malignant neoplasm of skin of other specified sites of skin
173.81	Basal cell carcinoma of skin of other specified sites of skin
173.82	Squamous cell carcinoma of skin of other specified sites of skin
173.89	Other specified malignant neoplasm of skin of other specified sites of skin
173.90	Unspecified malignant neoplasm of skin, site unspecified
173.91	Basal cell carcinoma of skin of skin, site unspecified
173.92	Squamous cell carcinoma of skin of skin, site unspecified
173.99	Other specified malignant neoplasm of skin of skin, site unspecified
174.0	Malignant neoplasm of nipple and areola of female breast
174.1	Malignant neoplasm of central portion of female breast
174.2	Malignant neoplasm of upper-inner quadrant of female breast
174.3	Malignant neoplasm of lower-inner quadrant of female breast
174.4	Malignant neoplasm of upper-outer quadrant of female breast
174.5	Malignant neoplasm of lower-outer quadrant of female breast
174.6	Malignant neoplasm of axillary tail of female breast
174.8	Malignant neoplasm of other specified sites of female breast
174.9	Malignant neoplasm of breast (female), unspecified

176.0	Kaposi’s sarcoma, skin
176.1	Kaposi’s sarcoma, soft tissue
176.2	Kaposi’s sarcoma, palate
176.3	Kaposi’s sarcoma, gastrointestinal sites
176.4	Kaposi’s sarcoma, lung
176.5	Kaposi’s sarcoma, lymph nodes
176.8	Kaposi’s sarcoma, other specified sites
176.9	Kaposi’s sarcoma, unspecified site
179	Malignant neoplasm of uterus, part unspecified
180.0	Malignant neoplasm of endocervix
180.1	Malignant neoplasm of exocervix
180.8	Malignant neoplasm of other specified sites of cervix
180.9	Malignant neoplasm of cervix uteri, unspecified site
181	Malignant neoplasm of placenta
182.0	Malignant neoplasm of corpus uteri, except isthmus
182.1	Malignant neoplasm of isthmus
182.8	Malignant neoplasm of other specified sites of body of uterus
183.0	Malignant neoplasm of ovary
183.2	Malignant neoplasm of fallopian tub
183.3	Malignant neoplasm of broad ligament of uterus
183.4	Malignant neoplasm of parametrium
183.5	Malignant neoplasm of round ligament of uterus
183.8	Malignant neoplasm of other specified sites of uterine adnexa
183.9	Malignant neoplasm of uterine adnexa, unspecified site
184.0	Malignant neoplasm of vagina
184.1	Malignant neoplasm of labia majora
184.2	Malignant neoplasm of labia minora
184.3	Malignant neoplasm of clitoris
184.4	Malignant neoplasm of vulva, unspecified site
184.8	Malignant neoplasm of other specified sites of female genital organs
184.9	Malignant neoplasm of female genital organ, site unspecified
188.0	Malignant neoplasm of trigone of urinary bladder
188.1	Malignant neoplasm of dome of urinary bladder
188.2	Malignant neoplasm of lateral wall of urinary bladder
188.3	Malignant neoplasm of anterior wall of urinary bladder
188.4	Malignant neoplasm of posterior wall of urinary bladder
188.5	Malignant neoplasm of bladder neck
188.6	Malignant neoplasm of ureteric orifice
188.7	Malignant neoplasm of urachus
188.8	Malignant neoplasm of other specified sites of bladder

188.9	Malignant neoplasm of bladder, part unspecified
189.0	Malignant neoplasm of kidney, except pelvis
189.1	Malignant neoplasm of renal pelvis
189.2	Malignant neoplasm of ureter
189.3	Malignant neoplasm of urethra
189.4	Malignant neoplasm of paraurethral glands
189.8	Malignant neoplasm of other specified sites of urinary organs
189.9	Malignant neoplasm of urinary organ, site unspecified
190.0	Malignant neoplasm of eyeball, except conjunctiva, cornea, retina, and choroid
190.1	Malignant neoplasm of orbit
190.2	Malignant neoplasm of lacrimal gland
190.3	Malignant neoplasm of conjunctiva
190.4	Malignant neoplasm of cornea
190.5	Malignant neoplasm of retina
190.6	Malignant neoplasm of choroid
190.7	Malignant neoplasm of lacrimal duct
190.8	Malignant neoplasm of other specified sites of eye
190.9	Malignant neoplasm of eye, part unspecified
191.0	Malignant neoplasm of cerebrum, except lobes and ventricles
191.1	Malignant neoplasm of frontal lobe
191.2	Malignant neoplasm of temporal lobe
191.3	Malignant neoplasm of parietal lobe
191.4	Malignant neoplasm of occipital lobe
191.5	Malignant neoplasm of ventricles
191.6	Malignant neoplasm of cerebellum nos
191.7	Malignant neoplasm of brain stem
191.8	Malignant neoplasm of other parts of brain
191.9	Malignant neoplasm of brain, unspecified
192.0	Malignant neoplasm of cranial nerves
192.1	Malignant neoplasm of cerebral meninges
192.2	Malignant neoplasm of spinal cord
192.3	Malignant neoplasm of spinal meninges
192.8	Malignant neoplasm of other specified sites of nervous system
192.9	Malignant neoplasm of nervous system, part unspecified
193	Malignant neoplasm of thyroid gland
194.0	Malignant neoplasm of adrenal gland
194.1	Malignant neoplasm of parathyroid gland
194.3	Malignant neoplasm of pituitary gland and craniopharyngeal duct
194.4	Malignant neoplasm of pineal gland
194.5	Malignant neoplasm of carotid body

194.6	Malignant neoplasm of aortic body and other paraganglia
194.8	Malignant neoplasm of other endocrine gland and related structures
194.9	Malignant neoplasm of endocrine gland, site unspecified
195.0	Malignant neoplasm of head, face, and neck
195.1	Malignant neoplasm of thorax
195.2	Malignant neoplasm of abdomen
195.3	Malignant neoplasm of pelvis
195.4	Malignant neoplasm of upper limb
195.5	Malignant neoplasm of lower limn
195.8	Malignant neoplasm of other specified sites
196.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face, and neck
196.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
196.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
196.3	Secondary and unspecified malignant neoplasm of lymph nodes of axilla and upper limb
196.5	Secondary and unspecified malignant neoplasm of lymph nodes of inguinal region and lower limb
196.6	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
196.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple sites
196.9	Secondary and unspecified malignant neoplasm of lymph nodes, site unspecified
197.0	Secondary malignant neoplasm of lung
197.1	Secondary malignant neoplasm of mediastinum
197.2	Secondary malignant neoplasm of pleura
197.3	Secondary malignant neoplasm of other respiratory organs
197.4	Secondary malignant neoplasm of small intestine including duodenum
197.5	Secondary malignant neoplasm of large intestine and rectum
197.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
197.7	Secondary malignant neoplasm of liver, secondary
197.8	Secondary malignant neoplasm of other digestive organs and spleen
198.0	Secondary malignant neoplasm of kidney
198.1	Secondary malignant neoplasm of other urinary organs
198.2	Secondary malignant neoplasm of skin
198.3	Secondary malignant neoplasm of brain and spinal cord
198.4	Secondary malignant neoplasm of other parts of nervous system
198.5	Secondary malignant neoplasm of bone and bone marrow
198.6	Secondary malignant neoplasm of ovary
198.7	Secondary malignant neoplasm of adrenal gland
198.81	Secondary malignant neoplasm of breast
198.82	Secondary malignant neoplasm of genital organs
198.89	Secondary malignant neoplasm of other specified sites
199.0	Disseminated malignant neoplasm without specification of site

199.1	Other malignant neoplasm without specification of site
199.2	Malignant neoplasm associated with transplant organ
200.00	Reticulosarcoma, unspecified site, extranodal and solid organ sites
200.01	Reticulosarcoma, lymph nodes of head, face, and neck
200.02	Reticulosarcoma, intrathoracic lymph nodes
200.03	Reticulosarcoma, intra-abdominal lymph nodes
200.04	Reticulosarcoma, lymph nodes of axilla and upper limb
200.05	Reticulosarcoma, lymph nodes of inguinal region and lower limb
200.06	Reticulosarcoma, intrapelvic lymph nodes
200.07	Reticulosarcoma, spleen
200.08	Reticulosarcoma, lymph nodes of multiple sites
200.10	Lymphoscarcoma, unspecified site, extranodal and solid organ sites
200.11	Lymphoscarcoma, lymph nodes of head, face, and neck
200.12	Lymphoscarcoma, intrathoracic lymph nodes
200.13	Lymphoscarcoma, intra-abdominal lymph nodes
200.14	Lymphoscarcoma, lymph nodes of axilla and upper limb
200.15	Lymphoscarcoma, lymph nodes of inguinal region and lower limb
200.16	Lymphoscarcoma, intrapelvic lymph nodes
200.17	Lymphoscarcoma, spleen
200.18	Lymphoscarcoma, lymph nodes of multiple sites
200.20	Burkitt’s tumor or lymphoma, unspecified site, extranodal and solid organ sites
200.21	Burkitt’s tumor or lymphoma, lymph nodes of head, face, and neck
200.22	Burkitt’s tumor or lymphoma, intrathoracic lymph nodes
200.23	Burkitt’s tumor or lymphoma, intra-abdominal lymph nodes
200.24	Burkitt’s tumor or lymphoma, lymph nodes of axilla and upper limb
200.25	Burkitt’s tumor or lymphoma, lymph nodes of inguinal region and lower limb
200.26	Burkitt’s tumor or lymphoma, intrapelvic lymph nodes
200.27	Burkitt’s tumor or lymphoma, spleen
200.28	Burkitt’s tumor or lymphoma, lymph nodes of multiple sites
200.30	Marginal zone lymphoma, unspecified site, extranodal and solid organ sites
200.31	Marginal zone lymphoma, lymph nodes of head, face, and neck
200.32	Marginal zone lymphoma, intrathoracic lymph nodes
200.33	Marginal zone lymphoma, intra-abdominal lymph nodes
200.34	Marginal zone lymphoma, lymph nodes of axilla and upper limb
200.35	Marginal zone lymphoma, lymph nodes of inguinal region and lower limb
200.36	Marginal zone lymphoma, intrapelvic lymph nodes
200.37	Marginal zone lymphoma, spleen
200.38	Marginal zone lymphoma, lymph nodes of multiple sites
200.40	Mantle cell lymphoma, unspecified site, extranodal and solid organ sites
200.41	Mantle cell lymphoma, lymph nodes of head, face, and neck

200.42	Mantle cell lymphoma, intrathoracic lymph nodes
200.43	Mantle cell lymphoma, intra-abdominal lymph nodes
200.44	Mantle cell lymphoma, lymph nodes of axilla and upper limb
200.45	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
200.46	Mantle cell lymphoma, intrapelvic lymph nodes
200.47	Mantle cell lymphoma, spleen
200.48	Mantle cell lymphoma, lymph nodes of multiple sites
200.50	Primary central nervous system lymphoma, unspecified site, extranodal and solid organ sites
200.51	Primary central nervous system lymphoma, lymph nodes of head, face, and neck
200.52	Primary central nervous system lymphoma, intrathoracic lymph nodes
200.53	Primary central nervous system lymphoma, intra-abdominal lymph nodes
200.54	Primary central nervous system lymphoma, lymph nodes of axilla and upper limb
200.55	Primary central nervous system lymphoma, lymph nodes of inguinal region and lower limb
200.56	Primary central nervous system lymphoma, intrapelvic lymph nodes
200.57	Primary central nervous system lymphoma, spleen
200.58	Primary central nervous system lymphoma, lymph nodes of multiple sites
200.60	Anaplastic large cell lymphoma, unspecified site, extranodal and solid organ sites
200.61	Anaplastic large cell lymphoma, lymph nodes of head, face, and neck
200.62	Anaplastic large cell lymphoma, intrathoracic lymph nodes
200.63	Anaplastic large cell lymphoma, intra-abdominal lymph nodes
200.64	Anaplastic large cell lymphoma, lymph nodes of axilla and upper limb
200.65	Anaplastic large cell lymphoma, lymph nodes of inguinal region and lower limb
200.66	Anaplastic large cell lymphoma, intrapelvic lymph nodes
200.67	Anaplastic large cell lymphoma, spleen
200.68	Anaplastic large cell lymphoma, lymph nodes of multiple sites
200.70	Large cell lymphoma, unspecified site, extranodal and solid organ sites
200.71	Large cell lymphoma, lymph nodes of head, face, and neck
200.72	Large cell lymphoma, intrathoracic lymph nodes
200.73	Large cell lymphoma, intra-abdominal lymph nodes
200.74	Large cell lymphoma, lymph nodes of axilla and upper limb
200.75	Large cell lymphoma, lymph nodes of inguinal region and lower limb
200.76	Large cell lymphoma, intrapelvic lymph nodes
200.77	Large cell lymphoma, spleen
200.78	Large cell lymphoma, lymph nodes of multiple sites
200.80	Other named variants of lymphosarcoma and reticulosarcoma, unspecified site, extranodal and solid organ sites
200.81	Other named variants of lymphosarcoma and reticulosarcoma, lymph nodes of head, face, and neck
200.82	Other named variants of lymphosarcoma and reticulosarcoma, intrathoracic lymph nodes
200.83	Other named variants of lymphosarcoma and reticulosarcoma, intra-abdominal lymph nodes

200.84	Other named variants of lymphosarcoma and reticulosarcoma, lymph nodes of axilla and upper limb
200.85	Other named variants of lymphosarcoma and reticulosarcoma, lymph nodes of inguinal region and lower limb
200.86	Other named variants of lymphosarcoma and reticulosarcoma, intrapelvic lymph nodes
200.87	Other named variants of lymphosarcoma and reticulosarcoma, spleen
200.88	Other named variants of lymphosarcoma and reticulosarcoma, lymph nodes of multiple sites
201.00	Hodgkin's paragranuloma, unspecified site, extranodal and solid organ sites
201.01	Hodgkin's paragranuloma, lymph nodes of head, face, and neck
201.02	Hodgkin's paragranuloma, intrathoracic lymph nodes
201.03	Hodgkin's paragranuloma, intra-abdominal lymph nodes
201.04	Hodgkin's paragranuloma, lymph nodes of axilla and upper limb
201.05	Hodgkin's paragranuloma, lymph nodes of inguinal region and lower limb
201.06	Hodgkin's paragranuloma, intrapelvic lymph nodes
201.07	Hodgkin's paragranuloma, spleen
201.08	Hodgkin's paragranuloma, lymph nodes of multiple sites
201.10	Hodgkin's granuloma, unspecified site, extranodal and solid organ sites
201.11	Hodgkin's granuloma, lymph nodes of head, face, and neck
201.12	Hodgkin's granuloma, intrathoracic lymph nodes
201.13	Hodgkin's granuloma, intra-abdominal lymph nodes
201.14	Hodgkin's granuloma, lymph nodes of axilla and upper limb
201.15	Hodgkin's granuloma, lymph nodes of inguinal region and lower limb
201.16	Hodgkin's granuloma, intrapelvic lymph nodes
201.17	Hodgkin's granuloma, spleen
201.18	Hodgkin's granuloma, lymph nodes of multiple sites
201.20	Hodgkin's sarcoma, unspecified site, extranodal and solid organ sites
201.21	Hodgkin's sarcoma, lymph nodes of head, face, and neck
201.22	Hodgkin's sarcoma, intrathoracic lymph nodes
201.23	Hodgkin's sarcoma, intra-abdominal lymph nodes
201.24	Hodgkin's sarcoma, lymph nodes of axilla and upper limb
201.25	Hodgkin's sarcoma, lymph nodes of inguinal region and lower limb
201.26	Hodgkin's sarcoma, intrapelvic lymph nodes
201.27	Hodgkin's sarcoma, spleen
201.28	Hodgkin's sarcoma, lymph nodes of multiple sites
201.40	Hodgkin's disease, lymphocytic-histiocytic predominancy, unspecified site, extranodal and solid organ sites
201.41	Hodgkin's disease, lymphocytic-histiocytic predominancy, lymph nodes of head, face, and neck
201.42	Hodgkin's disease, lymphocytic-histiocytic predominancy, intrathoracic lymph nodes
201.43	Hodgkin's disease, lymphocytic-histiocytic predominancy, intra-abdominal lymph nodes

201.44	Hodgkin’s disease, lymphocytic-histiocytic predominancy, lymph nodes of axilla and upper limb
201.45	Hodgkin’s disease, lymphocytic-histiocytic predominancy, lymph nodes of inguinal region and lower limb
201.46	Hodgkin’s disease, lymphocytic-histiocytic predominancy, intrapelvic lymph nodes
201.47	Hodgkin’s disease, lymphocytic-histiocytic predominancy, spleen
201.48	Hodgkin’s disease, lymphocytic-histiocytic predominancy, lymph nodes of multiple sites
201.50	Hodgkin’s disease, nodular sclerosis, unspecified site, extranodal and solid organ sites
201.51	Hodgkin’s disease, nodular sclerosis, lymph nodes of head, face, and neck
201.52	Hodgkin’s disease, nodular sclerosis, intrathoracic lymph nodes
201.53	Hodgkin’s disease, nodular sclerosis, intra-abdominal lymph nodes
201.54	Hodgkin’s disease, nodular sclerosis, lymph nodes of axilla and upper limb
201.55	Hodgkin’s paragranuloma, lymph nodes of inguinal region and lower limb disease, nodular sclerosis
201.56	Hodgkin’s disease, nodular sclerosis, intrapelvic lymph nodes
201.57	Hodgkin’s disease, nodular sclerosis, spleen
201.58	Hodgkin’s disease, nodular sclerosis, lymph nodes of multiple sites
201.60	Hodgkin’s disease, mixed cellularity, unspecified site, extranodal and solid organ sites
201.61	Hodgkin’s disease, mixed cellularity, lymph nodes of head, face, and neck
201.62	Hodgkin’s disease, mixed cellularity, intrathoracic lymph nodes
201.63	Hodgkin’s disease, mixed cellularity, intra-abdominal lymph nodes
201.64	Hodgkin’s disease, mixed cellularity, lymph nodes of axilla and upper limb
201.65	Hodgkin’s disease, mixed cellularity, lymph nodes of inguinal region and lower limb
201.66	Hodgkin’s disease, mixed cellularity, intrapelvic lymph nodes
201.67	Hodgkin’s disease, mixed cellularity, spleen
201.68	Hodgkin’s disease, mixed cellularity, lymph nodes of multiple sites
201.70	Hodgkin’s disease, lymphocytic depletion, unspecified site, extranodal and solid organ sites
201.71	Hodgkin’s disease, lymphocytic depletion, lymph nodes of head, face, and neck
201.72	Hodgkin’s disease, lymphocytic depletion, intrathoracic lymph nodes
201.73	Hodgkin’s disease, lymphocytic depletion, intra-abdominal lymph nodes
201.74	Hodgkin’s disease, lymphocytic depletion, lymph nodes of axilla and upper limb
201.75	Hodgkin’s disease, lymphocytic depletion, lymph nodes of inguinal region and lower limb
201.76	Hodgkin’s disease, lymphocytic depletion, intrapelvic lymph nodes
201.77	Hodgkin’s disease, lymphocytic depletion, spleen
201.78	Hodgkin’s disease, lymphocytic depletion, lymph nodes of multiple sites
201.90	Hodgkin’s disease, unspecified type, unspecified site, extranodal and solid organ sites
201.91	Hodgkin’s disease, unspecified type, lymph nodes of head, face, and neck
201.92	Hodgkin’s disease, unspecified type, intrathoracic lymph nodes
201.93	Hodgkin’s disease, unspecified type, intra-abdominal lymph nodes
201.94	Hodgkin’s disease, unspecified type, lymph nodes of axilla and upper limb
201.95	Hodgkin’s disease, unspecified type, lymph nodes of inguinal region and lower limb

201.96	Hodgkin's disease, unspecified type, intrapelvic lymph nodes
201.97	Hodgkin's disease, unspecified type, spleen
201.98	Hodgkin's disease, unspecified type, lymph nodes of multiple sites
202.00	Nodular lymphoma, unspecified site, extranodal and solid organ sites
202.01	Nodular lymphoma, lymph nodes of head, face, and neck
202.02	Nodular lymphoma, intrathoracic lymph nodes
202.03	Nodular lymphoma, intra-abdominal lymph nodes
202.04	Nodular lymphoma, lymph nodes of axilla and upper limb
202.05	Nodular lymphoma, lymph nodes of inguinal region and lower limb
202.06	Nodular lymphoma, intrapelvic lymph nodes
202.07	Nodular lymphoma, spleen
202.08	Nodular lymphoma, lymph nodes of multiple sites
202.10	Mycosis fungoides, unspecified site, extranodal and solid organ sites
202.11	Mycosis fungoides, lymph nodes of head, face, and neck
202.12	Mycosis fungoides, intrathoracic lymph nodes
202.13	Mycosis fungoides, intra-abdominal lymph nodes
202.14	Mycosis fungoides, lymph nodes of axilla and upper limb
202.15	Mycosis fungoides, lymph nodes of inguinal region and lower limb
202.16	Mycosis fungoides, intrapelvic lymph nodes
202.17	Mycosis fungoides, spleen
202.18	Mycosis fungoides, lymph nodes of multiple sites
202.20	Sezary's disease, unspecified site, extranodal and solid organ sites
202.21	Sezary's disease, lymph nodes of head, face, and neck
202.22	Sezary's disease, intrathoracic lymph nodes
202.23	Sezary's disease, intra-abdominal lymph nodes
202.24	Sezary's disease, lymph nodes of axilla and upper limb
202.25	Sezary's disease, lymph nodes of inguinal region and lower limb
202.26	Sezary's disease, intrapelvic lymph nodes
202.27	Sezary's disease, spleen
202.28	Sezary's disease, lymph nodes of multiple sites
202.30	Malignant histiocytosis, unspecified site, extranodal and solid organ sites
202.31	Malignant histiocytosis, lymph nodes of head, face, and neck
202.32	Malignant histiocytosis, intrathoracic lymph nodes
202.33	Malignant histiocytosis, intra-abdominal lymph nodes
202.34	Malignant histiocytosis, lymph nodes of axilla and upper limb
202.35	Malignant histiocytosis, lymph nodes of inguinal region and lower limb
202.36	Malignant histiocytosis, intrapelvic lymph nodes
202.37	Malignant histiocytosis, spleen
202.38	Malignant histiocytosis, lymph nodes of multiple sites
202.40	Leukemic reticuloendotheliosis, unspecified site, extranodal and solid organ sites

202.41	Leukemic reticuloendotheliosis, lymph nodes of head, face, and neck
202.42	Leukemic reticuloendotheliosis, intrathoracic lymph nodes
202.43	Leukemic reticuloendotheliosis, intra-abdominal lymph nodes
202.44	Leukemic reticuloendotheliosis, lymph nodes of axilla and upper limb
202.45	Leukemic reticuloendotheliosis, lymph nodes of inguinal region and lower limb
202.46	Leukemic reticuloendotheliosis, intrapelvic lymph nodes
202.47	Leukemic reticuloendotheliosis, spleen
202.48	Leukemic reticuloendotheliosis, lymph nodes of multiple sites
202.50	Letterer-siwe disease, unspecified site, extranodal and solid organ sites
202.51	Letterer-siwe disease, lymph nodes of head, face, and neck
202.52	Letterer-siwe disease, intrathoracic lymph nodes
202.53	Letterer-siwe disease, intra-abdominal lymph nodes
202.54	Letterer-siwe disease, lymph nodes of axilla and upper limb
202.55	Letterer-siwe disease, lymph nodes of inguinal region and lower limb
202.56	Letterer-siwe disease, intrapelvic lymph nodes
202.57	Letterer-siwe disease, spleen
202.58	Letterer-siwe disease, lymph nodes of multiple sites
202.60	Malignant mast cell tumors, unspecified site, extranodal and solid organ sites
202.61	Malignant mast cell tumors, lymph nodes of head, face, and neck
202.62	Malignant mast cell tumors, intrathoracic lymph nodes
202.63	Malignant mast cell tumors, intra-abdominal lymph nodes
202.64	Malignant mast cell tumors, lymph nodes of axilla and upper limb
202.65	Malignant mast cell tumors, lymph nodes of inguinal region and lower limb
202.66	Malignant mast cell tumors, intrapelvic lymph nodes
202.67	Malignant mast cell tumors, spleen
202.68	Malignant mast cell tumors, lymph nodes of multiple sites
202.70	Peripheral T cell lymphoma, extranodal and solid organ sites
202.71	Peripheral T cell lymphoma, lymph nodes of head, face, and neck
202.72	Peripheral T cell lymphoma, intrathoracic lymph nodes
202.73	Peripheral T cell lymphoma, intra-abdominal lymph nodes
202.74	Peripheral T cell lymphoma, lymph nodes of axilla and upper limb
202.75	Peripheral T cell lymphoma, lymph nodes of inguinal region and lower limb
202.76	Peripheral T cell lymphoma, intrapelvic lymph nodes
202.77	Peripheral T cell lymphoma, spleen
202.78	Peripheral T cell lymphoma, lymph nodes of multiple sites
202.80	Other malignant lymphomas, unspecified site, extranodal and solid organ sites
202.81	Other malignant lymphomas, lymph nodes of head, face, and neck
202.82	Other malignant lymphomas, intrathoracic lymph nodes
202.83	Other malignant lymphomas, intra-abdominal lymph nodes
202.84	Other malignant lymphomas, lymph nodes of axilla and upper limb

202.85	Other malignant lymphomas, lymph nodes of inguinal region and lower limb
202.86	Other malignant lymphomas, intrapelvic lymph nodes
202.87	Other malignant lymphomas, spleen
202.88	Other malignant lymphomas, lymph nodes of multiple sites
202.90	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, unspecified site, extranodal and solid organ sites
202.91	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, lymph nodes of head, face, and neck
202.92	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, intrathoracic lymph nodes
202.93	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, intra-abdominal lymph nodes
202.94	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, lymph nodes of axilla and upper limb
202.95	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, lymph nodes of inguinal region and lower limb
202.96	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, intrapelvic lymph nodes
202.97	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, spleen
202.98	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, lymph nodes of multiple sites
203.00	Multiple myeloma, without mention of having achieved remission
203.01	Multiple myeloma, in remission
203.02	Multiple myeloma, in relapse
203.10	Plasma cell leukemia, without mention of having achieved remission
203.11	Plasma cell leukemia, in remission
203.12	Plasma cell leukemia, in relapse
203.80	Other immunoproliferative neoplasms, without mention of having achieved remission
203.81	Other immunoproliferative neoplasms, in remission
203.82	Other immunoproliferative neoplasms, in relapse
204.00	Acute lymphoid leukemia, without mention of having achieved remission
204.01	Acute lymphoid leukemia, in remission
204.02	Acute lymphoid leukemia, in relapse
204.10	Chronic lymphoid leukemia, without mention of having achieved remission
204.11	Chronic lymphoid leukemia, in remission
204.12	Chronic lymphoid leukemia, in relapse
204.20	Subacute lymphoid leukemia, without mention of having achieved remission
204.21	Subacute lymphoid leukemia, in remission
204.22	Subacute lymphoid leukemia, in relapse
204.80	Other lymphoid leukemia, without mention of having achieved remission
204.81	Other lymphoid leukemia, in remission
204.82	Other lymphoid leukemia, in relapse

204.90	Unspecified lymphoid leukemia, without mention of having achieved remission
204.91	Unspecified lymphoid leukemia, in remission
204.92	Unspecified lymphoid leukemia, in relapse
205.00	Acute myeloid leukemia, without mention of having achieved remission
205.01	Acute myeloid leukemia, in remission
205.02	Acute myeloid leukemia, in relapse
205.10	Chronic myeloid leukemia, without mention of having achieved remission
205.11	Chronic myeloid leukemia, in remission
205.12	Chronic myeloid leukemia, in relapse
205.20	Subacute myeloid leukemia, without mention of having achieved remission
205.21	Subacute myeloid leukemia, in remission
205.22	Subacute myeloid leukemia, in relapse
205.30	Myeloid sarcoma, without mention of having achieved remission
205.31	Myeloid sarcoma in remission
205.32	Myeloid sarcoma, in relapse
205.80	Other myeloid leukemia, without mention of having achieved remission
205.81	Other myeloid leukemia, in remission
205.82	Other myeloid leukemia, in relapse
205.90	Unspecified myeloid leukemia, without mention of having achieved remission
205.91	Unspecified myeloid leukemia, in remission
205.92	Unspecified myeloid leukemia, in relapse
206.00	Acute monocytic leukemia, without mention of having achieved remission
206.01	Acute monocytic leukemia, in remission
206.02	Acute monocytic leukemia, in relapse
206.10	Chronic monocytic leukemia, without mention of having achieved remission
206.11	Chronic monocytic leukemia, in remission
206.12	Chronic monocytic leukemia, in relapse
206.20	Subacute monocytic leukemia, without mention of having achieved remission
206.21	Subacute monocytic leukemia, in remission
206.22	Subacute monocytic leukemia, in relapse
206.80	Other monocytic leukemia, without mention of having achieved remission
206.81	Other monocytic leukemia, in remission
206.82	Other monocytic leukemia, in relapse
206.90	Unspecified monocytic leukemia, without mention of having achieved remission
206.91	Unspecified monocytic leukemia, in remission
206.92	Unspecified monocytic leukemia, in relapse
207.00	Acute erythremia and erythroleukemia, without mention of having achieved remission
207.01	Acute erythremia and erythroleukemia, in remission
207.02	Acute erythremia and erythroleukemia, in relapse
207.10	Chronic erythremia, without mention of having achieved remission

207.11	Chronic erythremia, in remission
207.12	Chronic erythremia, in relapse
207.20	Megakaryocytic leukemia, without mention of having achieved remission
207.21	Megakaryocytic leukemia, in remission
207.22	Megakaryocytic leukemia, in relapse
207.80	Other specified leukemia, without mention of having achieved remission
207.81	Other specified leukemia, in remission
207.82	Other specified leukemia, in relapse
208.00	Acute leukemia of unspecified type, without mention of having achieved remission
208.01	Acute leukemia of unspecified cell type, in remission
208.02	Acute leukemia of unspecified cell type, in relapse
208.10	Chronic leukemia of unspecified cell type, without mention of having achieved remission
208.11	Chronic leukemia of unspecified cell type, in remission
208.12	Chronic leukemia of unspecified cell type, in relapse
208.20	Subacute leukemia of unspecified cell type, without mention of having achieved remission
208.21	Subacute leukemia of unspecified cell type, in remission
208.22	Subacute leukemia of unspecified cell type, in relapse
208.80	Other leukemia of unspecified cell type, without mention of having achieved remission
208.81	Other leukemia of unspecified cell type, in remission
208.82	Other leukemia of unspecified cell type, in relapse
208.90	Unspecified leukemia, without mention of having achieved remission
208.91	Unspecified leukemia, in remission
208.92	Unspecified leukemia, in relapse
209.00	Malignant carcinoid tumor of the small intestine, unspecified portion
209.01	Malignant carcinoid tumor of the duodenum
209.02	Malignant carcinoid tumor of the jejunum
209.03	Malignant carcinoid tumor of the ileum
209.10	Malignant carcinoid tumor of the large intestine, unspecified portion
209.11	Malignant carcinoid tumor of the appendix
209.12	Malignant carcinoid tumor of the cecum
209.13	Malignant carcinoid tumor of the ascending colon
209.14	Malignant carcinoid tumor of the transverse colon
209.15	Malignant carcinoid tumor of the descending colon
209.16	Malignant carcinoid tumor of the sigmoid colon
209.17	Malignant carcinoid tumor of the rectum
209.20	Malignant carcinoid tumor of unknown primary site
209.21	Malignant carcinoid tumor of the bronchus and lung
209.22	Malignant carcinoid tumor of the thymus
209.23	Malignant carcinoid tumor of the stomach
209.24	Malignant carcinoid tumor of the kidney

209.25	Malignant carcinoid tumor of foregut, not otherwise specified
209.26	Malignant carcinoid tumor of midgut, not otherwise specified
209.27	Malignant carcinoid tumor of hindgut, not otherwise specified
209.29	Malignant carcinoid tumor of other sites
209.30	Malignant poorly differentiated neuroendocrine carcinoma, any site
209.31	Merkel cell carcinoma of the face
209.32	Merkel cell carcinoma of the scalp and neck
209.33	Merkel cell carcinoma of the upper limb
209.34	Merkel cell carcinoma of the lower limb
209.35	Merkel cell carcinoma of the trunk
209.36	Merkel cell carcinoma of other sites
209.70	Secondary neuroendocrine tumor, unspecified site
209.71	Secondary neuroendocrine tumor of distant lymph nodes
209.72	Secondary neuroendocrine tumor of liver
209.73	Secondary neuroendocrine tumor of bone
209.74	Secondary neuroendocrine tumor of peritoneum
209.75	Secondary Merkel cell carcinoma
209.79	Secondary neuroendocrine tumor of other sites
ICD-10	
C00.0	Malignant neoplasm of external upper lip
C00.1	Malignant neoplasm of external lower lop
C00.2	Malignant neoplasm of external lip, unspecified
C00.3	Malignant neoplasm of upper lip, inner aspect
C00.4	Malignant neoplasm of lower lip, inner aspect
C00.5	Malignant neoplasm of lip, unspecified, inner aspect
C00.6	Malignant neoplasm of commissure of lip, unspecified
C00.8	Malignant neoplasm of overlapping sites of lip
C00.9	Malignant neoplasm of lip, unspecified
C01	Malignant neoplasm of base of tongue
C02.0	Malignant neoplasm of dorsal surface of tongue
C02.1	Malignant neoplasm of border of tongue
C02.2	Malignant neoplasm of ventral surface of tongue
C02.3	Malignant neoplasm of anterior two-thirds of tongue, part unspecified
C02.4	Malignant neoplasm of lingual tonsil
C02.8	Malignant neoplasm of overlapping sites of tongue
C02.9	Malignant neoplasm of tongue, unspecified
C03.0	Malignant neoplasm of upper gum
C03.1	Malignant neoplasm of lower gum
C03.9	Malignant neoplasm of gum, unspecified
C04.0	Malignant neoplasm of anterior floor of mouth

C04.1	Malignant neoplasm of lateral floor of mouth
C04.8	Malignant neoplasm of overlapping sites of floor of mouth
C04.9	Malignant neoplasm of floor of mouth, unspecified
C05.0	Malignant neoplasm of hard palate
C05.1	Malignant neoplasm of soft palate
C05.2	Malignant neoplasm of uvula
C05.8	Malignant neoplasm of overlapping sites of palate
C05.9	Malignant neoplasm of palate, unspecified
C06.0	Malignant neoplasm of cheek mucosa
C06.1	Malignant neoplasm of vestibule of mouth
C06.2	Malignant neoplasm of retromolar area
C06.80	Malignant neoplasm of overlapping sites of unspecified parts of mouth
C06.89	Malignant neoplasm of overlapping sites of other parts of mouth
C06.9	Malignant neoplasm of mouth, unspecified
C07	Malignant neoplasm of parotid gland
C08.0	Malignant neoplasm of submandibular gland
C08.1	Malignant neoplasm of sublingual gland
C08.9	Malignant neoplasm of major salivary gland, unspecified
C09.0	Malignant neoplasm of tonsillar fossa
C09.1	Malignant neoplasm of tonsillar pillar (anterior) (posterior)
C09.8	Malignant neoplasm of overlapping sites of tonsil
C09.9	Malignant neoplasm of tonsil, unspecified
C10.0	Malignant neoplasm of vallecular
C10.1	Malignant neoplasm of anterior surface of epiglottis
C10.2	Malignant neoplasm of lateral wall of oropharynx
C10.3	Malignant neoplasm of posterior wall of oropharynx
C10.4	Malignant neoplasm of branchial cleft
C10.8	Malignant neoplasm of overlapping sites of oropharynx
C10.9	Malignant neoplasm of oropharynx, unspecified
C11.0	Malignant neoplasm of superior wall of nasopharynx
C11.1	Malignant neoplasm of posterior wall of nasopharynx
C11.2	Malignant neoplasm of lateral wall of nasopharynx
C11.3	Malignant neoplasm of anterior wall of nasopharynx
C11.8	Malignant neoplasm of overlapping sites of nasopharynx
C11.9	Malignant neoplasm of nasopharynx, unspecified
C12	Malignant neoplasm of pyriform sinus
C13.0	Malignant neoplasm of postcricoid region
C13.1	Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
C13.2	Malignant neoplasm of posterior wall of hypopharynx
C13.8	Malignant neoplasm of overlapping sites of hypopharynx

C13.9	Malignant neoplasm of hypopharynx, unspecified
C14.0	Malignant neoplasm of pharynx, unspecified
C14.2	Malignant neoplasm of Waldeyer's ring
C14.8	Malignant neoplasm of overlapping sites of lip, oral cavity and pharynx
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Merckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal

C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.2	Hepatoblastoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.1	Malignant neoplasm of ampulla of Vater
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C26.0	Malignant neoplasm of intestinal tract, part unspecified
C26.1	Malignant neoplasm of spleen
C26.9	Malignant neoplasm of ill-defined sites within the digestive system
C30.0	Malignant neoplasm of nasal cavity
C30.1	Malignant neoplasm of middle ear
C31.0	Malignant neoplasm of maxillary sinus
C31.1	Malignant neoplasm of ethmoidal sinus
C31.2	Malignant neoplasm of frontal sinus
C31.3	Malignant neoplasm of sphenoid sinus
C31.8	Malignant neoplasm of overlapping sites of accessory sinuses
C31.9	Malignant neoplasm of sinus, unspecified
C32.0	Malignant neoplasm of glottis
C32.1	Malignant neoplasm of supraglottis
C32.2	Malignant neoplasm of subglottis
C32.3	Malignant neoplasm of laryngeal cartilage
C32.8	Malignant neoplasm of overlapping sites of larynx
C32.9	Malignant neoplasm of larynx, unspecified
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus

C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C37	Malignant neoplasm of thymus
C38.0	Malignant neoplasm of heart
C38.1	Malignant neoplasm of anterior mediastinum
C38.2	Malignant neoplasm of posterior mediastinum
C38.3	Malignant neoplasm of mediastinum, part unspecified
C38.4	Malignant neoplasm of pleura
C38.8	Malignant neoplasm of overlapping sites of heart, mediastinum and pleura
C39.0	Malignant neoplasm of upper respiratory tract, part unspecified
C39.9	Malignant neoplasm of lower respiratory tract, part unspecified
C40.00	Malignant neoplasm of scapula and long bones of unspecified upper limb
C40.01	Malignant neoplasm of scapula and long bones of right upper limb
C40.02	Malignant neoplasm of scapula and long bones of left upper limb
C40.10	Malignant neoplasm of short bones of unspecified upper limb
C40.11	Malignant neoplasm of short bones of right upper limb
C40.12	Malignant neoplasm of short bones of left upper limb
C40.20	Malignant neoplasm of long bones of unspecified lower limb
C40.21	Malignant neoplasm of long bones of right lower limb
C40.22	Malignant neoplasm of long bones of left lower limb
C40.30	Malignant neoplasm of short bones unspecified lower limb
C40.31	Malignant neoplasm of short bones of right lower limb
C40.32	Malignant neoplasm of short bones of left lower limb
C40.80	Malignant neoplasm of overlapping sites of bone and articular cartilage of unspecified limb
C40.81	Malignant neoplasm of overlapping sites of bone and articular cartilage of right limb
C40.82	Malignant neoplasm of overlapping sites of bone and articular cartilage of left limb
C40.90	Malignant neoplasm of unspecified bones and articular cartilage of unspecified limb

C40.91	Malignant neoplasm of unspecified bones and articular cartilage of right limb
C40.92	Malignant neoplasm of unspecified bones and articular cartilage of left limb
C41.0	Malignant neoplasm of bones of skull and face
C41.1	Malignant neoplasm of mandible
C41.2	Malignant neoplasm of vertebral column
C41.3	Malignant neoplasm of ribs, sternum and clavicle
C41.4	Malignant neoplasm of pelvic bones, sacrum and coccyx
C41.9	Malignant neoplasm of bone and articular cartilage, unspecified
C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.11	Malignant melanoma of right eyelid, including canthus
C43.12	Malignant melanoma of left eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C4A.0	Merkel cell carcinoma of lip
C4A.10	Merkel cell carcinoma of unspecified eyelid, including canthus
C4A.11	Merkel cell carcinoma of right eyelid, including canthus
C4A.12	Merkel cell carcinoma of left eyelid, including canthus
C4A.20	Merkel cell carcinoma of unspecified ear and external auricular canal
C4A.21	Merkel cell carcinoma of right ear and external auricular canal
C4A.22	Merkel cell carcinoma of left ear and external auricular canal
C4A.30	Merkel cell carcinoma of unspecified part of face
C4A.31	Merkel cell carcinoma of nose
C4A.39	Merkel cell carcinoma of other parts of face

C4A.4	Merkel cell carcinoma ma of scalp and neck
C4A.51	Merkel cell carcinoma of anal skin
C4A.52	Merkel cell carcinoma of skin of breast
C4A.59	Merkel cell carcinoma of other part of trunk
C4A.60	Merkel cell carcinoma of unspecified upper limb, including shoulder
C4A.61	Merkel cell carcinoma of right upper limb, including shoulder
C4A.62	Merkel cell carcinoma of left upper limb, including shoulder
C4A.70	Merkel cell carcinoma of unspecified lower limb, including hip
C4A.71	Merkel cell carcinoma of right lower limb, including hip
C4A.72	Merkel cell carcinoma of left lower limb, including hip
C4A.8	Merkel cell carcinoma of overlapping sites of skin
C4A.9	Merkel cell carcinoma of skin, unspecified
C44.00	Unspecified malignant neoplasm of skin of lip
C44.01	Basal cell carcinoma of skin of lip
C44.02	Squamous cell carcinoma of skin of lip
C44.09	Other specified malignant neoplasm of skin of lip
C44.101	Unspecified malignant neoplasm of skin of unspecified eyelid, including canthus
C44.102	Unspecified malignant neoplasm of skin of right eyelid, including canthus
C44.109	Unspecified malignant neoplasm of skin of left eyelid, including canthus
C44.111	Basal cell carcinoma of skin of unspecified eyelid, including canthus
C44.112	Basal cell carcinoma of skin of right eyelid, including canthus
C44.119	Basal cell carcinoma of skin of left eyelid, including canthus
C44.121	Squamous cell carcinoma of skin of unspecified eyelid, including canthus
C44.122	Squamous cell carcinoma of skin of right eyelid, including canthus
C44.129	Squamous cell carcinoma of skin of left eyelid, including canthus
C44.191	Other specified malignant neoplasm of skin of unspecified eyelid, including canthus
C44.192	Other specified malignant neoplasm of skin of right eyelid, including canthus
C44.199	Other specified malignant neoplasm of skin of left eyelid, including canthus
C44.201	Unspecified malignant neoplasm of skin of unspecified ear and external auricular canal
C44.202	Unspecified malignant neoplasm of skin of right ear and external auricular canal
C44.209	Unspecified malignant neoplasm of skin of left ear and external auricular canal
C44.211	Basal cell carcinoma of skin of unspecified ear and external auricular canal
C44.212	Basal cell carcinoma of skin of right ear and external auricular canal
C44.219	Basal cell carcinoma of skin of left ear and external auricular canal
C44.221	Squamous cell carcinoma of skin of unspecified ear and external auricular canal
C44.222	Squamous cell carcinoma of skin of right ear and external auricular canal
C44.229	Squamous cell carcinoma of skin of left ear and external auricular canal
C44.291	Other specified malignant neoplasm of skin of unspecified ear and external auricular canal
C44.292	Other specified malignant neoplasm of skin of right ear and external auricular canal
C44.299	Other specified malignant neoplasm of skin of left ear and external auricular canal

C44.300	Unspecified malignant neoplasm of skin of unspecified part of face
C44.301	Unspecified malignant neoplasm of skin of nose
C44.309	Unspecified malignant neoplasm of skin of other parts of face
C44.310	Basal cell carcinoma of skin of unspecified part of face
C44.311	Basal cell carcinoma of skin of nose
C44.319	Basal cell carcinoma of skin of other parts of face
C44.320	Squamous cell carcinoma of skin of unspecified part of face
C44.321	Squamous cell carcinoma of skin of nose
C44.329	Squamous cell carcinoma of skin of other parts of face
C44.390	Other specified malignant neoplasm of skin of unspecified part of face
C44.391	Other specified malignant neoplasm of skin of nose
C44.399	Other specified malignant neoplasm of skin of other parts of face
C44.40	Unspecified malignant neoplasm of skin of scalp and neck
C44.41	Basal cell carcinoma of skin of scalp and neck
C44.42	Squamous cell carcinoma of skin of scalp and neck
C44.49	Other specified malignant neoplasm of skin of scalp and neck
C44.500	Unspecified malignant neoplasm of anal skin
C44.501	Unspecified malignant neoplasm of skin of breast
C44.509	Unspecified malignant neoplasm of skin of other part of trunk
C44.510	Basal cell carcinoma of anal skin
C44.511	Basal cell carcinoma of skin of breast
C44.519	Basal cell carcinoma of skin of other part of trunk
C44.520	Squamous cell carcinoma of anal skin
C44.521	Squamous cell carcinoma of skin of breast
C44.529	Squamous cell carcinoma of skin of other part of trunk
C44.590	Other specified malignant neoplasm of anal skin
C44.591	Other specified malignant neoplasm of skin of breast
C44.599	Other specified malignant neoplasm of skin of other part of trunk
C44.601	Unspecified malignant neoplasm of skin of unspecified upper limb, including shoulder
C44.602	Unspecified malignant neoplasm of skin of right upper limb, including shoulder
C44.609	Unspecified malignant neoplasm of skin of left upper limb, including shoulder
C44.611	Basal cell carcinoma of skin of unspecified upper limb, including shoulder
C44.612	Basal cell carcinoma of skin of right upper limb, including shoulder
C44.619	Basal cell carcinoma of skin of left upper limb, including shoulder
C44.621	Squamous cell carcinoma of skin of unspecified upper limb, including shoulder
C44.622	Squamous cell carcinoma of skin of right upper limb, including shoulder
C44.629	Squamous cell carcinoma of skin of left upper limb, including shoulder
C44.691	Other specified malignant neoplasm of skin of unspecified upper limb, including shoulder
C44.692	Other specified malignant neoplasm of skin of right upper limb, including shoulder
C44.699	Other specified malignant neoplasm of skin of left upper limb, including shoulder

C44.701	Unspecified malignant neoplasm of skin of unspecified lower limb, including hip
C44.702	Unspecified malignant neoplasm of skin of right lower limb, including hip
C44.709	Unspecified malignant neoplasm of skin of left lower limb, including hip
C44.711	Basal cell carcinoma of skin of unspecified lower limb, including hip
C44.712	Basal cell carcinoma of skin of right lower limb, including hip
C44.719	Basal cell carcinoma of skin of left lower limb, including hip
C44.721	Squamous cell carcinoma of skin of unspecified lower limb, including hip
C44.722	Squamous cell carcinoma of skin of right lower limb, including hip
C44.729	Squamous cell carcinoma of skin of left lower limb, including hip
C44.791	Other specified malignant neoplasm of skin of unspecified lower limb, including hip
C44.792	Other specified malignant neoplasm of skin of right lower limb, including hip
C44.799	Other specified malignant neoplasm of skin of left lower limb, including hip
C44.80	Unspecified malignant neoplasm of overlapping sites of skin
C44.81	Basal cell carcinoma of skin of overlapping sites of skin
C44.82	Squamous cell carcinoma of skin of overlapping sites of skin
C44.89	Other specified malignant neoplasm of skin, unspecified
C44.90	Unspecified malignant neoplasm of skin, unspecified
C44.91	Basal cell carcinoma of skin of skin, unspecified
C44.92	Squamous cell carcinoma of skin of skin, unspecified
C44.99	Other specified malignant neoplasm of skin, unspecified
C45.0	Mesothelioma of pleura
C45.1	Mesothelioma of peritoneum
C45.2	Mesothelioma of pericardium
C45.7	Mesothelioma of other sites
C45.9	Mesothelioma, unspecified
C46.0	Kaposi’s sarcoma of skin
C46.1	Kaposi’s sarcoma of soft tissue
C46.2	Kaposi’s sarcoma of palate
C46.3	Kaposi’s sarcoma of lymph nodes
C46.4	Kaposi’s sarcoma of gastrointestinal sites
C46.50	Kaposi’s sarcoma of unspecified lung
C46.51	Kaposi’s sarcoma of right lung
C46.52	Kaposi’s sarcoma of left lung
C46.7	Kaposi’s sarcoma of other sites
C46.9	Kaposi’s sarcoma, unspecified
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck
C47.10	Malignant neoplasm of peripheral nerves of unspecified upper limb, including shoulder
C47.11	Malignant neoplasm of peripheral nerves of right upper limb, including shoulder
C47.12	Malignant neoplasm of peripheral nerves of left upper limb, including shoulder
C47.20	Malignant neoplasm of peripheral nerves of unspecified lower limb, including hip

C47.21	Malignant neoplasm of peripheral nerves of right lower limb, including hip
C47.22	Malignant neoplasm of peripheral nerves of left lower limb, including hip
C47.3	Malignant neoplasm of peripheral nerves of thorax
C47.4	Malignant neoplasm of peripheral nerves of abdomen
C47.5	Malignant neoplasm of peripheral nerves of pelvis
C47.6	Malignant neoplasm of peripheral nerves of trunk, unspecified
C47.8	Malignant neoplasm of overlapping sites of peripheral nerves and autonomic nervous system
C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system, unspecified
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C49.10	Malignant neoplasm of connective and soft tissue of unspecified upper limb, including shoulder
C49.11	Malignant neoplasm of connective and soft tissue of right upper limb, including shoulder
C49.12	Malignant neoplasm of connective and soft tissue of left upper limb, including shoulder
C49.20	Malignant neoplasm of connective and soft tissue of unspecified lower limb, including hip
C49.21	Malignant neoplasm of connective and soft tissue of right lower limb, including hip
C49.22	Malignant neoplasm of connective and soft tissue of left lower limb, including hip
C49.3	Malignant neoplasm of connective and soft tissue of thorax
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.5	Malignant neoplasm of connective and soft tissue of pelvis
C49.6	Malignant neoplasm of connective and soft tissue of trunk, unspecified
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C49.A0	Gastrointestinal stromal tumor, unspecified site
C49.A1	Gastrointestinal stromal tumor of esophagus
C49.A2	Gastrointestinal stromal tumor of stomach
C49.A3	Gastrointestinal stromal tumor of small intestine
C49.A4	Gastrointestinal stromal tumor of large intestine
C49.A5	Gastrointestinal stromal tumor of rectum
C49.A9	Gastrointestinal stromal tumor of other sites
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast

C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C51.0	Malignant neoplasm of labium majus
C51.1	Malignant neoplasm of labium minus
C51.2	Malignant neoplasm of clitoris
C51.8	Malignant neoplasm of overlapping sites of vulva
C51.9	Malignant neoplasm of vulva, unspecified
C52	Malignant neoplasm of vagina
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C53.8	Malignant neoplasm of overlapping sites of cervix uteri
C53.9	Malignant neoplasm of cervix uteri, unspecified
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified
C55	Malignant neoplasm of uterus, part unspecified
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary

C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.10	Malignant neoplasm of unspecified broad ligament
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.20	Malignant neoplasm of unspecified round ligament
C57.21	Malignant neoplasm of right round ligament
C57.22	Malignant neoplasm of left round ligament
C57.3	Malignant neoplasm of parametrium
C57.4	Malignant neoplasm of uterine adnexa, unspecified
C57.7	Malignant neoplasm of other specified female genital organs
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C57.9	Malignant neoplasm of female genital organ, unspecified
C58	Malignant neoplasm of placenta
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C66.1	Malignant neoplasm of right ureter
C66.2	Malignant neoplasm of left ureter
C66.9	Malignant neoplasm of unspecified ureter
C67.0	Malignant neoplasm of trigone of bladder
C67.1	Malignant neoplasm of dome of bladder
C67.2	Malignant neoplasm of lateral wall of bladder
C67.3	Malignant neoplasm of anterior wall of bladder
C67.4	Malignant neoplasm of posterior wall of bladder
C67.5	Malignant neoplasm of bladder neck
C67.6	Malignant neoplasm of ureteric orifice
C67.7	Malignant neoplasm of urachus
C67.8	Malignant neoplasm of overlapping sites of bladder
C67.9	Malignant neoplasm of bladder, unspecified
C68.0	Malignant neoplasm of urethra
C68.1	Malignant neoplasm of paraurethral glands
C68.8	Malignant neoplasm of overlapping sites of urinary organs
C68.9	Malignant neoplasm of urinary organ, unspecified
C69.00	Malignant neoplasm of unspecified conjunctiva
C69.01	Malignant neoplasm of right conjunctiva

C69.02	Malignant neoplasm of left conjunctiva
C69.10	Malignant neoplasm of unspecified cornea
C69.11	Malignant neoplasm of right cornea
C69.12	Malignant neoplasm of left cornea
C69.20	Malignant neoplasm of unspecified retina
C69.21	Malignant neoplasm of right retina
C69.22	Malignant neoplasm of left retina
C69.30	Malignant neoplasm of unspecified retina
C69.31	Malignant neoplasm of right retina
C69.32	Malignant neoplasm of left retina
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.50	Malignant neoplasm of unspecified lacrimal gland and duct
C69.51	Malignant neoplasm of right lacrimal gland and duct
C69.52	Malignant neoplasm of left lacrimal gland and duct
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C69.80	Malignant neoplasm of overlapping sites unspecified eye and adnexa
C69.81	Malignant neoplasm of overlapping sites right eye and adnexa
C69.82	Malignant neoplasm of overlapping sites left eye and adnexa
C69.90	Malignant neoplasm of unspecified site of unspecified eye
C69.91	Malignant neoplasm of unspecified site of right conjunctiva
C69.92	Malignant neoplasm of unspecified site of left conjunctiva
C70.0	Malignant neoplasm of cerebral meninges
C70.1	Malignant neoplasm of spinal meninges
C70.9	Malignant neoplasm of meninges, unspecified
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral lobe
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina

C72.20	Malignant neoplasm of unspecified olfactory nerve
C72.21	Malignant neoplasm of right olfactory nerve
C72.22	Malignant neoplasm of left olfactory nerve
C72.30	Malignant neoplasm of unspecified optic nerve
C72.31	Malignant neoplasm of right optic nerve
C72.32	Malignant neoplasm of left optic nerve
C72.40	Malignant neoplasm of unspecified acoustic nerve
C72.41	Malignant neoplasm of right acoustic nerve
C72.42	Malignant neoplasm of left acoustic nerve
C72.50	Malignant neoplasm of unspecified cranial nerve
C72.59	Malignant neoplasm of other cranial nerves
C72.9	Malignant neoplasm of central nervous system, unspecified
C73	Malignant neoplasm of thyroid gland
C74.00	Malignant neoplasm of cortex of unspecified adrenal gland
C74.01	Malignant neoplasm of cortex of right adrenal gland
C74.02	Malignant neoplasm of cortex of left adrenal gland
C74.10	Malignant neoplasm of medulla of unspecified adrenal gland
C74.11	Malignant neoplasm of medulla of right adrenal gland
C74.12	Malignant neoplasm of medulla of left adrenal gland
C74.90	Malignant neoplasm of unspecified part of unspecified adrenal gland
C74.91	Malignant neoplasm of unspecified part of right adrenal gland
C74.92	Malignant neoplasm of unspecified part of left adrenal gland
C75.0	Malignant neoplasm of parathyroid gland
C75.1	Malignant neoplasm of pituitary gland
C75.2	Malignant neoplasm of craniopharyngeal duct
C75.3	Malignant neoplasm of pineal gland
C75.4	Malignant neoplasm of carotid body
C75.5	Malignant neoplasm of aortic body and other paraganglia
C75.8	Malignant neoplasm with pluriglandular involvement, unspecified
C75.9	Malignant neoplasm of endocrine gland, unspecified
C7A.00	Malignant carcinoid tumor of unspecified site
C7A.010	Malignant carcinoid tumor of the duodenum
C7A.011	Malignant carcinoid tumor of the jejunum
C7A.012	Malignant carcinoid tumor of the ileum
C7A.019	Malignant carcinoid tumor of the small intestine, unspecified portion
C7A.020	Malignant carcinoid tumor of the appendix
C7A.021	Malignant carcinoid tumor of the cecum
C7A.022	Malignant carcinoid tumor of the ascending colon
C7A.023	Malignant carcinoid tumor of the transverse colon
C7A.024	Malignant carcinoid tumor of the descending colon

C7A.025	Malignant carcinoid tumor of the sigmoid colon
C7A.026	Malignant carcinoid tumor of the rectum
C7A.029	Malignant carcinoid tumor of the large intestine, unspecified portion
C7A.090	Malignant carcinoid tumor of the bronchus and lung
C7A.091	Malignant carcinoid tumor of the thymus
C7A.092	Malignant carcinoid tumor of the stomach
C7A.093	Malignant carcinoid tumor of the kidney
C7A.094	Malignant carcinoid tumor of the foregut, unspecified
C7A.095	Malignant carcinoid tumor of the midgut, unspecified
C7A.096	Malignant carcinoid tumor of the hindgut, unspecified
C7A.098	Malignant carcinoid tumor of other sites
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7A.8	Other malignant neuroendocrine tumors
C7B.00	Secondary carcinoid tumors, unspecified site
C7B.01	Secondary carcinoid tumors of distant lymph nodes
C7B.02	Secondary carcinoid tumors of liver
C7B.03	Secondary carcinoid tumors of bone
C7B.04	Secondary carcinoid tumors of peritoneum
C7B.09	Secondary carcinoid tumors of other sites
C7B.1	Secondary Merkel cell carcinoma
C7B.8	Other secondary neuroendocrine tumors
C76.0	Malignant neoplasm of head, face and neck
C76.1	Malignant neoplasm of thorax
C76.2	Malignant neoplasm of abdomen
C76.3	Malignant neoplasm of pelvis
C76.40	Malignant neoplasm of unspecified upper limb
C76.41	Malignant neoplasm of right upper limb
C76.42	Malignant neoplasm of left upper limb
C76.50	Malignant neoplasm of unspecified lower limb
C76.51	Malignant neoplasm of right lower limb
C76.52	Malignant neoplasm of left lower limb
C76.8	Malignant neoplasm of other specified ill-defined sites
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C77.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
C77.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
C77.3	Secondary and unspecified malignant neoplasm of axilla and upper limb lymph nodes
C77.4	Secondary and unspecified malignant neoplasm of inguinal and lower limb lymph nodes
C77.5	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
C77.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions
C77.9	Secondary and unspecified malignant neoplasm of lymph node, unspecified

C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.1	Secondary malignant neoplasm of mediastinum
C78.2	Secondary malignant neoplasm of pleura
C78.30	Secondary malignant neoplasm of unspecified respiratory organs
C78.39	Secondary malignant neoplasm of other respiratory organs
C78.4	Secondary malignant neoplasm of small intestine
C78.5	Secondary malignant neoplasm of large intestine and rectum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of intrahepatic bile duct
C78.80	Secondary malignant neoplasm of unspecified digestive organ
C78.89	Secondary malignant neoplasm of other digestive organs
C79.00	Secondary malignant neoplasm of unspecified kidney and renal pelvis
C79.01	Secondary malignant neoplasm of right kidney and renal pelvis
C79.02	Secondary malignant neoplasm of left kidney and renal pelvis
C79.10	Secondary malignant neoplasm of unspecified urinary organs
C79.11	Secondary malignant neoplasm of bladder
C79.19	Secondary malignant neoplasm of other urinary organs
C79.2	Secondary malignant neoplasm of skin
C79.31	Secondary malignant neoplasm of brain
C79.32	Secondary malignant neoplasm of cerebral meninges
C79.40	Secondary malignant neoplasm of unspecified part of nervous system
C79.49	Secondary malignant neoplasm of other parts of nervous system
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C79.60	Secondary malignant neoplasm of unspecified ovary
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.70	Secondary malignant neoplasm of unspecified adrenal gland
C79.71	Secondary malignant neoplasm of right adrenal gland
C79.72	Secondary malignant neoplasm of left adrenal gland
C79.81	Secondary malignant neoplasm of breast
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
C79.9	Secondary malignant neoplasm of unspecified site
C80.0	Disseminated malignant neoplasm, unspecified
C80.1	Malignant (primary) neoplasm, unspecified
C80.2	Malignant neoplasm associated with transplanted organ
C81.00	Nodular lymphocyte predominant Hodgkin lymphoma, unspecified site

C81.01	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.02	Nodular lymphocyte predominant Hodgkin lymphoma, intrathoracic lymph nodes
C81.03	Nodular lymphocyte predominant Hodgkin lymphoma, intra-abdominal lymph nodes
C81.04	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.05	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.06	Nodular lymphocyte predominant Hodgkin lymphoma, intrapelvic lymph nodes
C81.07	Nodular lymphocyte predominant Hodgkin lymphoma, spleen
C81.08	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of multiple sites
C81.09	Nodular lymphocyte predominant Hodgkin lymphoma, extranodal and solid organ sites
C81.10	Nodular sclerosis Hodgkin lymphoma, unspecified site
C81.11	Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.12	Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes
C81.13	Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph nodes
C81.14	Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.15	Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.16	Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes
C81.17	Nodular sclerosis Hodgkin lymphoma, spleen
C81.18	Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites
C81.19	Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites
C81.20	Mixed cellularity Hodgkin lymphoma, unspecified site
C81.21	Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.22	Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes
C81.23	Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes
C81.24	Mixed cellularity Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.25	Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.26	Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes
C81.27	Mixed cellularity Hodgkin lymphoma, spleen
C81.28	Mixed cellularity Hodgkin lymphoma, lymph nodes of multiple sites
C81.29	Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites
C81.30	Lymphocyte depleted Hodgkin lymphoma, unspecified site
C81.31	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.32	Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes
C81.33	Lymphocyte depleted Hodgkin lymphoma, intra-abdominal lymph nodes
C81.34	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.35	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.36	Lymphocyte depleted Hodgkin lymphoma, intrapelvic lymph nodes
C81.37	Lymphocyte depleted Hodgkin lymphoma, spleen
C81.38	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of multiple sites
C81.39	Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites

C81.40	Lymphocyte-rich Hodgkin lymphoma, unspecified site
C81.41	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.42	Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes
C81.43	Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes
C81.44	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.45	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.46	Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes
C81.47	Lymphocyte-rich Hodgkin lymphoma, spleen
C81.48	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites
C81.49	Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites
C81.70	Other Hodgkin lymphoma, unspecified site
C81.71	Other Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.72	Other Hodgkin lymphoma, intrathoracic lymph nodes
C81.73	Other Hodgkin lymphoma, intra-abdominal lymph nodes
C81.74	Other Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.75	Other Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.76	Other Hodgkin lymphoma, intrapelvic lymph nodes
C81.77	Other Hodgkin lymphoma, spleen
C81.78	Other Hodgkin lymphoma, lymph nodes of multiple sites
C81.79	Other Hodgkin lymphoma, extranodal and solid organ sites
C81.90	Hodgkin lymphoma, unspecified, unspecified site
C81.91	Hodgkin lymphoma, unspecified lymph nodes of head, face, and neck
C81.92	Hodgkin lymphoma, unspecified intrathoracic lymph nodes
C81.93	Hodgkin lymphoma, unspecified intra-abdominal lymph nodes
C81.94	Hodgkin lymphoma, unspecified lymph nodes of axilla and upper limb
C81.95	Hodgkin lymphoma, unspecified lymph nodes of inguinal region and lower limb
C81.96	Hodgkin lymphoma, unspecified intrapelvic lymph nodes
C81.97	Hodgkin lymphoma, unspecified spleen
C81.98	Hodgkin lymphoma, unspecified lymph nodes of multiple sites
C81.99	Hodgkin lymphoma, unspecified extranodal and solid organ sites
C82.00	Follicular lymphoma grade I, unspecified site
C82.01	Follicular lymphoma grade I, lymph nodes of head, face, and neck
C82.02	Follicular lymphoma grade I, intrathoracic lymph nodes
C82.03	Follicular lymphoma grade I, intra-abdominal lymph nodes
C82.04	Follicular lymphoma grade I, lymph nodes of axilla and upper limb
C82.05	Follicular lymphoma grade I, lymph nodes of inguinal region and lower limb
C82.06	Follicular lymphoma grade I, intrapelvic lymph nodes
C82.07	Follicular lymphoma grade I, spleen
C82.08	Follicular lymphoma grade I, lymph nodes of multiple sites
C82.09	Follicular lymphoma grade I, extranodal and solid organ sites

C82.10	Follicular lymphoma grade II, unspecified site
C82.11	Follicular lymphoma grade II, lymph nodes of head, face, and neck
C82.12	Follicular lymphoma grade II, intrathoracic lymph nodes
C82.13	Follicular lymphoma grade II, intra-abdominal lymph nodes
C82.14	Follicular lymphoma grade II, lymph nodes of axilla and upper limb
C82.15	Follicular lymphoma grade II, lymph nodes of inguinal region and lower limb
C82.16	Follicular lymphoma grade II, intrapelvic lymph nodes
C82.17	Follicular lymphoma grade II, spleen
C82.18	Follicular lymphoma grade II, lymph nodes of multiple sites
C82.19	Follicular lymphoma grade II, extranodal and solid organ sites
C82.20	Follicular lymphoma grade III, unspecified, unspecified site
C82.21	Follicular lymphoma grade III, l unspecified, lymph nodes of head, face, and neck
C82.22	Follicular lymphoma grade III, unspecified, intrathoracic lymph nodes
C82.23	Follicular lymphoma grade III, unspecified, intra-abdominal lymph nodes
C82.24	Follicular lymphoma grade III, unspecified, lymph nodes of axilla and upper limb
C82.25	Follicular lymphoma grade III, unspecified, lymph nodes of inguinal region and lower limb
C82.26	Follicular lymphoma grade III, unspecified, intrapelvic lymph nodes
C82.27	Follicular lymphoma grade III, unspecified, spleen
C82.28	Follicular lymphoma grade III, unspecified, lymph nodes of multiple sites
C82.29	Follicular lymphoma grade III, unspecified, extranodal and solid organ sites
C82.30	Follicular lymphoma grade IIIa, unspecified site
C82.31	Follicular lymphoma grade IIIa, lymph nodes of head, face, and neck
C82.32	Follicular lymphoma grade IIIa, intrathoracic lymph nodes
C82.33	Follicular lymphoma grade IIIa, intra-abdominal lymph nodes
C82.34	Follicular lymphoma grade IIIa, lymph nodes of axilla and upper limb
C82.35	Follicular lymphoma grade IIIa, lymph nodes of inguinal region and lower limb
C82.36	Follicular lymphoma grade IIIa, intrapelvic lymph nodes
C82.37	Follicular lymphoma grade IIIa, spleen
C82.38	Follicular lymphoma grade IIIa, lymph nodes of multiple sites
C82.39	Follicular lymphoma grade IIIa, extranodal and solid organ sites
C82.40	Follicular lymphoma grade IIIb, unspecified site
C82.41	Follicular lymphoma grade IIIb, lymph nodes of head, face, and neck
C82.42	Follicular lymphoma grade IIIb, intrathoracic lymph nodes
C82.43	Follicular lymphoma grade IIIb, intra-abdominal lymph nodes
C82.44	Follicular lymphoma grade IIIb, lymph nodes of axilla and upper limb
C82.45	Follicular lymphoma grade IIIb, lymph nodes of inguinal region and lower limb
C82.46	Follicular lymphoma grade IIIb, intrapelvic lymph nodes
C82.47	Follicular lymphoma grade IIIb, spleen
C82.48	Follicular lymphoma grade IIIb, lymph nodes of multiple sites
C82.49	Follicular lymphoma grade IIIb, extranodal and solid organ sites

C82.50	Diffuse follicle center lymphoma, unspecified site
C82.51	Diffuse follicle center lymphoma, lymph nodes of head, face, and neck
C82.52	Diffuse follicle center lymphoma, intrathoracic lymph nodes
C82.53	Diffuse follicle center lymphoma, intra-abdominal lymph nodes
C82.54	Diffuse follicle center lymphoma, lymph nodes of axilla and upper limb
C82.55	Diffuse follicle center lymphoma, lymph nodes of inguinal region and lower limb
C82.56	Diffuse follicle center lymphoma, intrapelvic lymph nodes
C82.57	Diffuse follicle center lymphoma, spleen
C82.58	Diffuse follicle center lymphoma, lymph nodes of multiple sites
C82.59	Diffuse follicle center lymphoma, extranodal and solid organ sites
C82.60	Cutaneous follicle center lymphoma, unspecified site
C82.61	Cutaneous follicle center lymphoma, lymph nodes of head, face, and neck
C82.62	Cutaneous follicle center lymphoma, intrathoracic lymph nodes
C82.63	Cutaneous follicle center lymphoma, intra-abdominal lymph nodes
C82.64	Cutaneous follicle center lymphoma, lymph nodes of axilla and upper limb
C82.65	Cutaneous follicle center lymphoma, lymph nodes of inguinal region and lower limb
C82.66	Cutaneous follicle center lymphoma, intrapelvic lymph nodes
C82.67	Cutaneous follicle center lymphoma, spleen
C82.68	Cutaneous follicle center lymphoma, lymph nodes of multiple sites
C82.69	Cutaneous follicle center lymphoma, extranodal and solid organ sites
C82.80	Other types of follicular lymphoma, unspecified site
C82.81	Other types of follicular lymphoma, lymph nodes of head, face, and neck
C82.82	Other types of follicular lymphoma, intrathoracic lymph nodes
C82.83	Other types of follicular lymphoma, intra-abdominal lymph nodes
C82.84	Other types of follicular lymphoma, lymph nodes of axilla and upper limb
C82.85	Other types of follicular lymphoma, lymph nodes of inguinal region and lower limb
C82.86	Other types of follicular lymphoma, intrapelvic lymph nodes
C82.87	Other types of follicular lymphoma, spleen
C82.88	Other types of follicular lymphoma, lymph nodes of multiple sites
C82.89	Other types of follicular lymphoma, extranodal and solid organ sites
C82.90	Follicular lymphoma, unspecified, unspecified site
C82.91	Follicular lymphoma, unspecified, lymph nodes of head, face, and neck
C82.92	Follicular lymphoma, unspecified, intrathoracic lymph nodes
C82.93	Follicular lymphoma, unspecified, intra-abdominal lymph nodes
C82.94	Follicular lymphoma, unspecified, lymph nodes of axilla and upper limb
C82.95	Follicular lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C82.96	Follicular lymphoma, unspecified, intrapelvic lymph nodes
C82.97	Follicular lymphoma, unspecified, spleen
C82.98	Follicular lymphoma, unspecified, lymph nodes of multiple sites
C82.99	Follicular lymphoma, unspecified, extranodal and solid organ sites

C83.00	Small cell B-cell lymphoma, unspecified site
C83.01	Small cell B-cell lymphoma, lymph nodes of head, face, and neck
C83.02	Small cell B-cell lymphoma, intrathoracic lymph nodes
C83.03	Small cell B-cell lymphoma, intra-abdominal lymph nodes
C83.04	Small cell B-cell lymphoma, lymph nodes of axilla and upper limb
C83.05	Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.06	Small cell B-cell lymphoma, intrapelvic lymph nodes
C83.07	Small cell B-cell lymphoma, spleen
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.09	Small cell B-cell lymphoma, extranodal and solid organ sites
C83.10	Mantle cell lymphoma, unspecified site
C83.11	Mantle cell lymphoma, lymph nodes of head, face, and neck
C83.12	Mantle cell lymphoma, intrathoracic lymph nodes
C83.13	Mantle cell lymphoma, intra-abdominal lymph nodes
C83.14	Mantle cell lymphoma, lymph nodes of axilla and upper limb
C83.15	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
C83.16	Mantle cell lymphoma, intrapelvic lymph nodes
C83.17	Mantle cell lymphoma, spleen
C83.18	Mantle cell lymphoma, lymph nodes of multiple sites
C83.19	Mantle cell lymphoma, extranodal and solid organ sites
C83.30	Diffuse large B-cell lymphoma, unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma, intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma, intra-abdominal lymph nodes
C83.34	Diffuse large B-cell lymphoma, lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.36	Diffuse large B-cell lymphoma, intrapelvic lymph nodes
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma, lymph nodes of multiple sites
C83.39	Diffuse large B-cell lymphoma, extranodal and solid organ sites
C83.50	Lymphoblastic (diffuse) lymphoma, unspecified site
C83.51	Lymphoblastic (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.52	Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes
C83.53	Lymphoblastic (diffuse) lymphoma, intra-abdominal lymph nodes
C83.54	Lymphoblastic (diffuse) lymphoma, lymph nodes of axilla and upper limb
C83.55	Lymphoblastic (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.56	Lymphoblastic (diffuse) lymphoma, intrapelvic lymph nodes
C83.57	Lymphoblastic (diffuse) lymphoma, spleen
C83.58	Lymphoblastic (diffuse) lymphoma, lymph nodes of multiple sites
C83.59	Lymphoblastic (diffuse) lymphoma, extranodal and solid organ sites

C83.70	Burkitt lymphoma, unspecified site
C83.71	Burkitt lymphoma, lymph nodes of head, face, and neck
C83.72	Burkitt lymphoma, intrathoracic lymph nodes
C83.73	Burkitt lymphoma, intra-abdominal lymph nodes
C83.74	Burkitt lymphoma, lymph nodes of axilla and upper limb
C83.75	Burkitt lymphoma, lymph nodes of inguinal region and lower limb
C83.76	Burkitt lymphoma, intrapelvic lymph nodes
C83.77	Burkitt lymphoma, spleen
C83.78	Burkitt lymphoma, lymph nodes of multiple sites
C83.79	Burkitt lymphoma, extranodal and solid organ sites
C83.80	Other non-follicular lymphoma, unspecified site
C83.81	Other non-follicular lymphoma, lymph nodes of head, face, and neck
C83.82	Other non-follicular lymphoma, intrathoracic lymph nodes
C83.83	Other non-follicular lymphoma, intra-abdominal lymph nodes
C83.84	Other non-follicular lymphoma, lymph nodes of axilla and upper limb
C83.85	Other non-follicular lymphoma, lymph nodes of inguinal region and lower limb
C83.86	Other non-follicular lymphoma, intrapelvic lymph nodes
C83.87	Other non-follicular lymphoma, spleen
C83.88	Other non-follicular lymphoma, lymph nodes of multiple sites
C83.89	Other non-follicular lymphoma, extranodal and solid organ sites
C83.90	Non-follicular (diffuse) lymphoma, unspecified site
C83.91	Non-follicular (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.92	Non-follicular (diffuse) lymphoma, intrathoracic lymph nodes
C83.93	Non-follicular (diffuse) lymphoma, intra-abdominal lymph nodes
C83.94	Non-follicular (diffuse) lymphoma, lymph nodes of axilla and upper limb
C83.95	Non-follicular (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.96	Non-follicular (diffuse) lymphoma, intrapelvic lymph nodes
C83.97	Non-follicular (diffuse) lymphoma, spleen
C83.98	Non-follicular (diffuse) lymphoma, lymph nodes of multiple sites
C83.99	Non-follicular (diffuse) lymphoma, extranodal and solid organ sites
C84.00	Mycosis fungoides, unspecified site
C84.01	Mycosis fungoides, lymph nodes of head, face, and neck
C84.02	Mycosis fungoides, intrathoracic lymph nodes
C84.03	Mycosis fungoides, intra-abdominal lymph nodes
C84.04	Mycosis fungoides, lymph nodes of axilla and upper limb
C84.05	Mycosis fungoides, lymph nodes of inguinal region and lower limb
C84.06	Mycosis fungoides, intrapelvic lymph nodes
C84.07	Mycosis fungoides, spleen
C84.08	Mycosis fungoides, lymph nodes of multiple sites
C84.09	Mycosis fungoides, extranodal and solid organ sites

C84.10	Sezary disease, unspecified site
C84.11	Sezary disease, lymph nodes of head, face, and neck
C84.12	Sezary disease, intrathoracic lymph nodes
C84.13	Sezary disease, intra-abdominal lymph nodes
C84.14	Sezary disease, lymph nodes of axilla and upper limb
C84.15	Sezary disease, lymph nodes of inguinal region and lower limb
C84.16	Sezary disease, intrapelvic lymph nodes
C84.17	Sezary disease, spleen
C84.18	Sezary disease, lymph nodes of multiple sites
C84.19	Sezary disease, extranodal and solid organ sites
C84.40	Peripheral T-cell lymphoma, not classified, unspecified site
C84.41	Peripheral T-cell lymphoma, not classified, lymph nodes of head, face, and neck
C84.42	Peripheral T-cell lymphoma, not classified, intrathoracic lymph nodes
C84.43	Peripheral T-cell lymphoma, not classified, intra-abdominal lymph nodes
C84.44	Peripheral T-cell lymphoma, not classified, lymph nodes of axilla and upper limb
C84.45	Peripheral T-cell lymphoma, not classified, lymph nodes of inguinal region and lower limb
C84.46	Peripheral T-cell lymphoma, not classified, intrapelvic lymph nodes
C84.47	Peripheral T-cell lymphoma, not classified, spleen
C84.48	Peripheral T-cell lymphoma, not classified, lymph nodes of multiple sites
C84.49	Peripheral T-cell lymphoma, not classified, extranodal and solid organ sites
C84.60	Anaplastic large cell lymphoma, ALK-positive, unspecified site
C84.61	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of head, face, and neck
C84.62	Anaplastic large cell lymphoma, ALK-positive, intrathoracic lymph nodes
C84.63	Anaplastic large cell lymphoma, ALK-positive, intra-abdominal lymph nodes
C84.64	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of axilla and upper limb
C84.65	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of inguinal region and lower limb
C84.66	Anaplastic large cell lymphoma, ALK-positive, intrapelvic lymph nodes
C84.67	Anaplastic large cell lymphoma, ALK-positive, spleen
C84.68	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of multiple sites
C84.69	Anaplastic large cell lymphoma, ALK-positive, extranodal and solid organ sites
C84.70	Anaplastic large cell lymphoma, ALK-negative, unspecified site
C84.71	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of head, face, and neck
C84.72	Anaplastic large cell lymphoma, ALK-negative, intrathoracic lymph nodes
C84.73	Anaplastic large cell lymphoma, ALK-negative, intra-abdominal lymph nodes
C84.74	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of axilla and upper limb
C84.75	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of inguinal region and lower limb
C84.76	Anaplastic large cell lymphoma, ALK-negative, intrapelvic lymph nodes
C84.77	Anaplastic large cell lymphoma, ALK-negative, spleen
C84.78	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of multiple sites

C84.79	Anaplastic large cell lymphoma, ALK-negative, extranodal and solid organ sites
C84.A0	Cutaneous T-cell lymphoma, unspecified, unspecified site
C84.A1	Cutaneous T-cell lymphoma, unspecified, lymph nodes of head, face, and neck
C84.A2	Cutaneous T-cell lymphoma, unspecified, intrathoracic lymph nodes
C84.A3	Cutaneous T-cell lymphoma, unspecified, intra-abdominal lymph nodes
C84.A4	Cutaneous T-cell lymphoma, unspecified, lymph nodes of axilla and upper limb
C84.A5	Cutaneous T-cell lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C84.A6	Cutaneous T-cell lymphoma, unspecified, intrapelvic lymph nodes
C84.A7	Cutaneous T-cell lymphoma, unspecified, spleen
C84.A8	Cutaneous T-cell lymphoma, unspecified, lymph nodes of multiple sites
C84.A9	Cutaneous T-cell lymphoma, unspecified, extranodal and solid organ sites
C84.Z0	Other mature T/NK-cell lymphomas, unspecified site
C84.Z1	Other mature T/NK-cell lymphomas, lymph nodes of head, face, and neck
C84.Z2	Other mature T/NK-cell lymphomas, intrathoracic lymph nodes
C84.Z3	Other mature T/NK-cell lymphomas, intra-abdominal lymph nodes
C84.Z4	Other mature T/NK-cell lymphomas, lymph nodes of axilla and upper limb
C84.Z5	Other mature T/NK-cell lymphomas, lymph nodes of inguinal region and lower limb
C84.Z6	Other mature T/NK-cell lymphomas, intrapelvic lymph nodes
C84.Z7	Other mature T/NK-cell lymphomas, spleen
C84.Z8	Other mature T/NK-cell lymphomas, lymph nodes of multiple sites
C84.Z9	Other mature T/NK-cell lymphomas, extranodal and solid organ sites
C84.90	Mature T/NK-cell lymphomas, unspecified, unspecified site
C84.91	Mature T/NK-cell lymphomas, unspecified, lymph nodes of head, face, and neck
C84.92	Mature T/NK-cell lymphomas, unspecified, intrathoracic lymph nodes
C84.93	Mature T/NK-cell lymphomas, unspecified, intra-abdominal lymph nodes
C84.94	Mature T/NK-cell lymphomas, unspecified, lymph nodes of axilla and upper limb
C84.95	Mature T/NK-cell lymphomas, unspecified, lymph nodes of inguinal region and lower limb
C84.96	Mature T/NK-cell lymphomas, unspecified, intrapelvic lymph nodes
C84.97	Mature T/NK-cell lymphomas, unspecified, spleen
C84.98	Mature T/NK-cell lymphomas, unspecified, lymph nodes of multiple sites
C84.99	Mature T/NK-cell lymphomas, unspecified, extranodal and solid organ sites
C85.10	Unspecified B-cell lymphoma, unspecified site
C85.11	Unspecified B-cell lymphoma, lymph nodes of head, face, and neck
C85.12	Unspecified B-cell lymphoma, intrathoracic lymph nodes
C85.13	Unspecified B-cell lymphoma, intra-abdominal lymph nodes
C85.14	Unspecified B-cell lymphoma, lymph nodes of axilla and upper limb
C85.15	Unspecified B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.16	Unspecified B-cell lymphoma, intrapelvic lymph nodes
C85.17	Unspecified B-cell lymphoma, spleen
C85.18	Unspecified B-cell lymphoma, lymph nodes of multiple sites

C85.19	Unspecified B-cell lymphoma, extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma, unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face, and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites
C85.80	Other specified types of non-Hodgkin lymphoma, unspecified site
C85.81	Other specified types of non-Hodgkin lymphoma, lymph nodes of head, face, and neck
C85.82	Other specified types of non-Hodgkin lymphoma, intrathoracic lymph nodes
C85.83	Other specified types of non-Hodgkin lymphoma, intra-abdominal lymph nodes
C85.84	Other specified types of non-Hodgkin lymphoma, lymph nodes of axilla and upper limb
C85.85	Other specified types of non-Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C85.86	Other specified types of non-Hodgkin lymphoma, intrapelvic lymph nodes
C85.87	Other specified types of non-Hodgkin lymphoma, spleen
C85.88	Other specified types of non-Hodgkin lymphoma, lymph nodes of multiple sites
C85.89	Other specified types of non-Hodgkin lymphoma, extranodal and solid organ sites
C85.90	Non-Hodgkin lymphoma, unspecified, unspecified site
C85.91	Non-Hodgkin lymphoma, unspecified, lymph nodes of head, face, and neck
C85.92	Non-Hodgkin lymphoma, unspecified, intrathoracic lymph nodes
C85.93	Non-Hodgkin lymphoma, unspecified, intra-abdominal lymph nodes
C85.94	Non-Hodgkin lymphoma, unspecified, lymph nodes of axilla and upper limb
C85.95	Non-Hodgkin lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C85.96	Non-Hodgkin lymphoma, unspecified, intrapelvic lymph nodes
C85.97	Non-Hodgkin lymphoma, unspecified, spleen
C85.98	Non-Hodgkin lymphoma, unspecified, lymph nodes of multiple sites
C85.99	Non-Hodgkin lymphoma, unspecified, extranodal and solid organ sites
C86.0	Extranodal NK/T-cell lymphoma, nasal type
C86.1	Hepatosplenic T-cell lymphoma
C86.2	Enteropathy-type (intestinal) T-cell lymphoma
C86.3	Subcutaneous panniculitis-like T-cell lymphoma
C86.4	Blastic NK-cell lymphoma
C86.5	Angioimmunoblastic T-cell lymphoma
C86.6	Primary cutaneous CD30-positive T-cell proliferation
C88.0	Waldenstrom macroglobulinemia

C88.2	Heavy chain disease
C88.3	Immunoproliferative small intestinal disease
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma)
C88.8	Other malignant immunoproliferative diseases
C88.9	Malignant immunoproliferative disease, unspecified
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.11	Plasma cell leukemia in remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.21	Extramedullary plasmacytoma in remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.31	Solitary plasmacytoma in remission
C90.32	Solitary plasmacytoma in relapse
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia in remission
C91.02	Acute lymphoblastic leukemia in relapse
C91.10	Chronic lymphoblastic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphoblastic leukemia of B-cell type in remission
C91.12	Chronic lymphoblastic leukemia of B-cell type in relapse
C91.30	Prolymphocytic leukemia of B-cell type not having achieved remission
C91.31	Prolymphocytic leukemia of B-cell type in remission
C91.32	Prolymphocytic leukemia of B-cell type in relapse
C91.40	Hairy cell leukemia not having achieved remission
C91.41	Hairy cell leukemia in remission
C91.42	Hairy cell leukemia in relapse
C91.50	Adult T-cell lymphoma/leukemia (HTLV-1-associated) not having achieved remission
C91.51	Adult T-cell lymphoma/leukemia (HTLV-1-associated) in remission
C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated) in relapse
C91.60	Prolymphocytic leukemia of T-cell type not having achieved remission
C91.61	Prolymphocytic leukemia of T-cell type in remission
C91.62	Prolymphocytic leukemia of T-cell type in relapse
C91.A0	Mature B-cell leukemia Burkitt-type not having achieved remission
C91.A1	Mature B-cell leukemia Burkitt-type in remission
C91.A2	Mature B-cell leukemia Burkitt-type in relapse
C91.Z0	Other lymphoid leukemia not having achieved remission

C91.Z1	Other lymphoid leukemia in remission
C91.Z2	Other lymphoid leukemia in relapse
C91.90	Lymphoid leukemia, unspecified, not having achieved remission
C91.91	Lymphoid leukemia, unspecified, leukemia in remission
C91.92	Lymphoid leukemia, unspecified, leukemia in relapse
C92.00	Acute myeloblastic leukemia not having achieved remission
C92.01	Acute myeloblastic leukemia in remission
C92.02	Acute myeloblastic leukemia in relapse
C92.10	Chronic myeloblastic leukemia, BCR/ABL-positive not having achieved remission
C92.11	Chronic myeloblastic leukemia, BCR/ABL-positive in remission
C92.12	Chronic myeloblastic leukemia, BCR/ABL-positive in relapse
C92.20	Atypical chronic myeloid leukemia, BCR/ABL-negative not having achieved remission
C92.21	Atypical chronic myeloid leukemia, BCR/ABL-negative in remission
C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative in relapse
C92.30	Myeloid sarcoma not having achieved remission
C92.31	Myeloid sarcoma in remission
C92.32	Myeloid sarcoma in relapse
C92.40	Acute promyelocytic leukemia not having achieved remission
C92.41	Acute promyelocytic leukemia in remission
C92.42	Acute promyelocytic leukemia in relapse
C92.50	Acute myelomonocytic leukemia not having achieved remission
C92.51	Acute myelomonocytic leukemia in remission
C92.52	Acute myelomonocytic leukemia in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.61	Acute myeloid leukemia with 11q23-abnormality in remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia not having achieved remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia in remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia in relapse
C92.Z0	Other myeloid leukemia not having achieved remission
C92.Z1	Other myeloid leukemia in remission
C92.Z2	Other myeloid leukemia in relapse
C92.90	Myeloid leukemia, unspecified, not having achieved remission
C92.91	Myeloid leukemia, unspecified, in remission
C92.92	Myeloid leukemia, unspecified, in relapse
C93.00	Acute monoblastic/monocytic leukemia not having achieved remission
C93.01	Acute monoblastic/monocytic leukemia in remission
C93.02	Acute monoblastic/monocytic leukemia in relapse
C93.10	Chronic myelomonocytic leukemia not having achieved remission
C93.11	Chronic myelomonocytic leukemia in remission

C93.12	Chronic myelomonocytic leukemia in relapse
C93.30	Juvenile myelomonocytic leukemia not having achieved remission
C93.31	Juvenile myelomonocytic leukemia in remission
C93.32	Juvenile myelomonocytic leukemia in relapse
C93.Z0	Other monocytic leukemia not having achieved remission
C93.Z1	Other monocytic leukemia in remission
C93.Z2	Other monocytic leukemia in relapse
C93.90	Monocytic leukemia, unspecified, not having achieved remission
C93.91	Monocytic leukemia, unspecified, in remission
C93.92	Monocytic leukemia, unspecified, in relapse
C94.00	Acute erythroid leukemia, not having achieved remission
C94.01	Acute erythroid leukemia, in remission
C94.02	Acute erythroid leukemia, in relapse
C94.20	Acute megakaryoblastic leukemia, not having achieved remission
C94.21	Acute megakaryoblastic leukemia, in remission
C94.22	Acute megakaryoblastic leukemia, in relapse
C94.30	Mast cell leukemia, not having achieved remission
C94.31	Mast cell leukemia, in remission
C94.32	Mast cell leukemia, in relapse
C94.40	Acute panmyelosis with myelofibrosis, not having achieved remission
C94.41	Acute panmyelosis with myelofibrosis, in remission
C94.42	Acute panmyelosis with myelofibrosis, in relapse
C94.80	Other specified leukemias, not having achieved remission
C94.81	Other specified leukemias, in remission
C94.82	Other specified leukemias, in relapse
C95.00	Acute leukemia of unspecified cell type, not having achieved remission
C95.01	Acute leukemia of unspecified cell type, in remission
C95.02	Acute leukemia of unspecified cell type, in relapse
C95.10	Chronic leukemia of unspecified cell type, not having achieved remission
C95.11	Chronic leukemia of unspecified cell type, in remission
C95.12	Chronic leukemia of unspecified cell type, in relapse
C95.90	Leukemia, unspecified, not having achieved remission
C95.91	Leukemia, unspecified, in remission
C95.92	Leukemia, unspecified, in relapse
C96.0	Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
C96.20	Malignant mast cell neoplasm, unspecified
C96.21	Aggressive systemic mastocytosis
C96.22	Mast cell sarcoma
C96.29	Other malignant mast cell neoplasm
C96.4	Sarcoma of dendritic cells (accessory cells)

C96.5	Multifocal and unisystemic Langerhans-cell histiocytosis
C96.6	Unifocal Langerhans-cell histiocytosis
C96.A	Histiocytic sarcoma
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified

Annex 5. Protocol

Study Protocol - PASS Seasonique®

Non-Interventional PASS
Study # DR105-WH-50015

DOCUMENT APPROVAL FORM

Document Type:	Post-Authorisation Safety Study Protocol
Study No.:	DR105-WH-50015
Study Title:	A retrospective longitudinal cohort study assessing the safety of Seasonique® use: A post-marketing authorization safety study (PASS) to assess the risk of venous thromboembolic events (VTE) in women exposed to Seasonique®
Sponsor:	Teva Branded Pharmaceutical Products R&D, Inc.
Prepared By:	Sigal Kaplan

07 Feb 2017

Approved by: Wendy Huisman — Date

EU QPPV for Teva Pharmaceuticals Europe BV.

Approved by: Rainel Sanchez-de la Rosa MD, PhD, MSc — Date

Senior Medical Director, Spain & Portugal.

Europe Women's Health Medical Director

POST-AUTHORISATION SAFETY STUDY PROTOCOL

Draft Version 5.2 dated 7 February 2017

A retrospective longitudinal cohort study assessing the safety of Seasonique® use: A post-marketing authorization safety study (PASS) to assess the risk of venous thromboembolic events (VTE) in women exposed to Seasonique®

Non-interventional Phase IV study

Study#: DR105-WH-50015

Sponsor

Teva Branded Pharmaceutical Products R&D, Inc.

Confidentiality Statement

PASS Information

Title	A retrospective longitudinal cohort study assessing the safety of Seasonique® use: A post-marketing authorization safety study (PASS) to assess the risk of venous thromboembolic events (VTE) in women exposed to Seasonique®
Protocol Version Identifier	Version 5.2
Protocol Last Version Date	25 January 2017 (version 5.1)
EU PAS Register Number	Study has not yet 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	To be determined
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 PASS	No
Research Question and Objectives	Primary objective: • To compare incidence rates of venous thromboembolic events (VTE) in women exposed to SEASONIQUE with women exposed to 28-day cycle levonorgestrel-containing combined oral contraceptives (COC_{LNG}) Secondary objectives: • To compare users of SEASONIQUE to users of 28-day cycle COC_{LNG} with regard to the following events of interest: arterial thromboembolism (ATE), including acute myocardial infarction (AMI) and cerebrovascular accidents (CVA), pregnancy outcomes, breast cancers and other gynaecological cancers
Countries of Study	US
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LIST OF TABLES

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AEs	adverse events
AMI	acute myocardial infarction
ATE	arterial thromboembolism
BMI	body mass index
CHCs	combined hormonal contraceptives
CIs	confidence intervals
COC	combined oral contraceptive
COC_{LNG}	levonorgestrel-containing combined oral contraceptives
CV	cardiovascular
CVA	cerebrovascular accidents
DVT	deep vein thrombosis
EE	ethinyl estradiol
EMA	European Medicines Agency
EMR	electronic medical records
EU	Europe/European
HRs	Hazard ratios
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
OCs	oral contraceptive
PASS	post-authorisation safety study
PE	pulmonary embolism
US	United States
VTE	venous thromboembolism
WY	woman-years

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4. ABSTRACT

Title

A retrospective longitudinal cohort study assessing the safety of SEASONIQUE use

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 four episodes per year.

In the context of the regulatory submission for market authorisation of SEASONIQUE in Europe, the European Medicines Agency (EMA) has requested a post-marketing authorisation safety study (PASS) to assess the cardiovascular risk associated with SEASONIQUE during standard clinical practice.

Research question and objectives

Primary objective:

- To compare incidence rates of venous thromboembolic events (VTE) in women exposed to SEASONIQUE with women exposed to 28-day cycle levonorgestrel-containing combined oral contraceptives (COC_{LNG})

Secondary objectives:

- To compare users of SEASONIQUE to users of 28-day cycle COC_{LNG} with regard to the following events of interest: arterial thromboembolism (ATE), including acute myocardial infarction (AMI) and cerebrovascular accidents (CVA), pregnancy outcomes, breast cancers and other gynaecological cancers

Study design

This will be a comparative, retrospective cohort study.

Setting and Study Population

Data will be obtained from an existing US automated health care claims database. The study participants will consist of females who have a record of at least one prescription dispensed for SEASONIQUE or 28-day cycle COC_{LNG} during the study period. The COC prescription will be preceded by at least 12 months of continuous membership enrolment. More than 100,000 women will be included in the study, with a 1:2 ratio or more of SEASONIQUE users to 28-day cycle COC_{LNG} users, depending on the data availability. The study period will begin from the time the drug is available in the market, from 2006 through latest data available (at least December 2015).

Follow-up will be examined independently for each of the study outcomes. Study participants will be followed-up from date of COC drug initiation until the earliest of the following dates: study end point, cancer diagnosis or chemotherapy, end of the study period, end of enrollment in the health plan (lost to follow-up), or death.

Variables

Exposure

Exposure will be defined as a prescription claim for SEASONIQUE or 28-day cycle COC_{LNG}. Naïve users (starting use), new users, re-starters and switchers will be further identified in each of the SEASONIQUE and 28-day cycle COC_{LNG} cohorts.

Covariates:

Data on potential confounders or effect modifiers will be collected for each cohort member, including the presence of hypertension, cardiovascular (CV) disease, stroke, diabetes, hyperlipidemia, migraine, and other chronic medical conditions. These data will be collected from the diagnostic codes used in the hospital and/or ambulatory setting in the database (e.g., ICD-9-CM, ICD-10).

Data on concomitant medications and use of medications prescribed for the treatment of CV disease, diabetes, and other chronic medical conditions will be collected as well.

Other covariates, if available, will be identified, including age, smoking, body mass index, surgery and injury, pregnancy, duration of current use and family history of VTE, if available.

Study end points

Primary outcomes:

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

Secondary outcomes:

- ATEs, including AMI, ischemic stroke (IS) and CVA
- Pregnancy outcomes
- Fertility
- Delayed pregnancy detection
- Breast cancers and other gynaecological cancers

Data sources

Data for this risk assessment study will be obtained from an existing US automated health care claim database, Optum Research Database (ORD). The database collects information recorded by various health care providers such as physicians, pharmacies and hospitals in real-life setting and comprises a large number of patients and thus most suitable for investigating a relatively rare outcomes in routine clinical practice setting.

Study size

The sample size calculation is based on a background incidence rate of 6 VTE per 10,000 woman-years (WY) for COC_{LNG}. It is expected that SEASONIQUE is associated with a VTE risk that is not higher than the risk associated with COC_{LNG}. Given this background rate, a total of at least 100,000 women (ratio of 1:2 or more of SEASONIQUE and COC_{LNG} users) will be followed up for approximately 200,000 WY, during which a total of 120 VTE cases could be expected.

The study is designed to demonstrate non-inferiority of SEASONIQUE in terms of VTE risk versus the comparator (28-day cycle COC_{LNG}) with a detectable level of a 50% increase in risk (ie, hazard ratio of 1.5) at the level of $p<0.05$ and with a power of 80%.

Data analysis

Baseline characteristics of the SEASONIQUE and 28-day cycle COC_{LNG} cohorts will be compared. Differences between groups (SEASONIQUE and COC_{LNG}) will be evaluated using proportions for categorical variables and means for continuous variables (with 95% confidence intervals). Unadjusted incidence rate of VTE and other secondary outcomes of interest for each group (along with 95% confidence intervals) will be assessed and summary statistics for the incidence of these outcomes will be reported. In addition, the differences in incidence rates will also be calculated. Hazard ratios (HRs) with 95% confidence intervals will be calculated using Cox proportional hazards models, with adjustment for covariates.

Milestones

The US data collection will begin as soon as possible after protocol approval (expected time is 3 months after protocol approval). The end of data collection will be 18 months after start of data collection to accommodate the medical record review for validation of VTE. The final US study report will be submitted 12 months after end of data collection.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

The study milestones along with planned dates proposed for the US Database have been updated to align with the availability of the proposed database.

Based on feasibility assessment report, the US study period will be from the time period SEASONIQUE was available in the US database (2006) to the latest data available (at least December 2015) to reach the target sample size. Since health claims data for that time period are expected to be available already, the US data collection will begin as soon as possible after protocol approval (expected time is 3 months after protocol approval). The end of data collection will be 18 months after start of data collection to accommodate the medical record review for validation of VTE. The final US study report will be submitted 12 months after end of data collection in the US.

Study milestones along with planned dates are presented in Table 2 below.

Table 1: Milestones

Milestone	Planned date
Start of data collection	3 months after protocol approval
End of data collection	18 months after start of data collection
Registration in the EU PAS register	Prior to data collection
Final report of study results	12 months after end of data collection

7. RATIONALE AND BACKGROUND

SEASONIQUE is a 91-day extended combined oral contraceptive (COC), containing fixed-dose combination of 0.15 mg levonorgestrel (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 doses of this COC, i.e., 0.15 mg LNG and 0.03 mg EE are already used in other COCs authorized in Europe.

The standard 28-day cyclic regimen, consists 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. 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 extended-regimen of SEASONIQUE is designed to eliminate the withdrawal bleeding that regularly occurs with conventional COCs once every 28 days. This extended COC may improve compliance and reduce the risk of unwanted pregnancies by providing continuity and decreasing scheduled withdrawal bleeding to four episodes per year.

The first extended-regimen oral contraceptive, Seasonale, was approved in the United States (US) in 2003 and in Canada in 2007. Seasonale is a 91-day extended-regimen contraceptive with 84 days of active combination tablets (0.15 mg LNG and 0.03 mg EE) and 7 placebo tablets. SEASONIQUE was developed as a successor to Seasonale and approved in the US in 2006 and in Canada in 2010. 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).

Evidence suggests that oral hormonal combined contraceptive containing low dose of EE and a second generation progestin (conventional 28-day cycle regimen) are associated with venous thromboembolism (VTE) with an incidence rate of 20 cases per 100,000 women/year. However, the VTE incidence with levonorgestrel-EE containing combined hormonal contraceptives (CHCs) might be higher based on epidemiological data (EMA Assessment Report 2014).

During the clinical development of SEASONIQUE, few adverse events (AEs) of medical relevance in OC use were reported. One case of deep vein thrombosis (DVT) and one case of arterial thrombotic event were reported among the non-SEASONIQUE treatment group. In addition, sex-hormone-related malignancies were also examined. One case of ovarian cancer was reported with patient randomized to non-SEASONIQUE treatment group (DP3-84/30) one year after the first dose of treatment. From the data submitted, there were no cases of breast cancer or hepatocarcinoma reported with SEASONIQUE during the clinical program.

Given the limited number of women treated with SEASONIQUE in the clinical program as well as the limited patient length of exposure (one year for the pivotal study and 4 years for the extension study but with a very small size population), the safety profile of this extended-cycle

contraceptive regimen, regarding the risk of venous thromboembolic events and long term use of SEASONIQUE is not entirely elucidated. It is expected that the risk of VTE and other cardiovascular outcomes is not different between SEASONIQUE and standard 28-day cyclic regimen with combined LNG/EE.

In the context of the regulatory submission for market authorization of SEASONIQUE in Europe, the European Medicines Agency (EMA) has requested a post-authorisation safety study (PASS) to assess the cardiovascular risk associated with SEASONIQUE during standard clinical practice.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Primary Objective(s)

To compare the incidence rates of VTE in women exposed to SEASONIQUE with women exposed to 28-day cycle levonorgestrel-containing combined oral contraceptives (COC_{LNG})

8.2. Secondary Objective(s)

To compare users of SEASONIQUE to users of 28-day cycle COC_{LNG} with regard to the following events of interest: arterial thromboembolism (ATE), including acute myocardial infarction (AMI) and cerebrovascular accidents (CVA), pregnancy outcomes, breast cancers and other gynaecological cancers

9. RESEARCH METHODS

9.1. Study design

This will be a comparative, retrospective cohort study.

9.2. Setting and Study Population

The study population will be identified from an existing US automated health care claim database, Optum Research Database (ORD). This database collects information recorded by various health care providers such as physicians, pharmacies and hospital in real-life setting and comprises a large number of patients and thus most suitable for investigating a relatively rare outcomes in routine clinical practice setting.

Women who have a record of at least one prescription dispensed for SEASONIQUE or 28-day cycle COC_{LNG} (comparator) during the study period will be included. The study participants will be grouped into SEASONIQUE or 28-day cycle COC_{LNG} (comparator) cohorts. The date of receiving the first prescription of SEASONIQUE or the comparator in the study period will be defined as the index date. A minimum of 12 month continuous enrollment/membership within the database before the index date will be used to obtain information about the relevant medical history before drug exposure start. Of note, the minimum 12-months eligibility requirement increases the length of time available to observe baseline covariates (increasing validity), yet at the same time it decreases the number of eligible patients (reducing precision). Therefore, as a sensitivity analysis, a minimum of 6 month continuous enrollment/membership within the database before the index date will also be extracted and examined for VTE outcome.

A further incident user cohort design will be used comparing the incident cohort of naïve and new users (defined in section 9.3.1) in SEASONIQUE and 28-day cycle COC_{LNG}. This design has been chosen as it allows for a clear temporal sequence of confounder adjustment and reduces the confounding from including prevalent users of the drug.

9.2.1. Inclusion Criteria

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

- Have a record of at least one prescription dispensed for SEASONIQUE or 28-day cycle COC_{LNG} during the study period
- At least 12 months of continuous membership enrolment prior to first COC prescription

9.2.2. Exclusion Criteria

Patients will be excluded from participating in this study if they have a record or claim evidence for the following events before study entry:

- History of carcinoma of the breast, endometrial carcinoma, known or suspected estrogen dependent neoplasia

- Chemotherapy
- Pregnancy within 3 months before treatment initiation
- Previous major surgery (including lower limb orthopaedic surgery), major lower extremity or pelvic trauma within 3 months before treatment initiation

For this US database study, the study period will be from 2006 (the time the drug is available on the market and first captured in the US databases) through the latest data available (at least December 2015) to reach the target sample size.

Follow-up will be examined independently for each of the study outcomes. Study participants will be followed-up from index date (date of COC drug initiation) until the earliest of the following dates (individual are censored at the time of these events):

- Study end point (see section 9.3.2 Primary and Secondary Endpoints)
- Cancer diagnosis or chemotherapy (for assessing primary endpoint, VTE)
- End of the study period
- End of enrollment in the health plan (lost to follow up) (last date of continuous membership)
- Death

Other conditions known to substantially modify the VTE risk occurring during the follow-up will be examined. Patients with these conditions, including surgery/injury, and pregnancy, will not be censored. While these events are risk factors for VTE, they may occur after the index date and thus are in the causal pathway. Therefore, these conditions will be addressed in the analysis using technique such as stratification.

More than 100,000 women will be included in the study, with a 1:2 ratio or more of SEASONIQUE users to 28-day cycle COC_{LNG} users, depending on the data availability. The proportion of adolescents is expected to be in the range between 10% and 15%. The final number of women to be included in the study will be determined at the start of data collection based on their inclusion/exclusion criteria and the latest data available.

9.3. Variables

9.3.1. Exposure

Exposure will be defined as a recorded prescription claim for SEASONIQUE or 28-day cycle COC_{LNG}. Exposed women in each cohort will be categorized based on their exposure to CHC prior to the index date as follows: naïve users (starting use), new users, re-starters and switchers. This categorization is important for diminishing misclassification of new users that could potentially occur when comparing a new treatment with an established one. By definition, the starters of a newly launched novel preparation, such as SEASONIQUE, would only include new users, while the user group of an established COC drug may inevitably be misclassified and include re-starters. In addition, it is important to differentiate between these groups as they may have different VTE risk (Lidegaard 2014). The following definitions will be used for exposure categorization (Lidegaard 2011):

- **Naïve users (starting use)** are defined as women with first ever exposure to any study COC or comparator COC during the study period and no use of any dispensed CHC prior to the index date.
- **New users** are defined as women starting use of the study COC or comparator COC 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 COC drug (SEASONIQUE or 28-day cycle COC_{LNG}), either the same drug as before or a new COC, after a break of 4-11 weeks.
- **Switchers** are defined as women starting one COC preparation (SEASONIQUE or 28-day cycle COC_{LNG}) after a different CHC preparation with a break of less than four weeks.

The duration of use will be determined based on all filled prescriptions during the observation period. Episodes of SEASONIQUE or comparator treatment will be constructed using the number of day's supply, if available (e.g., claims database). An episode of therapy will be defined as a period of continuous usage of one or a series of prescriptions for SEASONIQUE or comparator for the same patient. The first episode of therapy will begin on the cohort entry date and continue through the number of days of supply of the prescription (90 days for SEASONIQUE and 28 day for comparator). If a subsequent prescription fill is recorded within 30 days (for SEASONIQUE) or 14 days (for comparator) 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 (or 14-day) grace period after the 90-day supply for SEASONIQUE (or 28-day supply for COC_{LNG}) 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. Pattern of drug use will be explored in both groups, taking into account the possibility of misuse in the 28-day COC_{LNG} group. In the 28-day COC_{LNG} group, the "standard" 21-day COC may be used continuously without exercising the 7-day pill-free interval. The group of patients with overlapping prescriptions will be identified. In the main analyses of the main outcomes, patients with overlapping prescriptions will be excluded. A sensitivity analysis will be performed to include patients with overlapping prescriptions, assuming the 28-day regimen was used as prescribed. In that case, the start date of the successive prescription will be modified to correspond to the date following of the preceding prescription end date. This procedure will be repeated until the time period covered by successive prescriptions ends or when a prescription for a different COC is filled, thus ending the exposure period of the preceding COC.

If a new different COC is either added to or replaced the initial drug (ie, new COC other than the drug used on index date), the first ongoing prescription of two overlapping prescriptions will be

truncated and will be considered discontinued on the date of the new subsequent prescription is issued.

If the gap between adjacent prescriptions is longer than 30 days for SEASONIQUE (or 7 days for comparator), then the episode of therapy ends on the last day of the days of supply 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. Exposure time will be reset to zero for every new episode. The exposure episodes in those patients will be identified sequentially and every episode will have a separate record in the analytic dataset. Patients can contribute to several exposure episodes but could contribute only one outcome event to the study. Estimation of exposure as treated enables a more realistic time-to-event analysis especially with potential of drug switching of the studied group of drugs.

To reduce misclassification, periods of drug exposure to the drug of interest will be identified to account for any remaining physiological effects of COCs on cardiovascular risk (ie, increased coagulability) and classified as follows:

- Current exposure: from the date of beginning of episode to the last day of episode of therapy of COC treatment course
- Recent exposure: from the end of current exposure to 30 days later (from 1 to 30 days after the end of COC treatment course)
- Intermediate exposure: from the end of recent exposure to 60 days later (from 31 to 60 days after the end of COC treatment course)
- Remote exposure: from the end of intermediate exposure to end of follow-up (from 61 days after the end of COC treatment course)

9.3.2. Primary and Secondary Endpoints

The primary study objective is to compare incidence rates of venous thromboembolic events (VTE) in women exposed to SEASONIQUE with women exposed to 28-day cycle levonorgestrel-containing oral contraceptives. VTE is defined as Deep Venous Thrombosis (DVT) and/or Pulmonary Embolism (PE).

Primary outcomes:

- *VTE, defined as deep venous thrombosis (DVT) and/or pulmonary embolism (PE) –*
  - VTE will be identified in either the outpatient or hospital settings

VTE codes in the hospital settings will be used only if identified in the primary position. The International Classification of Diseases, 9th Revision (ICD-9-CM) diagnosis codes for venous thromboembolism had high predictive value when present in the primary position, and lower predictive value when in a secondary position (White 2010). Outpatient DVT will be identified by a diagnosis of DVT in conjunction with a first prescription for an anticoagulant during the 30-day period subsequent to the date of diagnosis. ICD-9-CM and ICD-10-CM diagnosis codes for defining VTE outcomes are described in Annex 3.2.

Based on previous database studies (Lidegaard 2011, Grimes 2011), a potential misclassification of the VTE may occur as a result of high level of unconfirmed diagnoses. Thus, as part of the study, a separate validation of the diagnosis of VTE in medical records will be conducted in both inpatient and outpatient settings.

Secondary outcomes:

- *Arterial thromboembolism thromboembolic events (ATEs), including acute myocardial infarction (AMI), ischemic stroke (IS) and cerebrovascular accidents (CVA) –*
    - ATEs will be identified in the hospital setting only in the first (or second, depending if the second position corresponds to secondary diagnosis) position of the hospital discharge diagnosis

The ICD-9 and ICD-10 diagnosis codes for defining ATE outcomes are described in Annex 3.3. Arterial thromboembolism thromboembolic events subsection. Codes for AMI and stroke have been consistently well validated in previous studies using administrative claims data. These codes have shown to have a high positive predictive value (92% to 100%) when located as the primary or secondary diagnosis for AMI or the primary diagnosis for stroke in the hospital discharge claim (McCormick 2015; McCormick 2014; Birman-Deych 2005; Choma 2009; Kiyota 2004; Kokotailo 2005; Roumie 2008).

- *Pregnancy outcomes –*
    - Periods of pregnancy will be estimated by identifying claims for pregnancy terminations and deliveries. Pregnancy will be identified through delivery code or abortion code. ICD-9-CM and ICD-10-CM diagnosis codes for defining pregnancy and pregnancy outcomes are described in Annex 3.4. For each delivery, a period of pregnancy will be estimated as 270 days prior to the date of delivery. For each abortion, a period of pregnancy will be estimated as 120 days prior to the date of abortion. COC exposure and events occurring within 90 days after the delivery or abortion will be excluded, to correspond to the 3-month cut-off used in the study exclusion criteria. This 90-day period was chosen to account for the period during which the risk of VTE is increased. A large prospective primary care database from the United Kingdom found that the first 6 weeks postpartum was associated with a 22-fold increase in risk, with the peak occurring in the first 3 weeks (Sultan 2012). This suggests that an increased VTE risk still remains long after the 6 weeks period and a period of 90 days following delivery could be used for tapering off the risk.
- *Fertility –*
    - For women who stopped taking SEASONIQUE or comparator and did not switch to any other contraceptive and became pregnant, the time from the end of drug exposure to the pregnancy delivery or termination will be calculated. The fertility rate, defined as the number of births per 1000 women exposed to SEASONIQUE or comparator will be estimated. It should be noted that this definition assumes that women are sexually active.
- *Delayed pregnancy detection –*
    - Women whose COC exposures occurred during periods of pregnancy will be identified. The time period the COC is in use while the woman is pregnant will be estimated.
- *Breast cancers and other gynecological cancers –*
    - Breast, cervical, endometrial and ovary cancers will be identified. ICD-9-CM and ICD-10-CM diagnosis codes for defining gynecological cancers are described in Annex 3.5.

9.3.3. Other Variables

Covariates:

Baseline characteristics and demographic information will be collected from the database in the 365 days 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:

- Age at index date
- Smoking status, if available
- Body mass index (BMI), if available
- Pregnancy (within 3 months before treatment initiation or after index date)

- History of the following study endpoint:
  - Thromboembolic event (including VTE or DVT), or ATE (including acute myocardial infarction (AMI) and ischemic stroke), vascular disease, cerebral vascular or coronary artery disease, family history of VTE
  - History of uncontrolled or untreated hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg)
  - Previous pregnancy
  - History of abortion (recent or recurrent miscarriage)
  - Family history of venous thromboembolism or other cardiovascular disease

In addition, medical history potentially related to an increased risk of VTE and data on potential confounders or effect modifiers will be collected for each cohort member. These data will be collected from the diagnostic codes used in the hospital and/or ambulatory setting in the database (e.g., ICD-9-CM, ICD-10-CM), if available, including:

- Life-threatening diseases (e.g., HIV, liver failure, Hepatitis C positive, renal failure)
- Presence of hypertension, cardiovascular (CV) disease, stroke, diabetes, hyperlipidemia, migraine, and other chronic medical conditions
- Polycystic ovary syndrome (PCOS)
- Concomitant use of other COC or other forms of contraception
- Data on concomitant and use of medications prescribed for the treatment of CV disease, diabetes, and other chronic medical conditions
- Data on other diagnoses, medications, and procedures will be compared between SEASONIQUE and the 28-day COC_{LNG} cohorts in order to empirically identify other variables that might be included in the propensity score

9.4. Data sources

Data for this risk assessment study will be obtained from an existing US automated health care claim database, Optum Research Database (ORD). This database addresses the need for a large sample size required from this study.

It should be noted that the proposal to use US deviated from the study synopsis submitted previously where at least 2 EU databases were proposed. When selecting data source, various factors should be taken into account, including the country where the drug will be marketed, the launch date and the availability of the drug in the database. In Europe, data on SEASONIQUE still need to be accumulated in automated databases since the drug was only recently launched and only in a few countries. Moreover, oral contraceptives may not be reimbursed in several countries in Europe (e.g., Germany), so SEASONIQUE may not be captured in major large EU databases. As a result, it may not be feasible to reach the total target number of women required for the study to assess VTE risk within reasonable time period. On the other hand, SEASONIQUE was approved in the US in 2006. Since oral contraceptives are generally reimbursed in the US, it was expected that the drug was captured in various US automated databases and ample data have already been accumulated to achieve the target sample size and readily available for analysis. The adequacy of the sample size and the selected study period in the US database was confirmed in a feasibility assessment (see feasibility assessment report).

Given the difficulties in carrying-out the study within European countries in a reasonable timeframe (recent launch, only in a few countries and non-reimbursed status), there are advantages of using US database to retrieve a large sample size required to identify a relatively rare outcome and conduct the study in readily available data source with relatively long market experience in US.

For this risk assessment study in the US, data will be extracted using Optum Research Database (ORD) from 2006 (the time the drug is available in the market) through the latest data available (at least December 2015) to reach the target sample size. This database was selected based on feasibility report that assessed patient counts of SEASONIQUE and 28-day COC_{LNG}, study time period and availability of key data in the database. Additional key factors were the experience of the data vendor investigators conducting the study and publication in similar topic.

This database contains longitudinal medical and pharmacy claims data from a large commercially insured population geographically dispersed across the US. Specifically, the healthcare database includes individual-level information on patient demographics, inpatient and outpatient diagnoses, reported with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) or ICD-10-CM diagnosis codes, and procedures, reported with ICD-9-CM or ICD-10-CM, Current Procedural Terminology,(CPT), and Healthcare Common Procedure Coding System (HCPCS) procedure codes. Outpatient pharmacy claims include national drug codes (NDC), drug dosage form, fill date, days supplied, and quantity of drug supplied for dispensed medications. This healthcare database consists of de-identified data and is compliant with local regulations. In addition, linkage to medical records for outcome validation is feasible within this database.

Exposure to the drug of interest, medical history, comorbidities, concomitant medications, primary and secondary outcomes, and other relevant covariates will be extracted. Existing US automated health care database is proposed to obtain large sample size that will be required in

order to identify a relatively rare outcome of interest, such as VTE. In addition, a sample of medical records will be used for validation of VTE based on a unique identifier.

In order to perform a valid extrapolation of the risk estimates calculated from the US data to the EU female population, the study will use the following analyses and adjustments. To account for the possible demographic differences between US and EU female population, the data analyses will be stratified by age. An attempt will be made to stratify the analyses also by BMI, provided that this parameter will be sufficiently reported for study participants. This will provide age group-specific and BMI group-specific risk estimates, which should be applicable to a population with different distribution of age and BMI than in the US. The adjustment of statistical models to study variables (subject to availability), including medical history, concomitant medication and smoking, should provide the independent effect of SEASONIQUE on VTE risk. The goal of the study is to estimate whether SEASONIQUE affects the rate of VTE relative to LNG. It was previously demonstrated that the geographical region has no substantial impact on the relative risk estimates of VTE in EU and US (Dinger 2014). Accordingly, the differences in absolute risk of VTE between US and EU should not impede the extrapolation of the adjusted relative risk from the US to EU population. Therefore, the relative risk estimates calculated in these analyses for the US population should be applicable to the EU female population.

9.5. Study Size

The sample size considerations are based on the expected VTE incidence for COC_{LNG} as provided in Annex I from the RMS Day 180 Assessment report dated October 17, 2013. The sample size calculation is based on a background incidence rate of 6 VTE per 10,000 woman-years (WY) for COC_{LNG} (according to last PRAC's conclusion on COC referral of October 2013 that VTE incidence in LNG users is 6/10 000 WY rather than 10/10 000 WY). This rate was based on a study conducted in Europe (Lidegaard 2011). According to recent publication (Dinger 2014), the incidence of VTE among the US and EU COC users is in the range of 7-10 cases /10000 WY. Therefore, using the baseline rate of 6/10000 provides a more stringent assumption and a larger sample size, which will allow the detection of VTE and substantiation of the study hypothesis. It is expected that SEASONIQUE is associated with a VTE risk that is not higher than the risk associated with COC_{LNG}.

The study should be designed to demonstrate non-inferiority of SEASONIQUE in terms of VTE risk versus the comparator (28-day cycle COC_{LNG}) with a detectable level of a 50% increase in risk (ie, hazard ratio of 1.5) at the significance level of 0.05 and with a power of 80%.

The ratio between exposed (SEASONIQUE) and unexposed (28-day cycle COC_{LNG}) groups will be 1:2 or more. This ratio may be subject to change (e.g., 1:4) depending on the available sample size.

At an incidence rate of 6/10,000 WY, a total of 120 VTE cases could be expected within 200,000 WY. For this purpose a total of at least 100,000 women will be followed up.

The sample size needed for assessing VTE risk is also sufficient for the evaluation of the secondary outcomes – except ATE. AMI and stroke are very rare in women of reproductive age. This study is powered to exclude a 2.5-fold risk of ATE.

The number of women to be included in the study will be determined at the start of data collection based on their inclusion/exclusion criteria.

9.6. Data management

The study will use an existing health care claims database with anonymized information on the individual patients. In addition, patient's medical records will be extracted. Data extraction, analysis will be performed according to the standard practices of the data vendors. Datasets extracted from the database will be stored to allow future analysis, if needed.

9.7. Data analysis

9.7.1. General Considerations

Descriptive statistics will be provided for baseline characteristics of SEASONIQUE and 28-day cycle COC_{LNG} cohorts. Differences between groups (SEASONIQUE and COC_{LNG}) will be evaluated using proportions for categorical variables and means for continuous variables (with 95% confidence intervals). The incidence rate of VTE and other secondary outcomes of interest (along with 95% confidence intervals) for each group will be assessed and summary statistics for the incidence of these outcomes will be reported. In addition, the differences in incidence rates will also be calculated.

The primary analysis will focus on VTE events comparing current exposure to SEASONIQUE vs. 28-day cycle COC_{LNG} (reference group). Rates for VTE events per person-year of observation will be calculated for all exposure episodes. Unadjusted incidence rates with 95% confidence intervals (CIs) of VTE and other secondary outcomes of interest between the treatment groups (SEASONIQUE and 28-day cycle COC_{LNG}) will be calculated. Kaplan-Meier cumulative incidence plots will be generated to depict time to event for all end points. In addition, the effect of potential confounding variables on the VTE rate will be explored in multivariate regression models. Cox-proportional hazards (PH) models will be used to estimate hazard ratios (HRs) and their 95% CI, with adjustment for covariates. The analysis will take into account the correlation among exposure episodes from patients contributing more than one episode to the analysis dataset. Assumptions for normal approximation will be investigated; exact methods will be used if the assumptions do not hold.

A comparison between SEASONIQUE and 28-day cycle COC_{LNG} will be carried out through careful analysis of key covariates with methods to account for any observed differences. Conditions known to substantially modify the VTE risk occurring during the follow-up, including surgery/injury or pregnancy, will be examined and addressed in the analysis (e.g.

stratification). Age, history of VTE, calendar year of study entry will be included in all models. In the ATE models, cardiovascular related risk factors (hypertension, hyperlipidemia and diabetes mellitus) will be included. In the absence of information of relevant risk factors in the database, propensity score matching approach will be used to balance for differences in diagnoses/medications and other risk factors for VTE preceding the initiation of SEASONIQUE and 28-day cycle COC_{LNG} between the two cohorts. Selected variables derived from a woman's history of claims preceding initiation will be used to form matched cohorts.

In addition, a sub-group analysis including only females aged 15-49 years will be performed. An attempt will be made to provide a subgroup analysis by BMI groups, depending on the proportion of patients for whom BMI will be reported. A subgroup analysis for patients with code for obesity and patients without such code will be performed across the two cohorts. In addition, patients will be compared according to their age, length of time in the database and other variables to evaluate any differences between the cohorts.

Each of the potential covariates will be tested individually in these models, with an inclusion rule of 20% change or more in the relative risk estimate of the study COCs. Covariates not meeting this criterion for the models will not be included in the final modeling. The null hypothesis for the main analysis to be tested is: $HR_{VTE} > 1.5$ (ie, the VTE rate ratio for SEASONIQUE vs. 28-day cycle COC_{LNG} is higher than or equal to 1.5). The alternative hypothesis is: $HR_{VTE} < 1.5$. The main analysis of VTE events will be conducted comparing the incident cohort of naïve and new SEASONIQUE users with those of 28-day cycle COC_{LNG} users. Using these groups will allow assessing the overall difference between the two incident user cohorts. In addition, it will increase the power of the study and will also allow for generalizability of the study results. Additional stratum-specific analyses will be performed for the four groups: (1) naïve users, (2) new users, (3) re-starters, and (4) switchers. Since there could be a difference between patients never using the drug (naïve users) in term of time past prior to the index date, a sensitivity analysis for the assessment of CHC history for each of the following subsets of patients will be performed: (1) patients with medical history of more than 24 months, (2) up to 36, and (3) >36 months -prior to the index date. In addition, a sensitivity analysis will be performed with other potential confounders to examine the appropriateness of the model and to examine the risk of VTE using the one-month definition for the restarter. Similar analyses will be performed for the secondary outcomes, including, arterial thromboembolism (e.g., acute myocardial infarction and stroke) and other events of interest.

To examine the nature of VTE risk with COC use, exposure person-time will be analyzed according to periods of drug exposure determined a priori based on the duration of use of the drugs.

All analyses will be performed using SAS for Windows 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. Standard operating procedures (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.

The following steps will be undertaken to ensure quality and accuracy of all programming developed during the course of the study:

- Data for analysis will be extracted by a competent programmer of the respective database.
- The statistical analysis plan along with the table shells will be reviewed and approved by the project leader or senior staff member of the data vendor.
- All programming code developed for this study will be reviewed by a senior researcher for the respective database.
- Study report including results and tables will be reviewed by senior staff member of the data vendor.

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 in an existing US automated health care claims database employing a robust design with large number of patients in routine care settings followed over several years. The use of this database will ascertain a large geographically and demographically diverse cohort of COC users required for identifying a rare outcome such as VTE. In addition, it will be possible to characterize the drug safety profile of SEASONIQUE compared to 28-day cycle COC_{LNG} and examine data across various populations enhancing the weight of evidence gathered from post-marketing observational studies.

Given the observational study design and the use of health care database, the study has several limitations.

Misclassification of exposure or outcome is a potential limitation of observational studies. Assessment of COC exposure periods is based on the electronic pharmacy records of filled prescriptions rather than information on actual intake. Thus, patients may be classified as exposed when they have actually stopped taking the drug. In addition, it is possible that the COC is used continuously, especially monophasic COCs, without a pill-free interval (for several packages or even indefinitely) until breakthrough bleeding occurs. To evaluate the exposure and to address this potential misclassification, the assumption of using the drug regimen as prescribed will be examined and patient misusing the drug will be excluded from analyses.

While electronic pharmacy data may not represent the actual consumption of the medications, these data have been extensively studied and shown to provide sound and fairly unbiased information on medication use from real world data. To address any potential misclassification of the outcome, a separate validation of the diagnosis of VTE in medical records will be performed. Restricting the analysis to a sample of validated cases will enable to provide a quantitative assessment of the misclassification of the main outcome of interest.

Confounding by indication is not expected in this study as both SEASONIQUE and comparator are COC containing similar active ingredients (LNG combined with EE) and thus physicians' decision to prescribe SEASONIQUE is not expected to be based on a presumed higher risk of VTE in SEASONIQUE group. Nonetheless, selection bias could occur if physicians tend to prescribe SEASONIQUE to women with specific characteristics that may also be risk factors for VTE. High risk of VTE can be explained by important covariates that may not be available in the database, including, obesity, smoking, family history of thrombosis, and lifetime use of hormonal contraceptives. Subject to availability, data will be extracted on various variables known or suspected to be associated with the outcomes of interest, as well as many variables related to general health. These variables will be used to handle the bias in the design stage by matching SEASONIQUE patients to patients on comparator or in the analysis stage using stratification and modelling to adjust for most of the known clinical risk factors for venous thromboembolism that may account for the medication prescribed.

Information regarding fertility is expected to be limited in this study, especially since the study is designed in claims data. Information regarding fertility may be more comprehensive in EMR but even then it should be used with caution due to potential under-reporting of fertility. Also, the definition for fertility assumes that women are sexually active, though this may not be the case. Moreover, is unclear whether any pregnancy identified during the study period is actually planned. Women wishing to receive a long regimen of COC, such as SEASONIQUE, are likely to be those excluding pregnancy in the short term. Therefore, the fertility rate between SEASONIQUE and comparator may not accurately reflect any impediment related to fertility due to study drug.

Delayed pregnancy detection cannot be accurately estimated is another limitation in the study. Since the drug is prescribed for 3 months and 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 is not recorded in the database. Consequently, it will not be possible to accurately estimate whether the women are still on the drug while pregnant.

Additional limitation derives from the length of follow-up available in administrative healthcare database. The typical length of follow-up in these databases is 2 years and thus long-term outcomes, such as cancer (secondary outcome in this study), may not be identified due to the limited follow-up time. Even so, various studies have been conducted in these databases using cancer as the main outcome of interest. Moreover, there will be a subset of the cohort that will have longer enrollment allowing for assessment of long-term outcome.

As noted above, missing information on unmeasured confounders and residual confounding cannot be entirely eliminated in observational studies. To examine the extent of this potential

residual confounding, a subset of patients that have this information (e.g., code for obesity) will be identified from both groups and will be examined for any differences compared to the main study results.

9.10. Other aspects

None

10. PROTECTION OF HUMAN SUBJECTS

This study will be conducted in accordance with the 2012 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 2008), and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP 2012) as well as the ENCePP Code of Conduct (ENCePP 2014).

All data used for the study will be de-identified with no breach of confidentiality with regards to personal identifiers or 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 subjects remains protected. The data and all study documents will be kept until MAH’s written notification 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

As 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 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 reporting results of this study, 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 2014) guidelines. In addition, communication in appropriate scientific meetings will be considered.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title

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"

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

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 page number(s) 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-authorisation safety studies). Note, 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 retrospective longitudinal cohort study assessing the safety of short- and long-term use of Seasonique®: A post-marketing authorization safety study (PASS) to assess the risk of venous thromboembolic events (VTE) in women exposed to Seasonique®

Study reference number:
To be determined

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	15
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

[1] 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.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	18
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which formal 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**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	19-20
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	22-24
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	26

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	19-20
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	19-20
4.2.2 Age and sex?	☒	☐	☐	
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Co-morbidity?	☒	☐	☐	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19-20

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	20-22
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	20-22
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	20-22
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	20-22
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	22-24
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	22-24

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	24
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	24

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	25-26
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	
8.1.3 Covariates?	☒	☐	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				25-26
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	24
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	22-24
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	20-22
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	26

Comments:

The coding system is provided in Annex 3

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	26-27

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	27-28
10.2 Is the choice of statistical techniques described?	☒	☐	☐	27-28
10.3 Are descriptive analyses included?	☒	☐	☐	27-28
10.4 Are stratified analyses included?	☒	☐	☐	27-28
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	27-28
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	27-28

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	28
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	27, 29
11.3 Are methods of quality assurance described?	☒	☐	☐	29
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	29
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	29

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	29-31
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	25
12.3 Does the protocol address other limitations?	☒	☐	☐	29-31

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	32

Comments:

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

Comments:

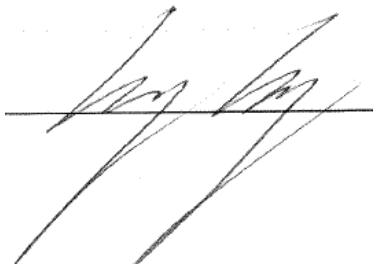
Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	34
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	34

Comments:

Name of the main author of the protocol: _Sigal Kaplan_____

Date: 21/11/2016

Signature:



ANNEX 3. ADDITIONAL INFORMATION

1. POSSIBLE INDICATION RELATED TO COC USE

A 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.[11]
The search will include the following ICD-9 diagnosis (claims or events): counseling/encounter for contraceptive management (V25), acne (Diseases of sebaceous glands -706), Premenstrual syndrome/ premenstrual dysphoric disorder (Pain and other symptoms associated with female genital organs -625), genital bleeding disorders (Disorders of menstruation and other abnormal bleeding from female genital tract – 626), Endometriosis (617).

Diagnoses related to prescribing COC

ICD-9 codes:

Contraceptive management	
V25	Counseling/encounter for contraceptive management
Menstrual cycle (ir)regularity (cycle control)	
626	Disorders of menstruation and other abnormal bleeding from female genital tract
626.4	Irregular menstrual cycle
V25.3	Menstrual extraction, Menstrual regulation
Treatment of menorrhagia	
626.2	Excessive or frequent menstruation: Heavy periods, Menometrorrhagia, Menorrhagia
Treatment of dysmenorrhea	
625.3	Dysmenorrhea, Painful menstruation
Inducing amenorrhea for lifestyle considerations	
626.0	Absence of menstruation, Amenorrhea
Treatment of premenstrual syndrome	
625.4	Premenstrual tension syndromes
Prevention of menstrual migraines	
346.4	Menstrual migraine
Decrease in risk of endometrial cancer, ovarian cancer, and colorectal cancer	
TBD	Use codes for cancers (Annex 3.5)
153	Malignant neoplasm of colon
154	Malignant neoplasm of rectum, rectosigmoid junction, and anus
Treatment of acne or hirsutism	
706	Diseases of sebaceous glands
Improved bone mineral density	

733.0	Osteoporosis

Treatment of bleeding due to leiomyomas

218.xx	Uterine leiomyoma

Treatment of pelvic pain due to endometriosis

617.0	Endometriosis of uterus
617.3	Endometriosis of pelvic peritoneum

2. VENOUS THROMBOEMBOLISM (VTE) OUTCOME DEFINITIONS

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

Venous Thromboembolism (VTE)

Place of service: outpatient or inpatient settings
Diagnosis location (inpatient setting): primary

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

ICD-9 codes:

PE	
415.1	Pulmonary embolism and infarction
DVT	
451.1	Phlebitis and thrombophlebitis of deep vessels of lower extremities
451.1x	Phlebitis and thrombophlebitis of deep vessels of lower extremities
451.2	Phlebitis and thrombophlebitis of lower extremities, unspecified
451.8	Phlebitis and thrombophlebitis of other sites
451.81	Phlebitis and thrombophlebitis of other sites, Iliac vein
451.83	Phlebitis and thrombophlebitis of other sites, of deep veins of upper extremities
451.84	Phlebitis and thrombophlebitis of other sites, of upper extremities, unspecified
451.89	Phlebitis and thrombophlebitis of other sites, other
453.0	Other venous embolism and thrombosis, Budd-Chiari syndrome
453.1	Other venous embolism and thrombosis, Thrombophlebitis migrans
453.2	Other venous embolism and thrombosis, of vena cava
453.3	Other venous embolism and thrombosis, of renal vein
453.4	Other venous embolism and thrombosis, venous embolism and thrombosis of deep vessels of lower extremity
453.8	Other venous embolism and thrombosis, of other specified veins
453.9	Other venous embolism and thrombosis, of unspecified site

ICD-10 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
PE	
I26	Pulmonary Embolism (PE)

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 thromboembolism thromboembolic events (ATEs)

Place of service: inpatient setting

Diagnosis location (inpatient setting): primary or secondary for AMI, and primary for stoke

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

ICD-9 codes:

AMI	
410.xx	Acute myocardial infarction
IS	
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432.0	Other and unspecified intracranial hemorrhage
432.9	Unspecified intracranial hemorrhage
433.x	Occlusion and stenosis of precerebral arteries
434.x	Occlusion of cerebral arteries
CVA	
436	Acute, but ill-defined, cerebrovascular disease

ICD-10 codes:

AMI	
I21	Acute myocardial infarction
Stroke	

I60	Subarachnoid hemorrhage
I61	Intracerebral hemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction

4. PREGNANCY IDENTIFICATION AND OUTCOME DEFINITIONS

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

Pregnancy identification & outcomes

Place of service: inpatient setting

ICD-9 codes:

Delivery diagnosis codes

V27.xx	Outcome of delivery
650.xx - 659.xx	Normal delivery, and other indications for care in pregnancy, labor, and delivery

Delivery procedure codes

72.xx - 74.xx	Obstetrical procedures

Delivery CPT Procedure Codes

59400-59410	Vaginal delivery, antepartum, postpartum care
59510-59515	Cesarean delivery
59610	Routine obstetric care including…vaginal delivery…
59612	Vaginal delivery only, after previous cesarean delivery
59614	Vaginal delivery only…including postpartum care
59618	Routine obstetrical care including cesarean delivery…
59620	Cesarean delivery only…
59622	Cesarean delivery, including postpartum care

Pregnancy with abortive outcome

634	Spontaneous abortion
635	Legally induced abortion
636	Illegally induced abortion
637	Unspecified abortion
638	Failed attempt abortion
639	Complications following abortion and ectopic and molar pregnancies

ICD-10 codes:

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

5. GYNECOLOGICAL CANCER DEFINITIONS

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

Gynecological cancers

ICD-9 codes:

Breast cancer

174.xx	Malignant neoplasm of female breast

Cervical cancer

180.xx	Malignant neoplasm of cervix uteri

Endometrial cancer

182.0	Corpus uteri, except isthmus, Endometrium

Ovary cancer

183.xx	Malignant neoplasm of ovary and other uterine adnexa

ICD-10 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

Annex 6. Statistical Analysis Plan

PASS Information

Title	Statistical Analysis Plan (SAP) for the Protocol: A retrospective longitudinal cohort study assessing the safety of Seasonique® use: A post-marketing authorization safety study (PASS) to assess the risk of venous thromboembolic events (VTE) in women exposed to Seasonique® SAP for Study No. DR105-WH-50015
Study identifier / Protocol number	DR105-WH-50015
Statistical Analysis Plan version:	Version: 1.3 Date: 18 June 2019 Corresponds to Protocol Version 5.2 (7 Feb 2017)
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	Seasonique NL42237
Procedure number	FR/H/0516/001
Marketing authorization holder(s)	Theramex Ireland Limited, 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin 1 D01YE64, Ireland
Joint PASS	☐ Yes ☒ No

Research question and objectives	The primary objective of this study is: • To compare incidence rates of venous thromboembolic events (VTE) in women exposed to Seasonique® with women exposed to 28-day cycle levonorgestrel-containing combined oral contraceptives (COC_{LNG})

	The secondary objectives of this study are: • To compare users of Seasonique® to users of 28-day cycle COC_{LNG} with regard to the following events of interest: arterial thromboembolism (ATE), including acute myocardial infarction (AMI) and cerebrovascular accidents (CVA), pregnancy outcomes, breast cancers and other gynaecological cancers

Countries of study	US
Number of Sites or Data Sources	1
Author	John D Seeger, PharmD, DrPH, FISPE Chief Scientific Officer, Optum Epidemiology Monica L Bertoia, MPH, PhD Sr. Epidemiologist, Optum Epidemiology 1325 Boylston Street, 10th floor, Boston, MA 02215 USA +1 (617) 530-2546

Marketing authorization holder

Marketing authorization holder(s)	Theramex Ireland Limited, 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin 1 D01YE64, Ireland
MAH contact person, Europe	Peter Kohut, PhD Arriello s.r.o. Olivova 2096/4, Prague 1, 110 00, Czech Republic peter.kohut@arriello.com +420 222 367 765

1 SAP TABLE OF CONTENTS

2 ABBREVIATIONS AND DEFINITIONS OF KEY TERMS

AE	Adverse Event
AMI	Acute Myocardial Infarction
ASO	Administrative Services Only
ATE	Arterial Thromboembolism
CHC	Combined Hormonal Contraceptive
CI	Confidence Interval
COC	Combined Oral Contraceptive
COC_{LNG}	Levonorgestrel-Containing Combined Oral Contraceptives
COPD	Chronic Obstructive Pulmonary Disease
COX	Cyclooxygenase
CMS	Centers for Medicare & Medicaid Services
CPT	Current Procedural Terminology
CVA	Cerebrovascular Accidents
DVT	Deep Venous Thromboembolism
EE	Ethinyl Estradiol
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCFA	Health Care Financing Agency
HCPCS	HCFA Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HFI	Hormone-Free Interval
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HR	Hazard Ratio
ICD-10-CM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IQR	Interquartile Range
IRB	Institutional Review Board
IS	Ischemic Stroke
ISPE	International Society for Pharmacoepidemiology
KDE	Kernel Density Estimate
LNG	Levonorgestrel

MAH	Marketing Authorization Holder
mg	Milligrams
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OC	Oral Contraceptive
ORD	Optum Research Database
PASS	Post-Authorization Safety Study
PB	Privacy Board
PE	Pulmonary Embolism
PH	Proportional Hazards
PII	Patient-Identifiable Information
PS	Propensity Score
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
US	United States
VTE	Venous Thromboembolic Events
WY	Woman-Years

Terms	Definition of terms
Naïve users	Women with first ever exposure to Seasonique® or 28-day cycle COC_{LNG} during the study period and no dispensing or evidence of use (including device implantation or removal) of any CHC prior to the index date (i.e., use first available dispensing date at index date).
New users	Women starting use of Seasonique® or 28-day cycle COC_{LNG} after a break of at least 12 weeks from any CHC prior to the index date (i.e., no dispensing of any CHC with a days' supply that covers any part of the 84-day period preceding the index date but one or more dispensings of any CHC with days' supply that ends prior to this period; or device removal more than 84 days prior to index date).
Re-starters	Women with a dispensing for Seasonique® or 28-day cycle COC_{LNG} after a break of 4-11 weeks from any COC prior to the index date (i.e., no dispensing of any COC with a days' supply that covers any part of the 27-day period preceding the index date but one or more dispensings of any COC with a days' supply that covers at least one day in the period spanning 28 to 83 days preceding the index date).
Switchers	Women starting on Seasonique® or 28-day cycle COC_{LNG} after a different CHC preparation with a break of less than four weeks (i.e., one or more dispensings of any CHC other than the index CHC with a days' supply that covers at least one day in the 27-day period preceding the index date; or device removal within the 27-day period preceding the index date).
Current exposure	*Current* exposure will include the time from the date of beginning of an episode to the last day of episode of therapy of index Seasonique® or 28-day cycle COC_{LNG} treatment course.
Recent exposure	*Recent* exposure will include the time from the end of current exposure to 30 days later (from 1 to 30 days after the end of Seasonique® or 28-day cycle COC_{LNG} treatment course).
Intermediate exposure	*Intermediate* exposure will include the time from the end of recent exposure to 30 days later (from 31 to 60 days after the end of Seasonique® or 28-day cycle COC_{LNG} treatment course).
Remote exposure	*Remote* exposure will include the time from the end of intermediate exposure (from 61 days after the end of Seasonique® or 28-day cycle COC_{LNG} treatment course) to end of follow-up.

3 RESPONSIBLE PARTIES

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4 ABSTRACT

Date and Version # of Protocol Synopsis: **28 Jul 2017, Version 1.0**

Sponsor: **Theramex**

Protocol Number ISN: DR105-WH-50015

EU PAS #: EUPAS18976 (registered May 8, 2017)

Name of Assessed Drug(s):

Seasonique®

Type of Study (refer to Global Definition STL-141):

Check One below:

☒ Mandated Study – European Medicines Agency

☐ Non-mandated Study

Check One below:

☐ Primary data collection

☒ Secondary data collection

☐ Mix of primary and secondary data collection

Check One below:

☒ Post-authorization safety study (PASS)

☐ Post-authorization efficacy study (PAES)

☐ Post-authorization study (PAS, non-PASS and non-PAES)

☐ Other

Title of Study:

Statistical Analysis Plan for Protocol DR105-WH-50015: A retrospective longitudinal cohort study assessing the safety of Seasonique® use: A post-marketing authorization safety study (PASS) to assess the risk of venous thromboembolic events (VTE) in women exposed to Seasonique®

This document has been developed to provide details of the statistical analyses that are planned for the study: A retrospective longitudinal cohort study assessing the safety of Seasonique® use: A post-marketing authorization safety study (PASS) to assess the risk of venous thromboembolic events (VTE) in women exposed to SEASONIQUE (Protocol No. DR105-WH-50015).

5 AMENDMENTS AND UPDATES

5.1 Version 1.1 Updates

- Follow-up censoring criteria: noted that cancer is a censoring event for the VTE outcome only (*Section 9.2.3 Follow-up Criteria*).
- Added references to table numbers in the text.
- Propensity score building: revised wording of overall description of application of propensity scores. Clarified that treatment episodes will be matched within each calendar block and within each exposure cohort (naïve users, new users, re-starters, switchers, *Section 9.7.4.2 Matching*).
- Pregnancy code list (Appendix): minor code updates.
- Cancer code list (Appendix): minor code updates.

5.2 Version 1.2 Updates

- Setting and study population and inclusion criteria: noted that we restricted the study population to females of 12 years or older rather than females of any age (*Section 9.2 Setting and Study Population*). The age cut-off of 12 years was empirically defined based on the distribution of observed patient age at each SEASONIQUE or 28-day cycle COC_{LNG} dispensing.
- Exclusion criteria: noted that patients with a history of any cancer (rather than a gynaecological cancer) will be excluded and examined for the primary outcome of VTE as a sensitivity analysis (*Section 9.2.2 Exclusion*).

- Follow-up censoring criteria: noted that cancer is a general censoring event for the identification of all outcomes (rather than a censoring event for VTE outcomes only, *Section 9.2.3 Follow-up Criteria*).

- Propensity score matching: noted that patients were matched within calendar block only. Patients were not matched within categories of user group (naïve users, new users, restarters, switchers, *Section 9.7.4.4 Matching*). Instead, indicators for user group and interaction terms between each user group and the 5 highest C-statistic variables were included in the propensity score models to maximize balance within user group.

- Pregnancy code list (*Appendix 16.3 Pregnancy Outcomes*): minor modifications.

- Added prenatal care code list (*Appendix 16.3 Pregnancy Outcomes*).

- General structure: moved references to sensitivity analyses to the end of each section and summarized all planned sensitivity analyses in *Section 9.7.5.5 Sensitivity Analyses*.

5.3 Version 1.3 Updates

- Contact information: updated marketing authorization holder and responsible parties.

- Censoring criteria: clarified that some censoring criteria apply to the length of the treatment episode (current exposure time) whereas other censoring criteria apply to the length of follow-up (*Section 9.3.1 Exposure*).

- Treatment episode length (*Section 9.3.1 Exposure*): clarified the calculation of treatment episode length for 28-day cycle COC_{LNG} users with continuous use (users who skip their placebo week) in the sensitivity analysis that does not censor at the second consecutive early dispensing. Clarified how the grace period is factored into the calculation of treatment episode length.

- Propensity score modelling: justified the *a priori* plan to include 20 interaction terms between the 4 users groups and 5 variables with the highest c-statistic in the propensity score models (*Section 9.7.4.1 Building the PS*).

- Added a reference to Tables 2f.1 and 2f.2 (*Section 9.3.2.2 Secondary Outcomes*).

6 MILESTONES

Table A Milestones for Development and Conduct of Study DR105-WH-50015

Milestone	Planned Periods
Start of data collection	3 months after protocol approval
End of data collection	18 months after start of data collection
Registration in the EU PAS register	Prior to data collection
Final report of study results	12 months after end of data collection

7 RATIONALE AND BACKGROUND

SEASONIQUE is a 91-day extended combined oral contraceptive (COC), containing a fixed-dose combination of 0.15 mg levonorgestrel (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 doses of this COC, (0.15 mg LNG and 0.03 mg EE) are already used in other COCs authorized in Europe. The standard 28-day cyclic regimen, consists of 21 days of active combination pills followed by 7 pill-free days or 7 days of placebo pills. This was designed to induce withdrawal bleeding once every 28 days (13 times per year), imitating the normal menstrual cycle, as it was presumed that regular withdrawal bleeding was essential to the acceptance of oral contraceptives (OCs) by women. 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 extended-regimen of SEASONIQUE is designed to eliminate the withdrawal bleeding that regularly occurs with conventional COCs once every 28 days. This extended COC may improve compliance and reduce the risk of unwanted pregnancies by providing continuity and decreasing scheduled withdrawal bleeding to four episodes per year. The first extended-regimen COC, Seasonale, was approved in the United States (US) in 2003 and in Canada in 2007. Seasonale is a 91-day extended-regimen contraceptive with 84 days of active combination tablets (0.15 mg LNG and 0.03 mg EE) and 7 placebo tablets. SEASONIQUE was developed as a successor to Seasonale and approved in the US in 2006 and in Canada in 2010. In Europe, the first extended-regimen OC was authorized in 2012 (Yvidually, which contains drospirenone and ethinylestradiol, and intended to be taken up to 120 days continuously).

Evidence suggests that oral COCs containing a low dose of EE and a second generation progestin (conventional 28-day cycle regimen) are associated with venous thromboembolism (VTE) with an incidence rate of 20 cases per 100,000 women/year. However, the incidence of VTE with levonorgestrel-EE containing COCs might be higher based on epidemiological

data (EMA Assessment Report 2014). During the clinical development of SEASONIQUE, few adverse events (AEs) of medical relevance were reported; one case of deep vein thrombosis (DVT) and one case of an arterial thrombotic event were reported among the non-SEASONIQUE treatment group. In addition, sex-hormone-related malignancies were also examined. One case of ovarian cancer was reported in the patient randomized to non-SEASONIQUE treatment group one year after the first dose of treatment. From the data submitted, there were no cases of breast cancer or hepatocarcinoma reported with SEASONIQUE use during the clinical program.

Given the limited number of women treated with SEASONIQUE in the clinical program and the limited patient length of exposure (one year for the pivotal study and 4 years for the extension study but with a very small size population), the safety profile of this extended-cycle contraceptive regimen, regarding the risk of VTEs and long term use of SEASONIQUE is not entirely elucidated. It is expected that the risk of VTE and other cardiovascular outcomes will not differ between SEASONIQUE and the standard 28-day cyclic regimen with combined LNG/EE. In the context of the regulatory submission for market authorization of SEASONIQUE in Europe, the European Medicines Agency (EMA) has requested that a post-authorization safety study (PASS) be conducted to assess the cardiovascular risk associated with SEASONIQUE during standard clinical practice.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of this study is to compare the incidence rates of VTE in women exposed to SEASONIQUE with women exposed to 28-day cycle levonorgestrel-containing combined oral contraceptives (COC_{LNG}).

8.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to compare users of SEASONIQUE to users of 28-day cycle COC_{LNG} with regard to the following events of interest:

- Arterial thromboembolism (ATE), including acute myocardial infarction (AMI) and cerebrovascular accidents (CVA)
- Pregnancy outcomes
- Breast cancers and other gynaecological cancers

9 RESEARCH METHODS

9.1 Study Design

This is a comparative, retrospective cohort study comparing women exposed to SEASONIQUE with women exposed to 28-day cycle COC_{LNG}.

9.1.1 Comparative Groups

The exposure group of interest will comprise SEASONIQUE and its generic equivalents (i.e., 91-day extended COC products, containing a fixed-dose combination of 0.15 mg LNG and 0.03 mg EE, to be taken without interruption for 84 days followed by 0.01 mg EE tablets for 7 days). The comparator of interest will be 28-day cycle LNG-containing COC products. LoSeasonique® (91-day extended COC products, containing a fixed-dose combination of 0.1 mg LNG and 0.02 mg EE, to be taken without interruption for 84 days followed by 0.01 mg EE tablets for 7 days) and its generics and Seasonale® (91-day extended COC products, containing a fixed-dose combination of 0.15 mg LNG and 0.03 mg EE, to be taken without interruption for 84 days followed by placebo tablets for 7 days) and its generics will be excluded from both the exposure and comparator groups.

9.2 Setting and Study Population

The study population will be identified from the Optum Research Database (ORD), a US automated healthcare claims database. The ORD collects information submitted for reimbursement by various healthcare providers such as physicians, pharmacies, and hospitals in real-life settings and comprises a large number of patients. It is therefore suitable for investigating relatively rare outcomes in routine clinical practice settings.

The study population will consist of females age 12 years or older who use SEASONIQUE or a 28-day cycle COC_{LNG} between 01 January 2006 and 30 June 2017. The age cutoff of 12 years was empirically defined based on the distribution of observed patient age at each SEASONIQUE or 28-day cycle COC_{LNG} dispensing. Four exposure cohorts will be created in which women will be categorized based on exposure to CHCs prior to index date as a naïve user, new user, re-starter, or switcher. This categorization aims to reduce misclassification of new users that could potentially occur when comparing a new treatment with an established one. In addition, it is important to differentiate between these groups as they may have different VTE risk.[1] The four exposure cohorts are described below in *Section 9.3.1. Exposure*. For each cohort, the index date will be defined as the date of the SEASONIQUE or 28-day cycle COC_{LNG} dispensing that qualifies a woman for a given exposure cohort.

A minimum of 12 months of continuous enrollment in the health plan before the index date will be required to obtain information about the relevant medical history before drug exposure start. The minimum 12-month eligibility requirement increases the length of time available to observe baseline covariates (increasing validity), but decreases the number of

eligible patients (reducing precision). Therefore, in a sensitivity analysis, the relative rates for the primary outcome of VTE will be examined among qualifying patients with a minimum of 6 months continuous health plan enrollment before the index date.

9.2.1 Inclusion

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

- Have a record of at least one prescription dispensed for SEASONIQUE or 28-day cycle COC_{LNG} during the study period
- At least 12 months of continuous health plan enrollment prior to first SEASONIQUE or 28-day cycle COC_{LNG} prescription
- 12 years of age or older at dispensing of SEAONIQUE or 28-day cycle COC_{LNG}
- Note that for the analysis of pregnancy outcomes, we will restrict to a maximum patient age of 45 years

9.2.2 Exclusion

Patients will be excluded from the study if they have claims for any of the following:

- One or more codes for breast cancer, cervical cancer, endometrial cancer, or ovary cancer using codes (3-digit level) listed in *Section 16.4 Breast Cancers and Other Gynaecological Cancers* within 12 months before and including the index date . Note that as a sensitivity analysis, patients with a history of any cancer will be excluded and examined for the primary outcome of VTE. Since the majority of cohort patients are young and healthy, and those with a history of gynaecological cancers or receipt of chemotherapy are already excluded, this additional exclusion of the history of any cancer is expected to be applicable to few patients.
- Chemotherapy within 12 months before and including the index date.
- Pregnancy within 3 months before and including the index date defined as a pregnancy period that overlaps one or more days with the period 90 days before and including the index date, based on the pregnancy outcome definition described below. Note that the delivery or termination may occur either (1) during the 90 days before and including the index date, **or** (2) after the index date as long as the start of the pregnancy period is before the index date (less likely to occur because very commonly a CHC is started during the first days of the cycle meaning that the pregnancy diagnosis has been ruled-out). Pregnancies that conclude after the index date (in the future) as noted above will be flagged and enumerated.
- Previous major surgery (including lower limb orthopaedic surgery), major lower extremity or pelvic trauma within 3 months before and including the index date.

9.2.3 Follow-up Criteria

Follow-up of eligible patient treatment episodes will start on the day after the index dispensing for SEASONIQUE or 28-day cycle COC_{LNG}. Patients may experience multiple types of study outcomes (e.g., VTE and breast cancer); follow-up will be examined independently for each study outcome. Within each patient treatment episode, follow-up for each study outcome will end at the earliest of the following dates:

- Study outcome (see *Section 9.3.2. Outcomes*)
- End of the study period
- End of enrollment in the health plan (last date of continuous membership)
- Death
- Cancer diagnosis (see Appendix for ICD-9 and ICD-10 codes; censoring for cancer diagnosis will require at least two ICD codes that are identical at the 3-digit level and that occur at least 7 days but no more than 90 days apart [from any setting, in any position]) or chemotherapy
- Start of a new SEASONIQUE or 28-day cycle COC_{LNG} treatment episode

For each patient, follow-up for a study outcome (e.g., VTE) in all subsequent treatment episodes will be censored after the earliest qualifying outcome (e.g., VTE) date.

Note: The study protocol originally noted the following:

"Other conditions known to substantially modify the VTE risk occurring during the follow-up will be examined. Patients with these conditions, including surgery/injury, and pregnancy, will not be censored. While these events are risk factors for VTE, they may occur after the index date and thus are in the causal pathway. Therefore, these conditions will be addressed in the analysis using technique such as stratification."

Since surgery/injury are not likely to be in the causal pathway because they are not likely to be affected by contraceptive use, we will perform a stratified analysis as described below in the *Section 9.7.5 Analysis of Outcomes*. In addition, when following up for the VTE outcome, we will not explicitly censor for pregnancy but flag these women and stratify follow-up by pregnancy status.

9.3 Variables

9.3.1 Exposure

Exposure will be defined as a recorded dispensing of SEASONIQUE or 28-day cycle COC_{LNG}. Exposed women in each cohort will be categorized based on their exposure to CHC (CHCs will be defined as all combined estrogen and progestin contraceptives, including levonorgestrel plus ethinyl estradiol-containing emergency contraceptives as women exposed to these products cannot be considered CHC-naïve; CHCs will exclude postmenopausal hormone products) prior to the index date as follows: naïve users (starting OC for the first time), new users, re-starters and switchers. The following definitions will be used for

exposure categorization:[2]

- **Naïve users (starting use)** are defined as women with first ever exposure to SEASONIQUE or 28-day cycle COC_{LNG} during the study period and no dispensing or evidence of use (including device implantation or removal) of any CHC prior to the index date (i.e., use first available dispensing date at index date).
- **New users** are defined as women starting use of SEASONIQUE or 28-day cycle COC_{LNG} after a break of at least 12 weeks from any CHC prior to the index date (i.e., no dispensing of any CHC with a days' supply that covers any part of the 84-day period preceding the index date but one or more dispensings of any CHC with days' supply that ends prior to this period; or device removal more than 84 days prior to index date).
- **Re-starters** are defined as women with a dispensing for SEASONIQUE or 28-day cycle COC_{LNG} after a break of 4-11 weeks from any COC prior to the index date (i.e., no dispensing of any COC (defined as the subset of CHCs in oral dosage forms) with a days' supply that covers any part of the 27-day period preceding the index date but one or more dispensings of any COC with a days' supply that covers at least one day in the period spanning 28 to 83 days preceding the index date). Note: patients can be re-starting the same COC or a different COC to be considered a re-starter.
- **Switchers** are defined as women starting one SEASONIQUE or 28-day cycle COC_{LNG} after a different CHC preparation with a break of less than four weeks (i.e., one or more dispensings of any CHC other than the index CHC with a days' supply that covers at least one day in the 27-day period preceding the index date; or device removal within the 27-day period preceding the index date).

The primary analysis will combine the naïve user and new user groups. Separate analyses will be performed for each of the four exposure groups.

The duration of use will be determined based on all filled prescriptions during the observation period. Episodes of SEASONIQUE or 28-day cycle COC_{LNG} treatment will be constructed using the number of days' supply from the drug dispensing claims. An episode of therapy will be defined as a period of continuous usage of one or a series of prescriptions for SEASONIQUE or 28-day cycle COC_{LNG} for the same patient. The first episode of therapy will begin on the index date and continue through the number of days of supply of the prescription (91 days for SEASONIQUE and 28 days for 28-day cycle COC_{LNG}), plus 30 days for SEASONIQUE and 14 days for 28-day cycle COC_{LNG}. If a subsequent prescription fill is recorded within 30 days (for SEASONIQUE) or 14 days (for 28-day cycle COC_{LNG}) 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. The treatment period will include any gaps between dispensings that are within the grace period. These gaps allow for some variability in fill date.[3,4]

If the gap between adjacent prescriptions is longer than 30 days for SEASONIQUE (or 14 days for 28-day cycle COC_{LNG}), then the episode ends on the last day of the days of supply of the previous prescription, plus 30 (or 14) days. Including a 30 (or 14) day grace period between prescriptions better reflects the true exposure period, as some patients may be

delayed in refilling their prescriptions. The consecutive prescription (if any) will be considered as the start of a new episode of exposure rather than as a continuation of the previous one, according to the definitions above. Exposure time will be reset to zero for every new episode. The exposure episodes in those patients will be identified sequentially and every episode will have a separate record in the analytic dataset. Patients can contribute to several exposure episodes, but if women have more than one type of outcome (i.e., two VTE events), only the first will contribute to the analysis of that particular outcome. Estimation of exposure as treated enables a more realistic time-to-event analysis especially with potential of drug switching of the studied group of drugs.

In both groups, the treatment episode will end if a woman receives a prescription for any OC other than the index drug. Note that this affects the length of current treatment; it is not follow-up censoring criteria. The treatment episode end date will be defined as the date of dispensing of the new OC. If the new OC is a study drug (i.e., SEASONIQUE or 28-day cycle COC_{LNG}), then a new episode will begin as per the "switchers" definition above.

To reduce misclassification, periods of exposure to the drug of interest will be identified to account for any remaining physiological effects of COCs on cardiovascular risk (i.e., increased coagulability) and classified as follows:

- **Current exposure**: from the date of beginning of episode to the last day of episode of therapy of index SEASONIQUE or 28-day cycle COC_{LNG} treatment course or first day of exposure to another CHC
- **Recent exposure**: from the end of current exposure to 30 days later (from one to 30 days after the end of SEASONIQUE or 28-day cycle COC_{LNG} treatment course)
- **Intermediate exposure**: from the end of recent exposure to 30 days later (from 31 to 60 days after the end of SEASONIQUE or 28-day cycle COC_{LNG} treatment course)
- **Remote exposure**: from the end of intermediate exposure (from 61 days after the end of SEASONIQUE or 28-day cycle COC_{LNG} treatment course) to end of follow-up

In the event that the amount of person-time and numbers of events in the recent and intermediate exposure groups are too small to be presented separately, we will consider combining them into a single recent/intermediate exposure category.

Patterns of drug use will be explored in both groups to examine the possibility that some women in the 28-day cycle COC_{LNG} group might receive continuous hormonal exposure by consuming the 21 days of active pills and immediately starting a subsequent prescription fill without the 7-day hormone-free interval. In particular, women with overlapping prescriptions will be identified as those with two or more consecutive dispensings that occur at least 7 days prior to the end of the days' supply of the prior dispensing. Follow-up and contribution of person-time for these women will be censored on the date of the second consecutive dispensing that is at least 7 days early. These women will not be removed from the analysis.

Sensitivity Analyses Relating to Exposure

A sensitivity analysis that extends the gap length to 60 days for SEASONIQUE users and 28 days for 28-day cycle COC_{LNG} users will be performed (Tables 3f.1, 5b, 6b, 7b).

In a second sensitivity analysis, women in the 28-day cycle COC_{LNG} group identified as skipping their placebo weeks will not be censored at the second consecutive early dispensing. Instead, the start date of each refill will be modified to correspond to the day after the end of the days' supply of the preceding prescription (Tables 3f.2, 5b, 6b, 7b). In this analysis, all subsequent prescription refills (including dispensings with overlapping days' supply) will count toward the days on treatment. This process will be repeated until the end of the treatment episode.

9.3.2 Outcomes

Since the study period spans 01 October 2015, the date on which the US converted from ICD-9 to ICD-10, both ICD-9 (prior to 01 October 2015) and ICD-10 (starting on 01 October 2015) codes will be used to define outcomes.

9.3.2.1 Primary Outcomes

The primary outcome is VTE, defined as pulmonary embolism (PE) and/or deep venous thrombosis (DVT) (Tables 3a – 3g, 4).

PE will be defined as an inpatient diagnosis (including emergency departments) of PE (at least one of the corresponding ICD-9 or ICD-10 codes in the Appendix in the primary position).

DVT will be defined as (1) a DVT diagnosis (at least one of the corresponding ICD-9 or ICD-10 codes in the Appendix in the primary position) in an inpatient setting, including emergency departments; or (2) a DVT diagnosis (at least one of the corresponding ICD-9 or ICD-10 codes in the Appendix) in an outpatient setting in conjunction with a prescription for an anticoagulant (low molecular weight heparins [i.e., enoxaparin, dalteparin, tinzaparin], apixaban, argatroban, bivalirudin, dabigatran, desirudin, drotrecogin alfa, danaparoid, edoxaban, fondaparinux, lepirudin, rivaroxaban, warfarin) or alteplase during the 30-day period following the date of DVT diagnosis. Note that heparin is excluded from a DVT outpatient diagnosis because it is only administered in an inpatient setting.

In addition, the dispensing of an anticoagulant that is not associated with an outcome as defined above (i.e., not within the 30-day period following the date of first inpatient or outpatient DVT diagnosis or date of first inpatient PE diagnosis in the primary position) will be captured. Women with these dispensings will be considered for medical record review. As it is unlikely for a woman of child-bearing age to receive an anticoagulant for conditions other than VTE, this will help ensure the sensitivity of the primary outcome definitions.

Medical chart validation studies will be performed for a sample of VTE cases (Table 4). Based on previous claims database studies,[2,6] potential misclassification of the VTE may occur as a result of high level of unconfirmed diagnoses. Thus, as part of the study, a separate validation of the diagnosis of VTE in medical records will be conducted in both inpatient and outpatient settings.

For the subset of the patient populations identified as non-administrative services only (non-ASO), Optum will attempt to obtain medical records to confirm the study outcomes. In this subset, Optum will work with an outside clinical consultant to perform a detailed review of

the chronological listing of relevant claims (i.e., clinical profile) for each of the potential cases in order to determine the medical site most likely to yield medical records with the necessary information to confirm case status or case non-status.

Optum will develop an abstraction checklist of medical record elements to be obtained for review and an adjudication form to be used by the clinical consultant to confirm the case status and date of VTE diagnosis. We anticipate requesting charts for all SEASONIQUE and 28-day cycle COC_{LNG} patients who have at least one administrative claim suggesting the occurrence of a VTE outcome. We will request up to 110 charts and abstract up to 110 charts, with options to exceed these numbers, if necessary. Optum has historically been able to successfully obtain medical record abstractions on approximately 70-85 percent of those requested. We have assumed that the application of the selection and matching criteria in the protocol will result in a cohort of approximately 12,000 SEASONIQUE users, and further assumed that the average follow-up for these 12,000 women will be one year so that the 12,000 women provide 12,000 woman-years of follow-up. At an expected VTE incidence of 6/10,000, we expect 8 confirmed VTE events. However, in order to arrive at the 8 confirmed events, we expect to review twice as many medical records in order to rule out the false positive cases, so this means 16 medical record reviews among the SEASONIQUE users. With 4:1 matching, there will be 4 times as many women in the 28-day cycle COC_{LNG} cohort (48,000 women) and we assumed the same average follow-up of one year (48,000 woman-years). If the same rate of VTE is observed in the 28-day cycle COC_{LNG} cohort, we will need to review 64 (4*16) medical records to arrive at the 32 confirmed outcomes in the 28-day cycle COC_{LNG} group. Thus, a total of 80 (16+64) medical record reviews will lead to 40 (8+32) confirmed VTE events. We had originally anticipated conducting medical record review for the ATE events, and had assumed an incidence rate for ATE of 2/10,000 (one-third of the VTE rate), which will translate into 27 medical records, and this was rounded to 30. Adding 80 and 30 results in 110 medical record reviews expected. Since medical record review will be performed only for VTE, these 30 reviews will be used for those women who receive an anticoagulant prescription during follow-up but do not meet the primary VTE case definition (i.e., do not have one of the PE or DVT diagnosis codes) (Table 4).

Sensitivity Analyses Relating to Primary Outcomes

As a sensitivity analysis, we will use the following algorithms for PE and DVT to define VTE (Tables 3a – 3f.7):[5]

PE will be defined as an inpatient diagnosis (including emergency departments) of PE (at least one of the corresponding ICD-9 or ICD-10 codes in the Appendix in the primary position) in conjunction with a first prescription of anticoagulant (including heparin) during the 30-day period following the date of PE diagnosis.

DVT will be defined as a DVT diagnosis (at least one of the corresponding ICD-9 or ICD-10 codes in the Appendix in any position) in either outpatient or inpatient settings, in conjunction with a first prescription for an anticoagulant (including heparin) during the 30-day period following the date of PE diagnosis.

9.3.2.2 Secondary Outcomes

The secondary outcomes are arterial thromboembolic events (ATEs), pregnancy outcomes (fertility and delayed pregnancy detection), and breast cancers and other gynaecological cancers.

ATEs

ATEs, which will be defined as acute myocardial infarction (AMI), ischemic stroke (IS) or cerebrovascular accidents (CVA), will be identified based on inpatient codes only (Tables 3a – 3f.7). Patients will be defined as having an ATE outcome if they have at least one of the corresponding ICD-9 or ICD-10 diagnosis codes in the Appendix on an inpatient claim. Codes for stroke (i.e., IS and CVA) must be in the primary position; codes for AMI can be in any position.

Pregnancy outcomes

Pregnancy outcomes will be assessed in the subset of patients with a maximum age of 45 years.

- *Periods of Pregnancy*

Periods of pregnancy will be determined by first identifying pregnancy outcomes from claims with codes for pregnancy terminations and deliveries. For each delivery, a period of pregnancy will be estimated as 270 days prior to the date of delivery. For each abortion, a period of pregnancy will be estimated as 120 days prior to the date of abortion. Delivery will be defined as any of the corresponding diagnosis or procedure codes in the Appendix for delivery in any position on an inpatient claim. Pregnancy with an abortive outcome will be defined as one of the corresponding diagnosis or procedure codes in the Appendix for abortive outcome in any position of an either inpatient or outpatient claims.

Note: The protocol indicates only inpatient codes for identifying pregnancy with an abortive outcome. However, Hornbrook et al evaluated a complex algorithm of outpatient codes for identifying pregnancy episodes and found high PPVs (96% for therapeutic abortion and 93% for spontaneous abortion).[7] Based on this validation study, abortive outcomes in any position of an either inpatient or outpatient setting are included.

- *Fertility*

Fertility will be assessed among women who stop taking SEASONIQUE or 28-day cycle COC_{LNG} and do not switch to any other contraceptive (Tables 5a – 5c). Women will contribute person-time following discontinuation of SEASONIQUE or 28-day cycle COC_{LNG} until they either become pregnant or resume contraception as evidenced by a new prescription dispensation or device implantation. The codes specified for delivery and pregnancy with abortive outcome will be used to define pregnancy. The fertility rate, which will be calculated separately for SEASONIQUE and 28-day cycle COC_{LNG} groups, will be estimated as the number of births per 1,000 person-years. Because the women who contribute to the analysis of the fertility outcome are a subgroup of the primary analysis cohort (i.e., those who stop SEASONIQUE or 28-day cycle COC_{LNG} and do not switch to any other contraceptive; those who switch will not be included in this analysis), we will

assess covariate balance between the two groups (i.e., those who stop SEASONIQUE and those who stop 28-day cycle COC_{LNG}) (Tables 2f.1 and 2f.2) as described below and adjust for individual variables that show imbalance in this subgroup by including them in the outcome regression models.

- *Delayed pregnancy detection*

For all pregnancy outcomes (both deliveries and terminations), delayed pregnancy detection will be assessed for the current exposure analysis as follows. First, the start of the pregnancy period will be estimated as described above in the periods of pregnancy section. The first encounter for prenatal care following the estimated start of the pregnancy period will be identified. The time between the estimated start of the pregnancy period and the first encounter for prenatal care will be measured. The mean (SD) and median (IQR) time between these two dates will be compared between SEASONIQUE and 28-day cycle COC_{LNG} groups using t-tests and Wilcoxon rank sum tests, respectively (Tables 6a – 6c).

Second, the time between estimated start of the pregnancy period and the estimated end date of SEASONIQUE or 28-day cycle COC_{LNG} exposure will be estimated for the current exposure analysis (Table 7a – 7c). The mean (SD) and median (IQR) time between these two dates will be compared between SEASONIQUE and 28-day cycle COC_{LNG} groups using t-tests and Wilcoxon rank sum tests, respectively. Because the days' supply of SEASONIQUE (i.e., 91 days) is larger than that for the 28-day cycle COC_{LNG}, we will conduct a sensitivity analysis restricting this analysis to only those pregnancies with estimated start dates that occur within the last 28 days of supply of a prescription (Table 7b).

Breast cancers and other gynaecological cancers

Breast, cervical, endometrial, and ovarian cancers will be identified (Tables 3a – 3f.7) using the corresponding ICD-9-CM or ICD-10-CM diagnosis codes in the Appendix, requiring at least two ICD codes that are identical at the 3-digit level and that occur at least 7 days but no more than 90 days apart (from any setting, in any position).

9.3.3 Covariates

We will account for potential differences in outcome risk between users of SEASONIQUE and the 28-day cycle COC_{LNG} through evaluation and adjustment for a broad range of baseline characteristics. The list of pre-specified covariates is summarized in Table B. These covariates will be included in the propensity score (PS) model, as described below. In summary, users of SEASONIQUE and the 28-day cycle COC_{LNG} will be matched by PS to produce balance between treatment groups on all variables that go into the PS model. We will evaluate balance on each covariate before and after matching. If any imbalances in covariates remain after matching, these covariates will be included in the Cox model. In addition to the pre-defined covariates, empirically-identified variables will also be considered by comparing the frequency of most commonly occurring diagnosis, procedure, and drug codes between SEASONIQUE and the 28-day cycle COC_{LNG} exposure cohorts.

Because follow-up does not begin until the day after the index date, in the unlikely event that a patient has an event on the index day, that event will be considered part of the covariate baseline data and will not be counted as an outcome associated with that dispensing.

Table B Pre-specified Covariates for Inclusion into the PS Models (Forced Entry Variables)

Variable(s)	Details	Assessment period
Age (continuous), in years	(index date – date of birth) / 365.25	Defined at each index date
Age (categorical), in years	12 to <15; ≥15 to ≤35; >35 to ≤50; >50	Defined at each index date
US geographic region	Northeast, South/Southeast, Midwest, West	Defined at each index date
Calendar month of index date	1-12	Defined at each index date
Cardiac dysrhythmias	0= No 1=Yes	past 12 months, including index date
Cerebral vascular or coronary artery disease	0= No 1=Yes	past 12 months, including index date
Coagulation defects	0= No 1=Yes	past 12 months, including index date
COPD*	0= No 1=Yes	past 12 months, including index date
Diabetes mellitus Type 1	0= No 1=Yes	past 12 months, including index date
Diabetes mellitus Type 2 (including gestational)	0= No 1=Yes	past 12 months, including index date
Hyperlipidemia	0= No 1=Yes	past 12 months, including index date
Hypertension (ICD-9 and ICD-10 diagnosis codes)	0= No 1=Yes	past 12 months, including index date
Overweight and obesity (ICD-9 and ICD-10 diagnosis codes)	0= No 1=Yes	past 12 months, including index date
Pregnancy (3 - 12 months before index date)	0= No 1=Yes	a pregnancy period that overlaps with the period between 90 and 365 days before index date based on the pregnancy outcome definition described above
Prior VTE (including PE and DVT)	0= No 1=Yes	past 12 months, including index date
Prior ATE (including AMI and ischemic stroke)	0= No 1=Yes	past 12 months, including index date

Variable(s)	Details	Assessment period
Tobacco use (smoking-related diagnoses, smoking cessation medications, procedures)	0= No 1=Yes	past 12 months, including index date
Unstable angina	0= No 1=Yes	past 12 months, including index date
Vascular disease, including peripheral vascular disease and varicose veins of lower extremity	0= No 1=Yes	past 12 months, including index date
Combined Charlson-Elixhauser comorbidity score	continuous	assessed over past 12 months, including index date
Anovulation	0= No 1=Yes	past 12 months, including index date
Asthma	0= No 1=Yes	past 12 months, including index date
Dysmenorrhea	0= No 1=Yes	past 12 months, including index date
Epilepsy	0= No 1=Yes	past 12 months, including index date
Gynaecological disorders, including endometriosis; disorders of menstruation; inflammatory disease of the cervix, vagina, vulva, ovary, pelvic and peritoneum; and uterine leiomyoma	0= No 1=Yes	past 12 months, including index date
Hepatitis C	0= No 1=Yes	past 12 months, including index date
History of abortion	0= No 1=Yes	one or more pregnancy terminations in the 90 to 365 days before the index date
HIV/AIDS	0= No 1=Yes	past 12 months, including index date
Liver failure	0= No 1=Yes	past 12 months, including index date
Migraine	0= No 1=Yes	past 12 months, including index date
Polycystic ovary syndrome	0= No 1=Yes	past 12 months, including index date
Renal failure	0= No 1=Yes	past 12 months, including index date
Thyroid disorder	0= No 1=Yes	past 12 months, including index date
Prior use of other forms of contraception, including intrauterine devices, patches, and depot injections	0= No 1=Yes	past 12 months, including index date
Prior time on CHCs (except for naïve users)	Categorical: 1-90 days; 91-180 days; 181-270 days; 271-365 days	past 12 months, excluding index date
Number of prior CHCs (unique dispensings, except for naïve users)	Categorical: 0, 1, ≥2	past 12 months, excluding index date

Variable(s)	Details	Assessment period
Anticoagulants	0= No 1=Yes	past 12 months, including index date
Angiotensin converting enzyme inhibitors/angiotensin II receptor blockers	0= No 1=Yes	past 12 months, including index date
Benzodiazepines	0= No 1=Yes	past 12 months, including index date
Beta-blockers	0= No 1=Yes	past 12 months, including index date
Calcium channel blockers	0= No 1=Yes	past 12 months, including index date
COX-2 inhibitors	0= No 1=Yes	past 12 months, including index date
Diabetes medications	0= No 1=Yes	past 12 months, including index date
NSAIDs other than COX-2 inhibitors	0= No 1=Yes	past 12 months, including index date
Spironolactone	0= No 1=Yes	past 12 months, including index date
Selective serotonin reuptake inhibitors/tricyclic antidepressants**	0= No 1=Yes	past 12 months, including index date
Statin/fibrate	0= No 1=Yes	past 12 months, including index date
Number of outpatient visits	Categorical: 0, 1-2, ≥3	past 12 months, including index date
Number of emergency room visits	Categorical: 0, 1, ≥2	past 12 months, including index date
Number of hospitalizations	Categorical: 0, 1, ≥2	past 12 months, including index date

* COPD is rare in young women of reproductive age. However, it may serve as a proxy for smoking since this measure may not be captured adequately in the database.

**Includes SSRIs, SNRIs, tetracyclics, and tricyclics

Descriptive statistics will be examined for all covariates. Continuous variables will be categorized, either into pre-defined categories or based on quantiles as appropriate for the distribution of each variable.

Empirically-defined covariates

Additional baseline covariates will be defined based on the most frequently occurring diagnoses, procedures, and medications using data in the 12 months prior to, and including, the index date. Healthcare utilization variables such as number of drugs dispensed and number of 3-digit ICD diagnoses will be considered as well. These empirically-defined covariates will provide some degree of protection against unaddressed confounding by expanding the covariates beyond those that can be identified in advance. Because data for each calendar time block will be modelled separately, the list of most frequently occurring variables may vary across time. This approach will address the fact that the list of the most

frequently occurring variables may change over time and particularly during the transition period between ICD-9 and ICD-10. The 100 most frequently observed baseline diagnoses will be derived using individual codes (i.e., ICD-9 codes at the 3-digit level) with the exception of the last calendar block which includes ICD-9 and ICD-10 codes, where the 200 most frequently observed baseline diagnoses will be identified. Similarly, the 100/200 most frequently observed procedures will be identified. The 100/200 most frequently observed medications will be identified at the therapeutic class level.

9.4 Data Sources

This study will use the Optum Research Database (ORD), formerly the Optum Life Sciences Research Database, which contains health insurance claims and enrollment data dating back to 1993. The database includes data from over 59.5 million individuals with pharmacy and medical benefits; an additional 40.5 million enrollees with medical benefits only are available. On average, individuals are enrolled in the health plan for 2.6 years. For 2015, data relating to approximately 13.5 million individuals with both medical and pharmacy benefit coverage are available. An additional 11.5 million enrollees with medical benefits only are available. Underlying information is geographically diverse across the US and fairly representative of the US population. Of the 13.5 million individuals, race/ethnicity, and financial resource information was available for approximately 75% of the individuals. The data undergo regular audits and quality control procedures by the insurer and are updated monthly. The insured population from which the data are drawn is geographically diverse across the US and comprises approximately 3 to 4% of the US population.

Optum research activities utilize de-identified data from the ORD. For a subset of patients in the ORD with administrative approval from the health plan, patient-identifiable information (PII) will be accessed for medical chart review. Access of PII is only done following approval of the study protocol by an appropriate institutional review board and privacy board. All data access conforms to applicable Health Insurance Portability and Accountability Act (HIPAA) policies.

Accessible information from the ORD includes demographics, pharmacy use, and medical and facility claims, which provide data on services, procedures, and their accompanying diagnoses.

The coding of medical claims conforms to insurance industry standards including:

- Use of designated claims forms (i.e., physicians use the Health Care Financing Agency (HCFA)-1500 format and hospitals use the UB-92/UB-04 format)
- International Classification of Diseases, Ninth Edition (ICD-9) diagnosis codes and procedure codes
- International Classification of Diseases, Tenth Edition (ICD-10) diagnosis codes and procedure codes
- Current Procedural Terminology (CPT) codes
- HCFA Common Procedure Coding System (HCPCS) codes

- Cost information
- De-identified patient and provider codes

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The claims history is a profile of outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications.

Medical claims or encounter data are collected from various health care sites (inpatient hospital, outpatient hospital, ER, physician's office, surgery center, etc.) for virtually all types of provided services, including specialty, preventive and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers, i.e., physicians, use the HCFA-1500 or CMS-1500 formats. Claims for facility services submitted by institutions, i.e., hospitals, use the UB-82, UB-92, UB-04, or CMS-1450 formats. Medical claims include: multiple diagnosis codes recorded with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes prior to October 2015 and recorded with the 10th Revision (ICD-10) since October 2015; procedures recorded with ICD-9-CM procedure codes prior to October 2015 (or with ICD-10 since October 2015), (prior to October 2015) or ICD-10 codes (since October 2015), Current Procedural Terminology (CPT), or Healthcare Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include medications dispensed in hospital.

Pharmacy claims are typically added to the research database within six weeks of dispensing. Approximately six months following the delivery of services are required for complete medical data.

9.5 Study Size

The number of women to be included in the study will be determined at the start of data collection based on the specified inclusion/exclusion criteria, but certain assumptions are provided in *Section 9.7.1. General Considerations.*

9.6 Data Management

The study will use an existing health care claims database with anonymized information on the individual patients. In addition, patients' medical records will be extracted. Data extraction and analysis will be performed according to the standard practices of the data vendors. Datasets extracted from the database will be stored to allow future analysis, if needed. Data management and analysis will be performed in SAS software (SAS Institute, Inc. Cary, North Carolina). Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs.

9.7 Data Analysis

9.7.1 General Considerations

We have assumed that the application of the selection and matching criteria in the protocol will result in a cohort of approximately 12,000 SEASONIQUE users, and further assumed that the average follow-up for these 12,000 women will be one year so that the 12,000 women provide 12,000 woman-years (WY) of follow-up. We anticipate matching up to 4 women in the comparison cohort to each SEASONIQUE user, so there will be 4 times as many women in the comparison cohort (48,000 women), among whom we assumed the same average follow-up of one year (48,000 WY). The final number of women and WY to be included in the study will be determined at the start of data collection based on the specified inclusion/exclusion criteria.

9.7.2 Handling of Missing Data

Missing values for the variables will be reported as missing and no imputation will be conducted (for example, geographic region, days' supply). Patients will be assumed not to have a covariate if there is no evidence for its presence (i.e., values for confounder variables will not be considered missing). For example, if a patient does not have a code for diabetes, we will assume that the patient does not have diabetes.

9.7.3 Descriptive Analysis

Descriptive statistics will be assessed for baseline characteristics of SEASONIQUE and 28-day cycle COC_{LNG} users separately for the four exposure cohorts of interest (i.e., naïve users, new users, re-starters and switchers), as well as for the combined group of naïve users and new users, on which the primary analysis will be performed (Tables 2a – 2e). Characteristics among the subset who stop SEASONIQUE or 28-day cycle COC_{LNG} will also be described (Tables 2f.1 and 2f.2). Differences between groups (SEASONIQUE and 28-day cycle COC_{LNG}) will be evaluated using proportions for categorical variables and means (SD) and medians (IQR) for continuous variables, along with standardized differences. Summaries will include information on days from index date until end of follow-up, and distributions of censoring reasons (Table 1).

9.7.4 PS Matching

9.7.4.1 Building the PS

Even though the study begins at a natural point (the start of SEASONIQUE availability), the study timeframe is arbitrary as are any divisions of it. The purpose of the PS is to address differential selection of women to SEASONIQUE relative to other oral contraceptives, and this selection could change over time as prescribing practices evolve. Building separate PS models in different eras allows flexibility in how the models accommodate prescribing practices that might have changed. For this study, the number of both SEASONIQUE and 28-day cycle COC_{LNG} treatment episodes will be enumerated throughout the study period of

01 January 2006 through 30 June 2017. Based on the number of treatment episodes available for matching by calendar time, appropriate blocks of calendar time will be selected and a PS model built for each time block. The proposed approach is to divide the time prior to the ICD-9 to ICD 10 transition (through 30 September 2015) into approximately two-year blocks; this is subject to change based on the number of treatment episodes per calendar year, as described above. The ICD-9 to ICD-10 transition (on 01 October 2015) creates a natural separation of cohort start dates since the PSs will be derived from covariates coded differently in the two coding eras. Thus, separate PS model(s) will be created for the calendar period of 01 October 2015 through 30 June 2017.

SEASONIQUE or 28-day cycle COC_{LNG} oral contraceptive episodes that qualify for cohort entry will be identified according to the four categories of cohort entry (naive users, new users, re-starters, switchers) in each calendar block. Each PS model will have the use of SEASONIQUE or 28-day cycle COC_{LNG} oral contraceptive as the outcome of the model, with SAP-specified and empiric covariates as predictors. In addition, the PS model will include indicator variables for the 4 categories of cohort entry, along with potential interactions between these cohort entry categories and the 5 variables with the greatest individual discrimination between SEASONIQUE and 28-day cycle COC_{LNG} oral contraceptive use as identified by univariate c-statistic. Given the similarities between these 2 groups of women (of reproductive age with few comorbidities), the inclusion of these interaction terms should adequately address any important interactions. In this way, the PSs will account for differential selection of SEASONIQUE relative to other oral contraceptives and for changes in how this selection is made over time along with differences in selection into each of the 4 categories of cohort entry and changes in this over time. As patients may have multiple episodes of oral contraceptive use over the course of the study, each treatment episode will be treated independently and a unique PS will be calculated for each of them (provided the episode met cohort entry criteria).

SEASONIQUE episodes will be matched to 28-day cycle COC_{LNG} oral contraceptive episodes by PSs within the calendar time blocks with the goal of matching up to 4 28-day cycle COC_{LNG} episodes to each SEASONIQUE episode.

Through an iterative process, post-matching covariate balance among the matched episodes will be reviewed and the need for any further adjustment of PS models assessed and addressed. Attributes that are notably imbalanced across the cohorts will be accounted for in the PS modeling.

9.7.4.2 Variable selection for PS

Since some pre-defined variables may be closely correlated with the empirically identified variables, a step to check the correlations among pre-defined covariates and the most common diagnoses, procedures, and medications will be included. For variable pairs with a correlation coefficient > 0.9, one will be eliminated based on the following criteria:

- If one variable in the high correlation pair has been specified in the pre-defined covariates section, this pre-defined covariate variable will be retained and the other eliminated.

- If both or neither variables in the pair have been pre-specified, the variable with the highest prevalence (count) will be retained. All empirically defined variables will be binary.
- Once a variable is eliminated, it will not be re-considered for model inclusion nor will it be evaluated for inclusion through the stepwise procedure (described below).

Since empirical variable identification runs the risk of including in the PS correlates of exposure that are not risk factors for the outcome (and therefore not confounders), manual review of the empirically defined list will be performed to identify and remove such variables from the PS. Univariate c-statistics will be determined and evaluated for each of the variables remaining after correlation checks (modeling SEASONIQUE or 28-day cycle COC_{LNG} treatment status as the dependent variable). Any individual variable with a c-statistic value > 0.95 will be evaluated by the research team for possible coding errors or by a clinician for clinical plausibility. If the variable is deemed to represent a surrogate of exposure and not a confounder (not a likely risk factor for VTE events), it will be removed from the available list of covariates but retained if the strong association with treatment is supported by clinical knowledge and the variable represents a plausible risk factor for VTE events. The remaining c-statistics will then be ranked in descending order and the top 10 will be selected as covariates to be forced into the model. The remaining variables will be allowed to enter the PS model through the stepwise automatic variable forward selection procedure. Each variable will be considered for inclusion in the model in a sequential manner. A variable will be entered into the model and will be included if it has a bivariate p-value ≤ 0.1. The variable will be dropped from the model and excluded from further consideration if the p-value is > 0.1. A variable that meets the threshold and is added to the model will remain in the model unless its p-value becomes larger than 0.30, at which point it will be dropped from the model and excluded from further consideration (See Sample of SAS syntax below).

9.7.4.3 Estimation of PS

The PS models will be unconditional logistic regression models of SEASONIQUE use relative to 28-day cycle COC_{LNG} use incorporating the predictors of SEASONIQUE use, with a stepwise selection of variables, using the calendar block-specific cohorts of SEASONIQUE and 28-day cycle COC_{LNG} users.

Predictor variables, including the covariates listed in *Section 9.3.3,* interaction terms, and the variables with the top 10 c-statistics will be forced into the model using the *include* option in SAS, which specifies the first number of variables "N" that are required in the model. As described above, additional empirically-defined variables will be allowed to enter the model via the stepwise variable selection procedure.

Sample of SAS syntax:

proc logistic data=dataset2006 descending; where year = 2006;

Model seasonique_group= variable list*/ selection=stepwise slentry=0.1 slstay=0.3 include= N lackfit;*

Output out=logistout2006 p=score2006;

run;

Univariate statistics of the distributions of the PS will be reviewed for potential coding errors, outliers and to identify patients with missing PSs.

9.7.4.4 Matching

From among all eligible SEASONIQUE treatment episodes, we will find the subset of episodes that match to eligible 28-day cycle COC_{LNG} episodes based on the PS. It is expected that matching on the PS balances all variables included in the PS model (i.e., all covariates listed in Table B, Tables 2a – 2e). Matching will be performed separately within each calendar block . We will consider matching up to 4 28-day cycle COC_{LNG} episodes to each SEASONIQUE episode, depending on the final cohort sizes. SEASONIQUE episodes that are not matched will be retained and followed for outcomes without a 28-day cycle COC_{LNG} comparison group.

9.7.4.5 Model Balance/Specification

To assess whether PS estimation and matching achieves suitable covariate balance, we will compare baseline covariates both before and after matching, evaluate the weighted standardized differences for each covariate in the model, and also re-run the final PS model among the matched cohorts to determine the pooled c-statistic after matching.

The standardized difference for variables retained in the final model will be calculated using the following equations (in which $\bar{X}$ represents the mean of the covariate and $\hat{p}$ represents the prevalence of that covariate):

Continuous variables:

$$d = \frac{\overline{X}_{treatment} - \overline{X}_{control}}{\sqrt{(s^2 treatment + s^2 control)/2}}$$

Binary variables:

$$d = \frac{\hat{p}_{treatment} - \hat{p}_{control}}{\sqrt{(\hat{p}_{treatment}(1 - \hat{p}_{treatment}) + \hat{p}_{control}(1 - \hat{p}_{control}))/2}}$$

The weighted standardized difference weights all SEASONIQUE episodes as one, all 28-day cycle COC_{LNG} episodes matched 1:1 as one, all 28-day cycle COC_{LNG} episodes matched 1:2 as 1/2, all 28-day cycle COC_{LNG} episodes matched 1:3 as 1/3, and all 28-day cycle COC_{LNG} episodes matched 1:4 as 1/4.[8] Variables with a standardized difference less than 0.1 will be considered well balanced. If a variable has a standardized difference greater than 0.1, it will be included in the Cox proportional hazards model.

The final model with all matched pairs will then be re-run to evaluate the ability of the model to discriminate between SEASONIQUE use relative to 28-day cycle COC_{LNG} treatment episodes. This model will be run 5 times (once for each category of cohort entry [naive users, new users, naïve + new users, re-starters, switchers] among the subset of matched episodes for each category) to create a final pooled c-statistic for each category of cohort entry (Tables 2a – 2e). This post-matching, pooled c-statistic will be used to evaluate overall covariate balance and the need for any further adjustment. Re-running the final PS model within the matched cohorts will provide an assessment of the remaining difference across all variables rather than individual variables. The desired result is a c-statistic close to 0.5, which would imply no remaining imbalance of baseline covariates between the matched cohorts. If the c-statistic is ≥ 0.8, suggesting important remaining imbalance, a reconsideration of the covariates (or covariate forms) to be included in the model will be required.[9]

An additional diagnostic step will include evaluation of the PS distributions as a kernel density estimate (KDE) to represent the probability density functions of the PSs for the SEASONIQUE and 28-day cycle COC_{LNG} episodes pre- and post-matching. The KDEs plotted on the same figure provide a visual assessment of the extent of overlap in PSs before and after matching, as a guide to the population from which study inferences are drawn and generalization might be made (i.e., assessment of external validity). A high degree of overlap implies exchangeability (similarity in covariate patterns) of patients between treatment groups and promotes external validity of the study findings (since most SEASONIQUE patients will contribute to effect measures). Areas of non-overlap indicate patients in one treatment group who, based on their covariate profiles, do not have comparable patients in the other treatment group. The study results will generalize most directly to those patients in the overlapping range of the PSs.

9.7.5 Analysis of Outcomes

9.7.5.1 Estimation and Comparison of Incidence Rates

Crude incidence rates of VTE and secondary outcomes of interest (along with 95% confidence intervals (CIs)) for each exposure group will be estimates and reported (Tables 3a – 3f.7). Incidence rates will be calculated by summing the number of cases and dividing the sum by the number of person-years of follow-up. Incidence rates will be presented as the number of cases per 1,000 person-years. The CIs for the incidence rates will be calculated using exact confidence limits

The primary analysis will focus on VTE events comparing current exposure to SEASONIQUE vs. 28-day cycle COC_{LNG} (reference group). Incidence rates and 95% CIs will be estimated and reported within the PS-matched cohorts. Kaplan-Meier cumulative incidence plots will be generated to depict time to event for all outcomes of interest in the PS-matched cohorts. Differences in incidence rates and 95% CIs will be calculated (Table 3a). Cox-proportional hazards (PH) models will be used to estimate hazard ratios (HRs) and corresponding 95% CI, with adjustment for covariates. The analysis will take into account

the correlation among exposure episodes from patients contributing more than one episode to the analysis dataset using a robust variance estimator.

The main analysis of VTE events will be conducted comparing current exposure in the combined cohorts of naïve and new SEASONIQUE users with naïve and new 28-day cycle COC_{LNG} users. Using these groups will allow assessing the overall difference between the two incident user cohorts. In addition, it will increase the power of the study and will also allow for generalizability of the study results. Additional stratum-specific analyses will be performed for each of the four exposure cohorts: (1) naïve users, (2) new users, (3) re-starters, and (4) switchers (Tables 3b – 3e).

9.7.5.2 Modelling of Outcomes

Separate outcome models will be created for each outcome. The primary analysis will be a Cox proportional hazard models to estimate the hazard ratios for outcomes that occur in the follow-up person-time; HRs will be used to compare occurrence of events within episodes of SEASONIQUE and 28-day cycle COC_{LNG} use.

Sample SAS code: *proc phreg data=DATA covs(aggregate) plots=survival;*

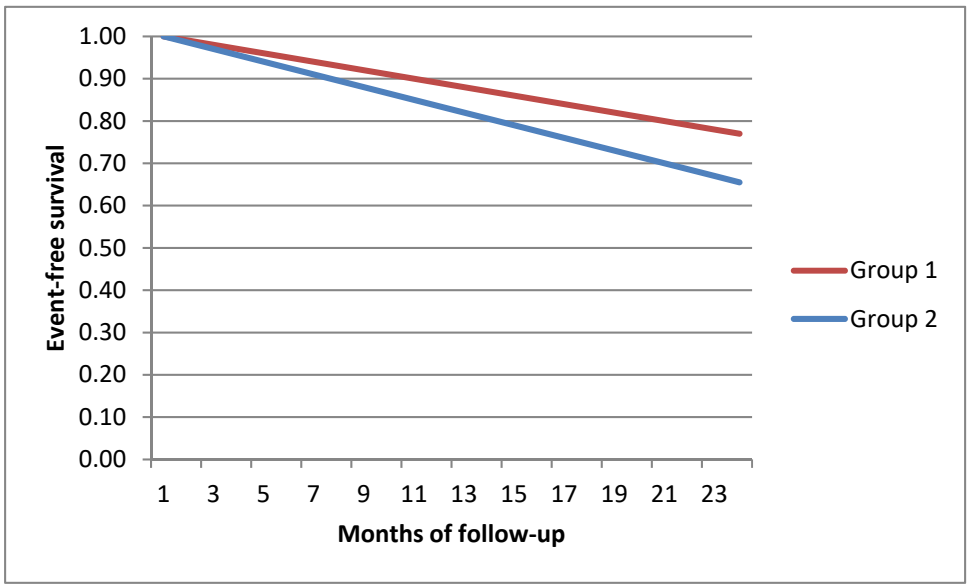
*model time_to_event*censored_status(0) = Treatment_group;*

The proportional hazards (PH) assumption will be assessed in two ways. First, we will use a graphical approach by comparing the log-log survival curves of treatment (SEASONIQUE vs. 28-day cycle COC_{LNG} users) and assessing parallelism. If the two curves are approximately parallel, we would conclude that the PH assumption is satisfied for the treatment variable; otherwise, if the curves differ substantially from parallel, we may conclude that the PH assumption is not satisfied, depending on what part of the curve is contributing to the lack of parallelism. Second, we will use the goodness of fit testing approach by using the likelihood ratio test comparing models with and without cross-product terms between the treatment and time. If the PH assumption does not hold across the study follow-up, the follow-up will be stratified into narrower time periods (at median follow-up) and the PH models re-run. Results for both the full follow-up model and the model stratified by follow-up time will be presented.

9.7.5.3 Kaplan-Meier Graphs

For each outcome, cumulative probability of survival for by drug exposure will be depicted using Kaplan-Meier plots. PROC LIFETEST (or similar STATA steps) will be used to compute and display the product-limit estimates of the survival distribution within each stratum. For each stratum, time in months to event vs. cumulative probability of survival will be plotted. The plot will include probability of survival (%) on the y-axis and time in months on the x-axis (Figure 1).

Figure 1 Example of Kaplan-Meier Plot



9.7.5.4 Subgroup Analyses

In addition to the main analyses, the following subgroup analyses will be performed (current use only, Tables 3f.7, 5c, 6c, 7c):

1) Age (years):
    a. 12 to <15
    b. ≥15 to ≤35
    c. >35 to <50
    d. ≥50
2) Overweight or obese (i.e., codes for overweight or obese)
    a. Yes
    b. No
3) Tobacco use (i.e., codes for smoking-related diagnoses, smoking cessation medications, procedures)
    a. Yes
    b. No

4) Smoking-by-age interaction
    a. Tobacco users, age > 35 years
    b. Tobacco non-users, > 35 years
    c. Tobacco users, age 12 to ≤ 35 years
    d. Tobacco non-users, age 12 to ≤ 35 years
5) Prior VTE or anticoagulant use
    a. Yes
    b. No
6) Surgery/injury during follow-up
    a. Yes
    b. No

    Note that although surgery/injury would be assessed during follow-up, we do not expect that stratifying on it will introduce bias because it is unlikely to be affected by prior exposure.

9.7.5.5 Sensitivity Analyses

As described in Section 9.2 Setting and Study Population, a sensitivity analysis requiring a minimum of 6 months of continuous health plan enrollment within the database before the index date for the primary analysis of the VTE outcome will be performed (Table 3f.6).

As described in Section 9.2.2 Exclusion, to explore the effect of including patients with a history of non-gynaecological cancer in baseline, such patients will be excluded and examined for the primary analysis of VTE. Since the majority of cohort patients are young and healthy, and patients with gynaecological cancers or receiving chemotherapy were already excluded, this analysis is expected to exclude few additional patients, as compared with the primary analysis.

As described in Section 9.3.1 Exposure, although the primary interest is in women currently exposed to SEASONIQUE and 28-day cycle COCLNG, comparisons will also be made between recent SEASONIQUE and 28-day cycle COCLNG users, intermediate SEASONIQUE and 28-day cycle COCLNG users, and remote SEASONIQUE and 28-day cycle COCLNG users (Tables 3a – 3f.6, 3g).

As described in Section 9.3.1. Exposure, a sensitivity analysis will be performed to vary the gap length to 60 days for SEASONIQUE users and 28 days for 28-day cycle COCLNG users (Tables 3f.1, 5b, 6b).

As described above in Section 9.3.1. Exposure, a sensitivity analysis will be performed that does not censor women who appear to be continuously exposed to COC by consuming only the 21 active pills before starting a new pack (Tables 3f.2, 5b, 6b, 7b). In the sensitivity analysis, the start date of each refill will be modified to correspond to the day after the end of

the days' supply of the preceding prescription. This process will be repeated until the end of the treatment episode.

As described in Section 9.3.2.1 Primary Outcomes, a sensitivity analysis will be conducted as follows. PE will be defined as an inpatient diagnosis (including emergency departments) of PE (at least one of the ICD-9 or ICD-10 codes in the Appendix in the primary position) in conjunction with first prescription of anticoagulant. DVT will be defined as a DVT diagnosis (at least one of the ICD-9 or ICD-10 codes in the Appendix in any position) in either outpatient or inpatient settings, in conjunction with a first prescription for an anticoagulant (Tables 3a – 3f.7).

As described in Section 9.3.2.2 Secondary Outcomes - Delayed pregnancy detection, a sensitivity analysis will be conducted restricting the analysis to only those pregnancies with estimated start dates that occur within the last 28 days of supply of a prescription to take into account the extended days' supply of SEASONIQUE (i.e., 91 days) compared to the 28-day cycle COCLNG (Table 7b).

As described in the protocol, it is possible that naïve users could have had prior CHC use more than 365 days before the index date. In three sensitivity analyses, we will increase the minimum CHC-free baseline period as follows: (1) restricted to women with at least 24 months of prior continuous enrollment and no CHC use in this period; (2) restricted to women with 24 to 36 months of prior continuous enrollment and no CHC use in this period; and (3) women with at least 36 months of prior continuous enrollment and no CHC use in this period (Tables 3f.3 – 3f.5, 5b, 6b, 7b).

9.8 Quality control

All key study documents, such as the SAP and study reports, will undergo quality control and scientific review. Standard operating procedures (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.

The following steps will be undertaken to ensure quality and accuracy of all programming developed during the course of the study:

- Data for analysis will be extracted by a competent Optum programmer.
- The SAP and table shells will be reviewed and approved by the Optum Senior Scientist.
- All programming code developed for this study will be validated by a senior Optum Analyst.
- Study report including results and tables will be reviewed by the Optum Senior Scientist.

Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP).[10]

9.9 Limitations of the research methods

This study is based on an analysis of automated medical and prescription claims, supplemented by information abstracted from the medical record. While claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, health care resource utilization, and costs, all claims databases have certain inherent limitations because the claims are collected for the purpose of payment and not research. Medications filled over-the-counter or provided as samples by the physician will not be observed in the claims data. In the case of drug administrations identified in the pharmacy records, the presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed, which may result in exposure misclassification. Patients may be classified as exposed when they have actually stopped taking the drug. In addition, it is possible that the 28-day cycle COC_{LNG} is used continuously, especially monophasic COCs, without a pill-free interval (for several packages or even indefinitely) until breakthrough bleeding occurs. To evaluate the exposure and to address this potential misclassification, the assumption of using the drug regimen as prescribed will be examined and patient misusing the drug will be excluded from analyses.

Presence of a diagnosis code on a medical claim may not represent true presence of a disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. To address potential misclassification of the primary VTE outcome, a separate validation of a sample of cases in medical records will be performed.

Confounding by indication is not expected in this study as both SEASONIQUE and 28-day cycle COC_{LNG} drugs are COC containing similar active ingredients (LNG combined with EE) and thus a physicians' decision to prescribe SEASONIQUE is not expected to be based on a presumed higher risk of VTE. Nonetheless, confounding could occur if physicians tend to prescribe SEASONIQUE to women with specific characteristics that may also be risk factors for VTE. High risk of VTE can be explained by important covariates that may not be available in the database, including, obesity, smoking, family history of thrombosis, and lifetime use of hormonal contraceptives. To the extent possible, we will use diagnosis and procedure codes to assess these potential confounders. We will also assess various variables known or suspected to be associated with the outcomes of interest, as well as many variables related to general health.

Delayed pregnancy detection may not be accurately estimated. Since each SEASONIQUE pack covers 91 days, it is not possible to know based on the claims whether a woman stopped taking the drug during those three months. In addition, date of conception is not recorded in the database. As such, whether women are still using the drug when they become pregnant cannot be determined with certainty. Information regarding fertility is limited in claims data. Also, the definition for fertility assumes that women are sexually active, and not using other forms of contraceptive that cannot be assessed in the data (i.e., condoms), though this may not be the case.

In addition, it is unclear whether any pregnancy identified during the study period is actually planned. Women wishing to receive a long regimen of CHC, such as SEASONIQUE, are likely to be those preventing pregnancy in the short term. Therefore, the fertility rate between SEASONIQUE and 28-day cycle COC_{LNG} may not accurately reflect any fertility impediment related to a study drug. Furthermore, claims data may not capture all pregnancies that end with abortive outcomes.

Additional limitations include the length of follow-up available in the ORD. The typical length of follow-up in these databases is 2 years and thus long-term outcomes, such as cancer (secondary outcome in this study), may not be identified. As noted above, missing information on unmeasured confounders and residual confounding cannot be entirely eliminated in observational studies. While information on potential confounders such as smoking and obesity may often be missing, we will perform subgroup analyses among women with codes for these factors, in which we expect the impact of residual confounding to be less.

9.10 Other aspects

Not applicable

10 PROTECTION OF HUMAN SUBJECTS

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy. All study reports will contain aggregated results only and will not identify individual patients or physicians. At no time during the study will Teva receive patient identifying information.

Optum will prepare and submit an application to a central Institutional Review Board (IRB) and affiliated Privacy Board (PB) for approval of the study process and to obtain a Waiver of Patient Authorization for medical record abstraction. Optum will submit the study protocol and medical chart abstraction form to the central IRB and PB.

Internal review and approval processes are also required. Optum will provide general study information and a copy of the IRB and PB approval and waiver documents to the relevant data sources for approval to utilize such data source's data in the study.

The study will be conducted in accordance with the ISPE Guidelines for GPP,[10] the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology[11] and guidelines for study conduct and reporting put forth in the FDA's draft guidance document Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.[12]

The ENCePP Checklist for Study Protocols[13] has been completed and the study will be conducted in accordance with accordance with the ENCePP Code of Conduct (ENCePP 2014).[14]

The study will comply with the definition of the non-interventional (observational) study provided in the EU pharmacovigilance legislation adopted 19 June 2012,[15] and the related

Guideline on Good Pharmacovigilance Practices (GVP) module VIII on Post-Authorisation Safety Studies.[16]

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

As 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 2014 module VI). No expedited reporting of adverse events or reactions is required.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The 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 reporting results of this study, 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 2014) guidelines. In addition, communication in appropriate scientific meetings will be considered.

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14 APPENDIX: CODES TO DEFINE OUTCOMES AND CENSORING

Note: The ICD codes list below contains only billable codes and avoids using wildcards

14.1 Venous thromboembolism (VTE)

Pulmonary embolism (PE)

Code	Description
ICD-9	
415.11	Iatrogenic pulmonary embolism and infarction
415.19	Other pulmonary embolism and infarction
ICD-10	
I26.99	Other pulmonary embolism without acute cor pulmonale

Deep venous thromboembolism (DVT)

Code	Description
ICD-9	
451.11	Phlebitis and thrombophlebitis of femoral vein (deep) (superficial)
451.19	Phlebitis and thrombophlebitis of deep veins of lower extremities, other
451.2	Phlebitis and thrombophlebitis of lower extremities, unspecified
451.81	Phlebitis and thrombophlebitis of iliac vein
451.83	Phlebitis and thrombophlebitis of deep veins of upper extremities
451.84	Phlebitis and thrombophlebitis of upper extremities, unspecified
451.89	Phlebitis and thrombophlebitis of other sites
453.1	Thrombophlebitis migrans
453.2	Other venous embolism and thrombosis of inferior vena cava
453.40	Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.41	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
453.42	Acute venous embolism and thrombosis of deep vessels of distal lower extremity
453.81	Acute venous embolism and thrombosis of superficial veins of upper extremity
453.82	Acute venous embolism and thrombosis of deep veins of upper extremity
453.83	Acute venous embolism and thrombosis of upper extremity, unspecified
453.84	Acute venous embolism and thrombosis of axillary veins
453.85	Acute venous embolism and thrombosis of subclavian veins
453.86	Acute venous embolism and thrombosis of internal jugular veins
453.87	Acute venous embolism and thrombosis of other thoracic veins
453.89	Acute venous embolism and thrombosis of other specified veins
453.9	Other venous embolism and thrombosis of unspecified site
ICD-10	
I80.10	Phlebitis and thrombophlebitis of unspecified femoral vein
I80.11	Phlebitis and thrombophlebitis of right femoral vein
I80.12	Phlebitis and thrombophlebitis of left femoral vein
I80.13	Phlebitis and thrombophlebitis of bilateral femoral veins
I80.201	Phlebitis and thrombophlebitis of unspecified deep vessels of right lower extremity
I80.202	Phlebitis and thrombophlebitis of unspecified deep vessels of left lower extremity
I80.203	Phlebitis and thrombophlebitis of unspecified deep vessels of bilateral lower extremities
I80.209	Phlebitis and thrombophlebitis of unspecified deep vessels of unspecified lower extremity
I80.211	Phlebitis and thrombophlebitis of right iliac vein
I80.212	Phlebitis and thrombophlebitis of left iliac vein
I80.213	Phlebitis and thrombophlebitis of bilateral iliac veins

I80.219	Phlebitis and thrombophlebitis of unspecified iliac vein
I80.221	Phlebitis and thrombophlebitis of right popliteal vein
I80.222	Phlebitis and thrombophlebitis of left popliteal vein
I80.223	Phlebitis and thrombophlebitis of bilateral popliteal veins
I80.229	Phlebitis and thrombophlebitis of unspecified popliteal vein
I80.231	Phlebitis and thrombophlebitis of right tibial vein
I80.232	Phlebitis and thrombophlebitis of left tibial vein
I80.233	Phlebitis and thrombophlebitis of bilateral tibial veins
I80.239	Phlebitis and thrombophlebitis of unspecified tibial vein
I80.291	Phlebitis and thrombophlebitis of other deep vessels of right lower extremity
I80.292	Phlebitis and thrombophlebitis of other deep vessels of left lower extremity
I80.293	Phlebitis and thrombophlebitis of other deep vessels of bilateral lower extremities
I80.299	Phlebitis and thrombophlebitis of other deep vessels of unspecified lower extremity
I80.3	Phlebitis and thrombophlebitis of lower extremities, unspecified
I82.210	Acute embolism and thrombosis of superior vena cava
I82.211	Chronic embolism and thrombosis of superior vena cava
I82.220	Acute embolism and thrombosis of inferior vena cava
I82.221	Chronic embolism and thrombosis of inferior vena cava
I82.290	Acute embolism and thrombosis of other thoracic veins
I82.291	Chronic embolism and thrombosis of other thoracic veins
I82.811	Embolism and thrombosis of superficial veins of right lower extremities
I82.812	Embolism and thrombosis of superficial veins of left lower extremities
I82.813	Embolism and thrombosis of superficial veins of bilateral lower extremities
I82.819	Embolism and thrombosis of superficial veins of unspecified lower extremities
I82.890	Acute embolism and thrombosis of other specified veins
I82.891	Chronic embolism and thrombosis of other specified veins
I82.90	Acute embolism and thrombosis of unspecified vein
I82.91	Chronic embolism and thrombosis of unspecified vein

14.2 Arterial thromboembolic events (ATEs)

Stroke

Code	Description
ICD-9	
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
434.01	Cerebral thrombosis with cerebral infarction
434.11	Cerebral embolism with cerebral infarction
434.91	Cerebral artery occlusion, unspecified with cerebral infarction
436	Acute, but ill-defined, cerebrovascular disease
ICD-10	
I60.00	Nontraumatic subarachnoid hemorrhage from unspecified carotid siphon and bifurcation
I60.01	Nontraumatic subarachnoid hemorrhage from right carotid siphon and bifurcation
I60.02	Nontraumatic subarachnoid hemorrhage from left carotid siphon and bifurcation
I60.10	Nontraumatic subarachnoid hemorrhage from unspecified middle cerebral artery
I60.11	Nontraumatic subarachnoid hemorrhage from right middle cerebral artery
I60.12	Nontraumatic subarachnoid hemorrhage from left middle cerebral artery
I60.2	Nontraumatic subarachnoid hemorrhage from anterior communicating artery
I60.30	Nontraumatic subarachnoid hemorrhage from unspecified posterior communicating artery
I60.31	Nontraumatic subarachnoid hemorrhage from right posterior communicating artery
I60.32	Nontraumatic subarachnoid hemorrhage from left posterior communicating artery
I60.4	Nontraumatic subarachnoid hemorrhage from basilar artery
I60.50	Nontraumatic subarachnoid hemorrhage from unspecified vertebral artery
I60.51	Nontraumatic subarachnoid hemorrhage from right vertebral artery
I60.52	Nontraumatic subarachnoid hemorrhage from left vertebral artery
I60.6	Nontraumatic subarachnoid hemorrhage from other intracranial arteries
I60.7	Nontraumatic subarachnoid hemorrhage from unspecified intracranial arteries
I60.8	Other nontraumatic subarachnoid hemorrhage
I60.9	Nontraumatic subarachnoid hemorrhage, unspecified
I61.0	Nontraumatic intracerebral hemorrhage in hemisphere, subcortical
I61.1	Nontraumatic intracerebral hemorrhage in hemisphere, cortical

I61.2	Nontraumatic intracerebral hemorrhage in hemisphere, unspecified
I61.3	Nontraumatic intracerebral hemorrhage in brain stem
I61.4	Nontraumatic intracerebral hemorrhage in cerebellum
I61.5	Nontraumatic intracerebral hemorrhage, intraventricular
I61.6	Nontraumatic intracerebral hemorrhage, multiple localized
I61.8	Other nontraumatic intracerebral hemorrhage
I61.9	Nontraumatic intracerebral hemorrhage, unspecified
I63.00	Cerebral infarction due to thrombosis of unspecified precerebral artery
I63.011	Cerebral infarction due to thrombosis of right vertebral artery
I63.012	Cerebral infarction due to thrombosis of left vertebral artery
I63.013	Cerebral infarction due to thrombosis of bilateral vertebral arteries
I63.019	Cerebral infarction due to thrombosis of unspecified vertebral artery
I63.02	Cerebral infarction due to thrombosis of basilar artery
I63.031	Cerebral infarction due to thrombosis of right carotid artery
I63.032	Cerebral infarction due to thrombosis of left carotid artery
I63.033	Cerebral infarction due to thrombosis of bilateral carotid arteries
I63.039	Cerebral infarction due to thrombosis of unspecified carotid artery
I63.09	Cerebral infarction due to thrombosis of other precerebral artery
I63.10	Cerebral infarction due to embolism of unspecified precerebral artery
I63.111	Cerebral infarction due to embolism of right vertebral artery
I63.112	Cerebral infarction due to embolism of left vertebral artery
I63.113	Cerebral infarction due to embolism of bilateral vertebral arteries
I63.119	Cerebral infarction due to embolism of unspecified vertebral artery
I63.12	Cerebral infarction due to embolism of basilar artery
I63.131	Cerebral infarction due to embolism of right carotid artery
I63.132	Cerebral infarction due to embolism of left carotid artery
I63.133	Cerebral infarction due to embolism of bilateral carotid arteries
I63.139	Cerebral infarction due to embolism of unspecified carotid artery
I63.19	Cerebral infarction due to embolism of other precerebral artery
I63.20	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries
I63.211	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral arteries
I63.212	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral arteries
I63.213	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries
I63.219	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral arteries
I63.22	Cerebral infarction due to unspecified occlusion or stenosis of basilar arteries
I63.231	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries
I63.232	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries

I63.233	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries
I63.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries
I63.29	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries
I63.30	Cerebral infarction due to thrombosis of unspecified cerebral artery
I63.311	Cerebral infarction due to thrombosis of right middle cerebral artery
I63.312	Cerebral infarction due to thrombosis of left middle cerebral artery
I63.313	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
I63.319	Cerebral infarction due to thrombosis of unspecified middle cerebral artery
I63.321	Cerebral infarction due to thrombosis of right anterior cerebral artery
I63.322	Cerebral infarction due to thrombosis of left anterior cerebral artery
I63.323	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries
I63.329	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
I63.331	Cerebral infarction due to thrombosis of right posterior cerebral artery
I63.332	Cerebral infarction due to thrombosis of left posterior cerebral artery
I63.333	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries
I63.339	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
I63.341	Cerebral infarction due to thrombosis of right cerebellar artery
I63.342	Cerebral infarction due to thrombosis of left cerebellar artery
I63.343	Cerebral infarction due to thrombosis of bilateral cerebellar arteries
I63.349	Cerebral infarction due to thrombosis of unspecified cerebellar artery
I63.39	Cerebral infarction due to thrombosis of other cerebral artery
I63.40	Cerebral infarction due to embolism of unspecified cerebral artery
I63.411	Cerebral infarction due to embolism of right middle cerebral artery
I63.412	Cerebral infarction due to embolism of left middle cerebral artery
I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries
I63.419	Cerebral infarction due to embolism of unspecified middle cerebral artery
I63.421	Cerebral infarction due to embolism of right anterior cerebral artery
I63.422	Cerebral infarction due to embolism of left anterior cerebral artery
I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries
I63.429	Cerebral infarction due to embolism of unspecified anterior cerebral artery
I63.431	Cerebral infarction due to embolism of right posterior cerebral artery
I63.432	Cerebral infarction due to embolism of left posterior cerebral artery
I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries
I63.439	Cerebral infarction due to embolism of unspecified posterior cerebral artery
I63.441	Cerebral infarction due to embolism of right cerebellar artery
I63.442	Cerebral infarction due to embolism of left cerebellar artery
I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries
I63.449	Cerebral infarction due to embolism of unspecified cerebellar artery

I63.49	Cerebral infarction due to embolism of other cerebral artery
I63.50	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
I63.513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries
I63.519	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries
I63.529	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery
I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries
I63.539	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery
I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
I63.549	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
	* code I64 (Stroke, not specified as haemorrhage or infarction) was omitted as the US ICD-10-CM version does not contain this code

AMI

Code	Description
ICD-9	
410.00	Acute myocardial infarction of anterolateral wall, episode of care unspecified
410.01	Acute myocardial infarction of anterolateral wall, initial episode of care
410.02	Acute myocardial infarction of anterolateral wall, subsequent episode of care
410.10	Acute myocardial infarction of other anterior wall, episode of care unspecified
410.11	Acute myocardial infarction of other anterior wall, initial episode of care
410.12	Acute myocardial infarction of other anterior wall, subsequent episode of care
410.20	Acute myocardial infarction of inferolateral wall, episode of care unspecified
410.21	Acute myocardial infarction of inferolateral wall, initial episode of care
410.22	Acute myocardial infarction of inferolateral wall, subsequent episode of care
410.30	Acute myocardial infarction of inferoposterior wall, episode of care unspecified
410.31	Acute myocardial infarction of inferoposterior wall, initial episode of care
410.32	Acute myocardial infarction of inferoposterior wall, subsequent episode of care
410.40	Acute myocardial infarction of other inferior wall, episode of care unspecified
410.41	Acute myocardial infarction of other inferior wall, initial episode of care
410.42	Acute myocardial infarction of other inferior wall, subsequent episode of care
410.50	Acute myocardial infarction of other lateral wall, episode of care unspecified
410.51	Acute myocardial infarction of other lateral wall, initial episode of care
410.52	Acute myocardial infarction of other lateral wall, subsequent episode of care
410.60	True posterior wall infarction, episode of care unspecified
410.61	True posterior wall infarction, initial episode of care
410.62	True posterior wall infarction, subsequent episode of care
410.70	Subendocardial infarction, episode of care unspecified
410.71	Subendocardial infarction, initial episode of care
410.72	Subendocardial infarction, subsequent episode of care
410.80	Acute myocardial infarction of other specified sites, episode of care unspecified
410.81	Acute myocardial infarction of other specified sites, initial episode of care
410.82	Acute myocardial infarction of other specified sites, subsequent episode of care
410.90	Acute myocardial infarction of unspecified site, episode of care unspecified
410.91	Acute myocardial infarction of other unspecified site, initial episode of care
410.92	Acute myocardial infarction of other unspecified site, subsequent episode of care
ICD-10	
I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery
I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery
I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall

I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
I21.19	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall
I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery
I21.29	ST elevation (STEMI) myocardial infarction involving other sites
I21.3	ST elevation (STEMI) myocardial infarction of unspecified site
I21.4	Non-ST elevation (NSTEMI) myocardial infarction

14.3 Pregnancy outcomes

Delivery

Code	Description
ICD-9 diagnosis codes	
V27.0	Outcome of delivery, single liveborn
V27.1	Outcome of delivery, single stillborn
V27.2	Outcome of delivery, twins, both liveborn
V27.3	Outcome of delivery, twins, one liveborn and one stillborn
V27.4	Outcome of delivery, twins, both stillborn
V27.5	Outcome of delivery, other multiple birth, all liveborn
V27.6	Outcome of delivery, other multiple birth, some liveborn
V27.7	Outcome of delivery, other multiple birth, all stillborn
V27.9	Outcome of delivery, unspecified outcome of delivery
645.11	Post term pregnancy, delivered, with or without mention of antepartum condition
645.21	Prolonged pregnancy, delivered, with or without mention of antepartum condition
650	Normal delivery
651.00	Twin pregnancy, unspecified as to episode of care or not applicable
651.01	Twin pregnancy, delivered, with or without mention of antepartum condition
651.03	Twin pregnancy, antepartum condition or complication
651.10	Triplet pregnancy, unspecified as to episode of care or not applicable
651.11	Triplet pregnancy, delivered, with or without mention of antepartum condition
651.13	Triplet pregnancy, antepartum condition or complication
651.20	Quadruplet pregnancy, unspecified as to episode of care or not applicable
651.21	Quadruplet pregnancy, delivered, with or without mention of antepartum condition
651.23	Quadruplet pregnancy, antepartum condition or complication
651.30	Twin pregnancy with fetal loss and retention of one fetus, unspecified as to episode of care or not applicable
651.31	Twin pregnancy with fetal loss and retention of one fetus, delivered, with or without mention of antepartum condition
651.33	Twin pregnancy with fetal loss and retention of one fetus, antepartum condition or complication
651.40	Triplet pregnancy with fetal loss and retention of one or more fetus(es), unspecified as to episode of care or not applicable
651.41	Triplet pregnancy with fetal loss and retention of one or more fetus(es), delivered, with or without mention of antepartum condition
651.43	Triplet pregnancy with fetal loss and retention of one or more fetus(es), antepartum condition or complication

651.50	Quadruplet pregnancy with fetal loss and retention of one or more fetus(es), unspecified as to episode of care or not applicable
651.51	Quadruplet pregnancy with fetal loss and retention of one or more fetus(es), delivered, with or without mention of antepartum condition
651.53	Quadruplet pregnancy with fetal loss and retention of one or more fetus(es), antepartum condition or complication
651.60	Other multiple pregnancy with fetal loss and retention of one or more fetus(es), unspecified as to episode of care or not applicable
651.61	Other multiple pregnancy with fetal loss and retention of one or more fetus(es), delivered, with or without mention of antepartum condition
651.63	Other multiple pregnancy with fetal loss and retention of one or more fetus(es), antepartum condition or complication
651.70	Multiple gestation following (elective) feta reduction, unspecified as to episode of care or not applicable
651.71	Multiple gestation following (elective) feta reduction, delivered, with or without mention of antepartum condition
651.73	Multiple gestation following (elective) feta reduction, antepartum condition or complication
651.80	Other specified multiple gestation, unspecified as to episode of care or not applicable
651.81	Other specified multiple gestation, delivered, with or without mention of antepartum condition
651.83	Other specified multiple gestation, antepartum condition or complication
651.90	Unspecified multiple gestation, unspecified as to episode of care or not applicable
651.91	Unspecified multiple gestation, delivered, with or without mention of antepartum condition
651.93	Unspecified multiple gestation, antepartum condition or complication
ICD-9 procedure codes	
72.0	Low forceps operation
72.1	Low forceps operation with episiotomy
72.21	Mid forceps operation with episiotomy
72.29	Other mid forceps operation
72.31	High forceps operation with episiotomy
72.39	Other high forceps operation
72.4	Forceps rotation of fetal head
72.51	Partial breech extraction with forceps to aftercoming head
72.52	Other partial breech extraction
72.53	Total breech extraction with forceps to aftercoming head
72.54	Other total breech extraction
72.6	Forceps application to aftercoming head
72.71	Vacuum extraction with episiotomy

72.79	Other vacuum extraction
72.8	Other specified instrumental delivery
72.9	Unspecified instrumental delivery
73.01	Induction of labor by artificial rupture of membranes
73.09	Other artificial rupture of membranes
73.1	Other surgical induction of labor
73.21	Internal and combined version without extraction
73.22	internal and combined version with extraction
73.3	Failed forceps
73.4	Medical induction of labor
73.51	Manual rotation of fetal head
73.59	Other manually assisted delivery
73.6	Episiotomy
73.8	Operations on fetus to facilitate delivery
73.91	External version
73.92	Replacement of prolapsed umbilical cord
73.93	Incision of cervix to assist delivery
73.94	Pubiotomy to assist delivery
73.99	Other operations assisting delivery
74.0	Classical cesarean section
74.1	Low cervical cesarean section
74.2	Extraperitoneal cesarean section
74.4	Cesarean section of other specified type
74.91	Hysterotomy to terminate pregnancy
74.99	Other cesarean section of unspecified type
CPT codes	
59409	Vaginal delivery only (with or without episiotomy and/or forceps)
59410	Vaginal delivery only (with or without episiotomy and/or forceps); including postpartum care
59514	Cesarean delivery only
59515	Cesarean delivery only; including postpartum care
59612	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy, and/or forceps)
59614	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy, and/or forceps); including postpartum care
59620	Cesarean delivery only, following attempted vaginal delivery after previous cesarean delivery
59622	Cesarean delivery only, following attempted vaginal delivery after previous cesarean delivery; including postpartum care
ICD-10 diagnosis	

codes	
O80	Encounter for full-term uncomplicated delivery
O82	Encounter for cesarean delivery without indication
	* Codes O83, O84 were omitted as the US ICD-10-CM version does not contain these codes

Pregnancy with abortive outcome

Code	Description
ICD-9 diagnosis codes	
634.00	Spontaneous abortion, complicated by genital tract and pelvic infection, unspecified
634.01	Spontaneous abortion, complicated by genital tract and pelvic infection, incomplete
634.02	Spontaneous abortion, complicated by genital tract and pelvic infection, complete
634.10	Spontaneous abortion, complicated by delayed or excessive hemorrhage, unspecified
634.11	Spontaneous abortion, complicated by delayed or excessive hemorrhage, incomplete
634.12	Spontaneous abortion, complicated by delayed or excessive hemorrhage, complete
634.20	Spontaneous abortion, complicated by damage to pelvic organs or tissues, unspecified
634.21	Spontaneous abortion, complicated by damage to pelvic organs or tissues, incomplete
634.22	Spontaneous abortion, complicated by damage to pelvic organs or tissues, complete
634.30	Spontaneous abortion, complicated by renal failure, unspecified
634.31	Spontaneous abortion, complicated by renal failure, incomplete
634.32	Spontaneous abortion, complicated by renal failure, complete
634.40	Spontaneous abortion, complicated by metabolic disorder, unspecified
634.41	Spontaneous abortion, complicated by metabolic disorder, incomplete
634.42	Spontaneous abortion, complicated by metabolic disorder, complete
634.50	Spontaneous abortion, complicated by shock, unspecified
634.51	Spontaneous abortion, complicated by shock, incomplete
634.52	Spontaneous abortion, complicated by shock, complete
634.60	Spontaneous abortion, complicated by embolism, unspecified
634.61	Spontaneous abortion, complicated by embolism, incomplete
634.62	Spontaneous abortion, complicated by embolism, complete
634.70	Spontaneous abortion, with other specified complications, unspecified
634.71	Spontaneous abortion, with other specified complications, incomplete
634.72	Spontaneous abortion, with other specified complications, complete
634.80	Spontaneous abortion, with unspecified complication, unspecified
634.81	Spontaneous abortion, with unspecified complication, incomplete
634.82	Spontaneous abortion, with unspecified complication, complete
634.90	Spontaneous abortion, without mention of complication, unspecified
634.91	Spontaneous abortion, without mention of complication, incomplete

634.92	Spontaneous abortion, without mention of complication, complete
635.00	Legally induced abortion, complicated by genital tract and pelvic infection, unspecified
635.01	Legally induced abortion, complicated by genital tract and pelvic infection, incomplete
635.02	Legally induced abortion, complicated by genital tract and pelvic infection, complete
635.10	Legally induced abortion, complicated by delayed or excessive hemorrhage, unspecified
635.11	Legally induced abortion, complicated by delayed or excessive hemorrhage, incomplete
635.12	Legally induced abortion, complicated by delayed or excessive hemorrhage, complete
635.20	Legally induced abortion, complicated by damage to pelvic organs or tissues, unspecified
635.21	Legally induced abortion, complicated by damage to pelvic organs or tissues, incomplete
635.22	Legally induced abortion, complicated by damage to pelvic organs or tissues, complete
635.30	Legally induced abortion, complicated by renal failure, unspecified
635.31	Legally induced abortion, complicated by renal failure, incomplete
635.32	Legally induced abortion, complicated by renal failure, complete
635.40	Legally induced abortion, complicated by metabolic disorder, unspecified
635.41	Legally induced abortion, complicated by metabolic disorder, incomplete
635.42	Legally induced abortion, complicated by metabolic disorder, complete
635.50	Legally induced abortion, complicated by shock, unspecified
635.51	Legally induced abortion, complicated by shock, incomplete
635.52	Legally induced abortion, complicated by shock, complete
635.60	Legally induced abortion, complicated by embolism, unspecified
635.61	Legally induced abortion, complicated by embolism, incomplete
635.62	Legally induced abortion, complicated by embolism, complete
635.70	Legally induced abortion, with other specified complications, unspecified
635.71	Legally induced abortion, with other specified complications, incomplete
635.72	Legally induced abortion, with other specified complications, complete
635.80	Legally induced abortion, with unspecified complication, unspecified
635.81	Legally induced abortion, with unspecified complication, incomplete
635.82	Legally induced abortion, with unspecified complication, complete
635.90	Legally induced abortion, without mention of complication, unspecified
635.91	Legally induced abortion, without mention of complication, incomplete
635.92	Legally induced abortion, without mention of complication, complete

636.00	Illegally induced abortion, complicated by genital tract and pelvic infection, unspecified
636.01	Illegally induced abortion, complicated by genital tract and pelvic infection, incomplete
636.02	Illegally induced abortion, complicated by genital tract and pelvic infection, complete
636.10	Illegally induced abortion, complicated by delayed or excessive hemorrhage, unspecified
636.11	Illegally induced abortion, complicated by delayed or excessive hemorrhage, incomplete
636.12	Illegally induced abortion, complicated by delayed or excessive hemorrhage, complete
636.20	Illegally induced abortion, complicated by damage to pelvic organs or tissues, unspecified
636.21	Illegally induced abortion, complicated by damage to pelvic organs or tissues, incomplete
636.22	Illegally induced abortion, complicated by damage to pelvic organs or tissues, complete
636.30	Illegally induced abortion, complicated by renal failure, unspecified
636.31	Illegally induced abortion, complicated by renal failure, incomplete
636.32	Illegally induced abortion, complicated by renal failure, complete
636.40	Illegally induced abortion, complicated by metabolic disorder, unspecified
636.41	Illegally induced abortion, complicated by metabolic disorder, incomplete
636.42	Illegally induced abortion, complicated by metabolic disorder, complete
636.50	Illegally induced abortion, complicated by shock, unspecified
636.51	Illegally induced abortion, complicated by shock, incomplete
636.52	Illegally induced abortion, complicated by shock, complete
636.60	Illegally induced abortion, complicated by embolism, unspecified
636.61	Illegally induced abortion, complicated by embolism, incomplete
636.62	Illegally induced abortion, complicated by embolism, complete
636.70	Illegally induced abortion, with other specified complications, unspecified
636.71	Illegally induced abortion, with other specified complications, incomplete
636.72	Illegally induced abortion, with other specified complications, complete
636.80	Illegally induced abortion, with unspecified complication, unspecified
636.81	Illegally induced abortion, with unspecified complication, incomplete
636.82	Illegally induced abortion, with unspecified complication, complete
636.90	Illegally induced abortion, without mention of complication, unspecified
636.91	Illegally induced abortion, without mention of complication, incomplete
636.92	Illegally induced abortion, without mention of complication, complete
637.00	Unspecified abortion, complicated by genital tract and pelvic infection, unspecified

637.01	Unspecified abortion, complicated by genital tract and pelvic infection, incomplete
637.02	Unspecified abortion, complicated by genital tract and pelvic infection, complete
637.10	Unspecified abortion, complicated by delayed or excessive hemorrhage, unspecified
637.11	Unspecified abortion, complicated by delayed or excessive hemorrhage, incomplete
637.12	Unspecified abortion, complicated by delayed or excessive hemorrhage, complete
637.20	Unspecified abortion, complicated by damage to pelvic organs or tissues, unspecified
637.21	Unspecified abortion, complicated by damage to pelvic organs or tissues, incomplete
637.22	Unspecified abortion, complicated by damage to pelvic organs or tissues, complete
637.30	Unspecified abortion, complicated by renal failure, unspecified
637.31	Unspecified abortion, complicated by renal failure, incomplete
637.32	Unspecified abortion, complicated by renal failure, complete
637.40	Unspecified abortion, complicated by metabolic disorder, unspecified
637.41	Unspecified abortion, complicated by metabolic disorder, incomplete
637.42	Unspecified abortion, complicated by metabolic disorder, complete
637.50	Unspecified abortion, complicated by shock, unspecified
637.51	Unspecified abortion, complicated by shock, incomplete
637.52	Unspecified abortion, complicated by shock, complete
637.60	Unspecified abortion, complicated by embolism, unspecified
637.61	Unspecified abortion, complicated by embolism, incomplete
637.62	Unspecified abortion, complicated by embolism, complete
637.70	Unspecified abortion, with other specified complications, unspecified
637.71	Unspecified abortion, with other specified complications, incomplete
637.72	Unspecified abortion, with other specified complications, complete
637.80	Unspecified abortion, with unspecified complication, unspecified
637.81	Unspecified abortion, with unspecified complication, incomplete
637.82	Unspecified abortion, with unspecified complication, complete
637.90	Unspecified abortion, without mention of complication, unspecified
637.91	Unspecified abortion, without mention of complication, incomplete
637.92	Unspecified abortion, without mention of complication, complete
638.0	Failed attempted abortion complicated by genital tract and pelvic infection
638.1	Failed attempted abortion complicated by delayed or excessive hemorrhage
638.2	Failed attempted abortion complicated by damage to pelvic organs or tissues
638.3	Failed attempted abortion complicated by renal failure

638.4	Failed attempted abortion complicated by metabolic disorder
638.5	Failed attempted abortion complicated by shock
638.6	Failed attempted abortion complicated by embolism
638.7	Failed attempted abortion with other specified complications
638.8	Failed attempted abortion with unspecified complication
638.9	Failed attempted abortion without mention of complication
639.0	Genital tract and pelvic infection following abortion or ectopic and molar pregnancies
639.1	Delayed or excessive hemorrhage following abortion or ectopic and molar pregnancies
639.2	Damage to pelvic organs following abortion or ectopic and molar pregnancies
639.3	Kidney failure following abortion or ectopic and molar pregnancies
639.4	Metabolic disorders following abortion or ectopic and molar pregnancies
639.5	Shock following abortion or ectopic and molar pregnancies
639.6	Embolism following abortion or ectopic and molar pregnancies
639.8	Other specified complications following abortion or ectopic and molar pregnancies
639.9	Unspecified complication following abortion or ectopic and molar pregnancies
ICD-9 procedure codes	
69.01	Dilation and curettage for termination of pregnancy
69.51	Aspiration curettage of uterus for termination of pregnancy
74.3	Removal of extratubal ectopic pregnancy
ICD-10 diagnosis codes	
O00.00	Abdominal pregnancy without intrauterine pregnancy
O00.01	Abdominal pregnancy with intrauterine pregnancy
O00.101	Right tubal pregnancy without intrauterine pregnancy
O00.102	Left tubal pregnancy without intrauterine pregnancy
O00.111	Right tubal pregnancy with intrauterine pregnancy
O00.112	Left tubal pregnancy with intrauterine pregnancy
O00.201	Right ovarian pregnancy without intrauterine pregnancy
O00.202	Left ovarian pregnancy without intrauterine pregnancy
O00.211	Right ovarian pregnancy with intrauterine pregnancy
O00.212	Left ovarian pregnancy with intrauterine pregnancy
O00.80	Other ectopic pregnancy without intrauterine pregnancy
O00.81	Other ectopic pregnancy with intrauterine pregnancy
O00.90	Unspecified ectopic pregnancy without intrauterine pregnancy
O00.91	Unspecified ectopic pregnancy with intrauterine pregnancy
O01.0	Classical hydatidiform mole
O01.1	Incomplete and partial hydatidiform mole

O01.9	Hydatidiform mole, unspecified
O02.0	Blighted ovum and nonhydatidiform mole
O02.1	Missed abortion
O02.81	Inappropriate change in quantitative human chorionic gonadotropin (hCG) in early pregnancy
O02.89	Other abnormal products of conception
O02.9	Abnormal product of conception, unspecified
O03.0	Genital tract and pelvic infection following incomplete spontaneous abortion
O03.1	Delayed or excessive hemorrhage following incomplete spontaneous abortion
O03.2	Embolism following incomplete spontaneous abortion
O03.30	Unspecified complication following incomplete spontaneous abortion
O03.31	Shock following incomplete spontaneous abortion
O03.32	Renal failure following incomplete spontaneous abortion
O03.33	Metabolic disorder following incomplete spontaneous abortion
O03.34	Damage to pelvic organs following incomplete spontaneous abortion
O03.35	Other venous complications following incomplete spontaneous abortion
O03.36	Cardiac arrest following incomplete spontaneous abortion
O03.37	Sepsis following incomplete spontaneous abortion
O03.38	Urinary tract infection following incomplete spontaneous abortion
O03.39	Incomplete spontaneous abortion with other complications
O03.4	Incomplete spontaneous abortion without complication
O03.5	Genital tract and pelvic infection following complete or unspecified spontaneous abortion
O03.6	Delayed or excessive hemorrhage following complete or unspecified spontaneous abortion
O03.7	Embolism following complete or unspecified spontaneous abortion
O03.80	Unspecified complication following complete or unspecified spontaneous abortion
O03.81	Shock following complete or unspecified spontaneous abortion
O03.82	Renal failure following complete or unspecified spontaneous abortion
O03.83	Metabolic disorder following complete or unspecified spontaneous abortion
O03.84	Damage to pelvic organs following complete or unspecified spontaneous abortion
O03.85	Other venous complications following complete or unspecified spontaneous abortion
O03.86	Cardiac arrest following complete or unspecified spontaneous abortion
O03.87	Sepsis following complete or unspecified spontaneous abortion
O03.88	Urinary tract infection following complete or unspecified spontaneous abortion
O03.89	Complete or unspecified spontaneous abortion with other complications
O03.9	Complete or unspecified spontaneous abortion without complication

O04.5	Genital tract and pelvic infection following (induced) termination of pregnancy
O04.6	Delayed or excessive hemorrhage following (induced) termination of pregnancy
O04.7	Embolism following (induced) termination of pregnancy
O04.80	(Induced) termination of pregnancy with unspecified complications
O04.81	Shock following (induced) termination of pregnancy
O04.82	Renal failure following (induced) termination of pregnancy
O04.83	Metabolic disorder following (induced) termination of pregnancy
O04.84	Damage to pelvic organs following (induced) termination of pregnancy
O04.85	Other venous complications following (induced) termination of pregnancy
O04.86	Cardiac arrest following (induced) termination of pregnancy
O04.87	Sepsis following (induced) termination of pregnancy
O04.88	Urinary tract infection following (induced) termination of pregnancy
O04.89	(Induced) termination of pregnancy with other complications
O07.0	Genital tract and pelvic infection following failed attempted termination of pregnancy
O07.1	Delayed or excessive hemorrhage following failed attempted termination of pregnancy
O07.2	Embolism following failed attempted termination of pregnancy
O07.30	Failed attempted termination of pregnancy with unspecified complications
O07.31	Shock following failed attempted termination of pregnancy
O07.32	Renal failure following failed attempted termination of pregnancy
O07.33	Metabolic disorder following failed attempted termination of pregnancy
O07.34	Damage to pelvic organs following failed attempted termination of pregnancy
O07.35	Other venous complications following failed attempted termination of pregnancy
O07.36	Cardiac arrest following failed attempted termination of pregnancy
O07.37	Sepsis following failed attempted termination of pregnancy
O07.38	Urinary tract infection following failed attempted termination of pregnancy
O07.39	Failed attempted termination of pregnancy with other complications
O07.4	Failed attempted termination of pregnancy without complication
O08.0	Genital tract and pelvic infection following ectopic and molar pregnancy
O08.1	Delayed or excessive hemorrhage following ectopic and molar pregnancy
O08.2	Embolism following ectopic and molar pregnancy
O08.3	Shock following ectopic and molar pregnancy
O08.4	Renal failure following ectopic and molar pregnancy
O08.5	Metabolic disorder following ectopic and molar pregnancy
O08.6	Damage to pelvic organs following ectopic and molar pregnancy
O08.7	Other venous complications following ectopic and molar pregnancy
O08.81	Cardiac arrest following ectopic and molar pregnancy

O08.82	Sepsis following ectopic and molar pregnancy
O08.83	Urinary tract infection ectopic and molar pregnancy
O08.89	Other complications following ectopic and molar pregnancy
O08.9	Unspecified complication following ectopic and molar pregnancy
	Codes O05 and O06 were omitted as the US ICD-10-CM version does not contain these codes
CPT codes	
59120	Surgical treatment of ectopic pregnancy; tubal or ovarian, requiring salpingectomy and/or oophorectomy, abdominal or vaginal approach
59121	Surgical treatment of ectopic pregnancy; tubal or ovarian, without salpingectomy and/or oophorectomy
59130	Surgical treatment of ectopic pregnancy; abdominal pregnancy
59135	Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy requiring total hysterectomy
59136	Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy with partial resection of uterus
59140	Surgical treatment of ectopic pregnancy; cervical, with evacuation
59150	Laparoscopic treatment of ectopic pregnancy; without salpingectomy and/or oophorectomy
59151	Laparoscopic treatment of ectopic pregnancy; with salpingectomy and/or oophorectomy
59840	Induced abortion, by dilation and curettage
59841	Induced abortion, by dilation and evacuation
59850	Induced abortion, by one or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines
59851	Induced abortion, by one or more intra-amniotic injections (amniocentesis injections), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation
59852	Induced abortion, by one or more intra-amniotic injections (amniocentesisinjections), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed intra-amniotic injection)
59855	Induced abortion, by one or more vaginal suppositories (i.e., prostaglandin) with or without cervical dilation (i.e., laminaria), including hospital admission and visits, delivery of fetus and secundines
59856	Induced abortion, by one or more vaginal suppositories (i.e., prostaglandin) with or without cervical dilation (i.e., laminaria), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation
59857	Induced abortion, by one or more vaginal suppositories (i.e., prostaglandin) with or without cervical dilation (i.e., laminaria), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed medical evacuation)
59866	Multifetal pregnancy reduction(s) (MPR)
59812	Treatment of incomplete abortion, any trimester, completed surgically

59820	Treatment of missed abortion, completed surgically; first trimester
59821	Treatment of missed abortion, completed surgically; second trimester
59830	Treatment of septic abortion, completed surgically

Prenatal Care

Code	Description
ICD-9 diagnosis codes	
640.xx	Hemorrhage in early pregnancy
641.xx	Antepartum hemorrhage, abruptio placentae, and placenta previa
642.xx	Hypertension complicating pregnancy, childbirth, and the puerperium
643.xx	Excessive vomiting in pregnancy
644.xx	Early or threatened labor
645.xx	Late pregnancy
646.xx	Other complications of pregnancy, not elsewhere classified
647.xx	Infectious and parasitic conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium
648.xx	Other current conditions in the mother classifiable elsewhere, but Complicating pregnancy, childbirth, or the puerperium
649.xx	Other conditions or status of the mother complicating pregnancy, childbirth, or puerperium
651.xx	Multiple gestation
652.xx	Malposition or malpresentation of fetus
653.xx	Disproportion
654.xx	Abnormality of organs and soft tissues of pelvis
655.xx	Known or suspected fetal abnormality affecting management of mother
656.xx	Other known or suspected fetal and placental problems affecting management of mother
657.xx	Polyhydramnios
658.xx	Other problems associated with amniotic cavity and membranes
659.xx	Other indications for care or intervention related to labor and delivery, not elsewhere classified
665.xx	Other obstetrical trauma
V22.x	Normal pregnancy
V23.xx	Supervision of high risk pregnancy
V28.xx	Encounter for antenatal screening of mother
V72.4x	Pregnancy examination or test
ICD-9 procedure codes	
75.xx	Other obstetric operations
ICD-10 diagnosis codes	
O09.xxx	Supervision of high risk pregnancy
O10.xxx	Pre-existing hypertension complicating pregnancy, childbirth, and the puerperium
O11.x	Pre-existing hypertension with pre-eclampsia

O12.xx	Gestational [pregnancy-induced] edema and proteinuria without hypertension
O13.x	Gestational [pregnancy-induced] hypertension without significant proteinuria
O14.xx	Pre-eclampsia
O16.x	Unspecified maternal hypertension
O20.x	Hemorrhage in early pregnancy
O21.x	Excessive vomiting in pregnancy
O22.xxx	Venous complications and hemorrhoids in pregnancy
O23.xxx	Infections of genitourinary tract in pregnancy
O24.xxx	Diabetes mellitus in pregnancy, childbirth, and the puerperium
025.xx	Malnutrition in pregnancy, childbirth and the puerperium
O26.xxx	Maternal care for other conditions predominantly related to pregnancy
O28.x	Abnormal findings on antenatal screening of mother
O29.xxx	Complications of anesthesia during pregnancy
O30.xxx	Multiple gestation
O31.xxxx	Complications specific to multiple gestation
O32.xxxx	Maternal care for malpresentation of fetus
O33.xxxx	Maternal care for disproportion
O34.xxx	Maternal care for abnormality of pelvic organs
O35.xxxx	Maternal care for known or suspected fetal abnormality and damage
O36.xxxx	Maternal care for other fetal problems
O40.xxxx	Polyhydramnios
O41.xxxx	Other disorders of amniotic fluid and membranes
O42.xxx	Premature rupture of membranes
O43.xxx	Placental disorders
O44.xx	Placenta previa
O45.xxx	Premature separation of placenta [abruptio placentae]
O46.xxx	Antepartum hemorrhage, not elsewhere classified
O47.xx	False labor
O48.x	Late pregnancy
O60.xxxx	Preterm labor
O61.x	Failed induction of labor
O62.x	Abnormalities of forces of labor
O63.x	Long labor
O88.xxx	Obstetric embolism
O91.xxx	Infections of the breast associated with pregnancy, the puerperium and lactation

O92.xxx	Other disorders of breast and disorders of lactation associated with pregnancy and the puerperium
O98.xxx	Maternal infectious and parasitic diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium
O99.xxx	Other maternal diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium
Z32.xx	Encounter for pregnancy test and childbirth and childcare instruction
Z33.x	Pregnant state
Z34.xx	Encounter for supervision of normal pregnancy
Z36.xx	Encounter for antenatal screening of mother
Z76.81	Expectant parent(s) prebirth pediatrician visit
ICD-10 procedure codes	
0UVC0CZ	Restriction of Cervix with Extralum Dev, Open Approach
0UVC0DZ	Restriction of Cervix with Intralum Dev, Open Approach
0UVC0ZZ	Restriction of Cervix, Open Approach
0UVC3CZ	Restriction of Cervix with Extralum Dev, Perc Approach
0UVC3DZ	Restriction of Cervix with Intralum Dev, Perc Approach
0UVC3ZZ	Restriction of Cervix, Percutaneous Approach
0UVC4CZ	Restriction of Cervix with Extralum Dev, Perc Endo Approach
0UVC4DZ	Restriction of Cervix with Intralum Dev, Perc Endo Approach
0UVC4ZZ	Restriction of Cervix, Percutaneous Endoscopic Approach
0UVC7DZ	Restriction of Cervix with Intraluminal Device, Via Opening
0UVC7ZZ	Restriction of Cervix, Via Natural or Artificial Opening
0UVC8DZ	Restriction of Cervix with Intraluminal Device, Endo
0UVC8ZZ	Restriction of Cervix, Endo
HCPCS codes	
H1001	Prenatal care, at-risk enhanced service; antepartum management
H1000	Prenatal care, at-risk assessment
H1002	Prenatal care, at risk enhanced service; care coordination
H1003	Prenatal care, at-risk enhanced service; education
H1005	Prenatal care, at-risk enhanced service package (includes H1001-H1004)
H1004	Prenatal care, at-risk enhanced service; follow-up home visit
CPT codes	
0500F	Initial prenatal care visit (report at first prenatal encounter with health care professional providing obstetrical care. Report also date of visit and, in a separate field, the date of the last menstrual period [LMP]) (Prenatal)
0501F	Prenatal flow sheet documented in medical record by first prenatal visit (documentation includes at minimum blood pressure, weight, urine protein, uterine size, fetal heart tones, and estimated date of delivery). Report also: date of visit and, in a separ

0502F	Subsequent prenatal care visit (Prenatal) [Excludes: patients who are seen for a condition unrelated to pregnancy or prenatal care (eg, an upper respiratory infection; patients seen for consultation only, not for continuing care)]
4178F	Anti-D immune globulin received between 26 and 30 weeks gestation (Pre-Cf)
59000	Amniocentesis; diagnostic
59015	Chorionic villus sampling, any method
59025	Fetal non-stress test
59030	Fetal scalp blood sampling
59070	Transabdominal amnioinfusion, including ultrasound guidance
59072	Fetal umbilical cord occlusion, including ultrasound guidance
59074	Fetal fluid drainage (eg, vesicocentesis, thoracocentesis, paracentesis), including ultrasound guidance
59076	Fetal shunt placement, including ultrasound guidance
59320	Cerclage of cervix, during pregnancy; vaginal
59425	Antepartum care only; 4-6 visits
59426	Antepartum care only; 7 or more visits
59897	Unlisted fetal invasie procedure, including ultrasound guidance, when performed
59898	Unlisted laparoscopy procedure, maternity care and delivery
59899	Unlisted procedure, maternity care and delivery
76801	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, first trimester (< 14 weeks 0 days), transabdominal approach; single or first gestation
76802	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, first trimester (< 14 weeks 0 days), transabdominal approach; each additional gestation (List separately in addition to code for primary procedure)
76805	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; single or first gestation
76810	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; each additional gestation (List separately in addition to code for primary procedure)
76811	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation plus detailed fetal anatomic examination, transabdominal approach; single or first gestation
76813	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation

76815	Ultrasound, pregnant uterus, real time with image documentation, limited (eg, fetal heart beat, placental location, fetal position and/or qualitative amniotic fluid volume), 1 or more fetuses
76816	Ultrasound, pregnant uterus, real time with image documentation, follow-up (eg, re-evaluation of fetal size by measuring standard growth parameters and amniotic fluid volume, re-evaluation of organ system(s) suspected or confirmed to be abnormal on a previous scan), transabdominal approach, per fetus
76817	Ultrasound, pregnant uterus, real time with image documentation, transvaginal
76818	Fetal biophysical profile; with non-stress testing
76819	Fetal biophysical profile; without non-stress testing
76820	Doppler velocimetry, fetal; umbilical artery
76821	Doppler velocimetry, fetal; middle cerebral artery
76825	Echocardiography, fetal, cardiovascular system, real time with image documentation (2D), with or without M-mode recording
76826	Echocardiography, fetal, cardiovascular system, real time with image documentation (2D), with or without M-mode recording; follow-up or repeat study
76827	Doppler echocardiography, fetal, pulsed wave and/or continuous wave with spectral display; complete
76828	Doppler echocardiography, fetal, pulsed wave and/or continuous wave with spectral display; follow-up or repeat study
76831	Saline infusion sonohysterography (SIS), including color flow Doppler, when performed
76941	Ultrasonic guidance for intrauterine fetal transfusion or cordocentesis, imaging supervision and interpretation
76945	Ultrasonic guidance for chorionic villus sampling, imaging supervision and interpretation
76946	Ultrasonic guidance for amniocentesis, imaging supervision and interpretation
80055	Obstetric panel This panel must include the following: Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Hepatitis B surface antigen (HBsAg) (87340) Antibody, rubella (86762) Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART) (86592) Antibody screen, RBC, each serum technique (86850) Blood typing, ABO (86900) AND Blood typing, Rh (D) (86901)
81025	Urine pregnancy test, by visual color comparison methods
82106	Alpha-fetoprotein (AFP); amniotic fluid
82677	Estriol
82731	Fetal fibronectin, cervicovaginal secretions, semi-quantitative
83632	Lactogen, human placental (HPL) human chorionic somatomammotropin
83661	Fetal lung maturity assessment; lecithin sphingomyelin (L/S) ratio

83662	Fetal lung maturity assessment; foam stability test
83663	Fetal lung maturity assessment; fluorescence polarization
84081	Phosphatidylglycerol
88235	Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells

14.4 Breast cancers and other gynaecological cancers

Breast cancer

Code	Description
ICD-9	
174.0	Malignant neoplasm of nipple and areola of female breast
174.1	Malignant neoplasm of central portion of female breast
174.2	Malignant neoplasm of upper-inner quadrant of female breast
174.3	Malignant neoplasm of lower-inner quadrant of female breast
174.4	Malignant neoplasm of upper-outer quadrant of female breast
174.5	Malignant neoplasm of lower-outer quadrant of female breast
174.6	Malignant neoplasm of axillary tail of female breast
174.8	Malignant neoplasm of other specified sites of female breast
174.9	Malignant neoplasm of breast (female), unspecified
ICD-10	
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.911	Malignant neoplasm of unspecified site of right female breast

C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast

Cervical cancer

Code	Description
ICD-9	
180.0	Malignant neoplasm of endocervix
180.1	Malignant neoplasm of exocervix
180.8	Malignant neoplasm of other specified sites of cervix
180.9	Malignant neoplasm of cervix uteri, unspecified site
ICD-10	
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C53.8	Malignant neoplasm of overlapping sites of cervix uteri
C53.9	Malignant neoplasm of cervix uteri, unspecified

Endometrial cancer

Code	Description
ICD-9	
182.0	Malignant neoplasm of corpus uteri, except isthmus
ICD-10	
C54.1	Malignant neoplasm of endometrium

Ovarian cancer

Code	Description
ICD-9	
183.0	Malignant neoplasm of ovary
ICD-10	
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary

Malignancies

Code	Description
ICD-9	
140.0	Malignant neoplasm of upper lip, vermilion border
140.1	Malignant neoplasm of lower lip, vermilion border
140.3	Malignant neoplasm of upper lip, inner aspect
140.4	Malignant neoplasm of lower lip, inner aspect
140.5	Malignant neoplasm of lip, unspecified, inner aspect
140.6	Malignant neoplasm of commissure of lip
140.8	Malignant neoplasm of other sites of lip
140.9	Malignant neoplasm of lip, unspecified, vermilion border
141.0	Malignant neoplasm of base of tongue
141.1	Malignant neoplasm of dorsal surface of tongue
141.2	Malignant neoplasm of tip and lateral border of tongue
141.3	Malignant neoplasm of tip of ventral surface of tongue
141.4	Malignant neoplasm of anterior two-thirds of tongue, part unspecified
141.5	Malignant neoplasm of junctional zone of tongue
141.6	Malignant neoplasm of lingual tonsil
141.8	Malignant neoplasm of other sites of tongue
141.9	Malignant neoplasm of tongue, unspecified
142.0	Malignant neoplasm of parotid gland
142.1	Malignant neoplasm of submandibular gland
142.2	Malignant neoplasm of sublingual gland
142.8	Malignant neoplasm of other major salivary glands
142.9	Malignant neoplasm of salivary gland, unspecified
143.0	Malignant neoplasm of upper gum
143.1	Malignant neoplasm of lower gum
143.8	Malignant neoplasm of other sites of gum
143.9	Malignant neoplasm of gum, unspecified
144.0	Malignant neoplasm of anterior portion of floor of mouth
144.1	Malignant neoplasm of lateral portion of floor of mouth
144.8	Malignant neoplasm of other sites of floor of mouth
144.9	Malignant neoplasm of floor of mouth, part unspecified
145.0	Malignant neoplasm of cheek mucosa
145.1	Malignant neoplasm of vestibule of mouth
145.2	Malignant neoplasm of hard palate
145.3	Malignant neoplasm of soft palate
145.4	Malignant neoplasm of uvula
145.5	Malignant neoplasm of palate, unspecified

145.6	Malignant neoplasm of retromolar area
145.8	Malignant neoplasm of other specified parts of mouth
145.9	Malignant neoplasm of mouth, unspecified
146.0	Malignant neoplasm of tonsil
146.1	Malignant neoplasm of tonsillar fossa
146.2	Malignant neoplasm of tonsillar pillars (anterior) (posterior)
146.3	Malignant neoplasm of vallecular epiglottica
146.4	Malignant neoplasm of anterior aspect of epiglottis
146.5	Malignant neoplasm of junctional region of oropharynx
146.6	Malignant neoplasm of lateral wall of oropharynx
146.7	Malignant neoplasm of posterior wall of oropharynx
146.8	Malignant neoplasm of other specified sites of oropharynx
146.9	Malignant neoplasm of oropharynx, unspecified site
147.0	Malignant neoplasm of superior wall of nasopharynx
147.1	Malignant neoplasm of posterior wall of nasopharynx
147.2	Malignant neoplasm of lateral wall of nasopharynx
147.3	Malignant neoplasm of anterior wall of nasopharynx
147.8	Malignant neoplasm of other specified sites of nasopharynx
147.9	Malignant neoplasm of nasopharynx, unspecified site
148.0	Malignant neoplasm of postcricoid region of hypopharynx
148.1	Malignant neoplasm of pyriform sinus
148.2	Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
148.3	Malignant neoplasm of posterior hypopharyngeal wall
148.8	Malignant neoplasm of other specified sites of hypopharynx
148.9	Malignant neoplasm of hypopharynx, unspecified site
149.0	Malignant neoplasm of pharynx, unspecified
149.1	Malignant neoplasm of waldeyer’s ring
149.8	Malignant neoplasm of other sites within the lip and oral cavity
149.9	Malignant neoplasm of ill-defined sites within the lip and oral cavity
150.0	Malignant neoplasm of cervical esophagus
150.1	Malignant neoplasm of thoracic esophagus
150.2	Malignant neoplasm of abdominal esophagus
150.3	Malignant neoplasm of upper third of esophagus
150.4	Malignant neoplasm of middle third of esophagus
150.5	Malignant neoplasm of lower third of esophagus
150.8	Malignant neoplasm of other specified part of esophagus
150.9	Malignant neoplasm of esophagus, unspecified site
151.0	Malignant neoplasm of cardia
151.1	Malignant neoplasm of pylorus

151.2	Malignant neoplasm of pyloric antrum
151.3	Malignant neoplasm of fundus of stomach
151.4	Malignant neoplasm of body of stomach
151.5	Malignant neoplasm of lesser curvature of stomach, unspecified
151.6	Malignant neoplasm of greater curvature of stomach, unspecified
151.8	Malignant neoplasm of other specified sites of stomach
151.9	Malignant neoplasm of stomach, unspecified site
152.0	Malignant neoplasm of duodenum
152.1	Malignant neoplasm of jejunum
152.2	Malignant neoplasm of ileum
152.3	Malignant neoplasm of Meckel's diverticulum
152.8	Malignant neoplasm of other specified sites of small intestine
152.9	Malignant neoplasm of small intestine, unspecified site
153.0	Malignant neoplasm of hepatic flexure
153.1	Malignant neoplasm of transverse colon
153.2	Malignant neoplasm of descending colon
153.3	Malignant neoplasm of sigmoid colon
153.4	Malignant neoplasm of cecum
153.5	Malignant neoplasm of appendix vermiformis
153.6	Malignant neoplasm of ascending colon
153.7	Malignant neoplasm of splenic flexure
153.8	Malignant neoplasm of other specified sites of large intestine
153.9	Malignant neoplasm of colon, unspecified site
154.0	Malignant neoplasm of rectosigmoid junction
154.1	Malignant neoplasm of rectum
154.2	Malignant neoplasm of anal canal
154.3	Malignant neoplasm of anus, unspecified site
154.8	Malignant neoplasm of other sites of rectum, rectosigmoid junction, and anus
155.0	Malignant neoplasm of liver, primary
155.1	Malignant neoplasm of intrahepatic bile duct
155.2	Malignant neoplasm of liver, not specified as primary or secondary
156.0	Malignant neoplasm of gallbladder
156.1	Malignant neoplasm of extrahepatic bile ducts
156.2	Malignant neoplasm of ampulla of vater
156.8	Malignant neoplasm of other specified sites of gallbladder and extrahepatic bile ducts
156.9	Malignant neoplasm of biliary tract, part unspecified site
157.0	Malignant neoplasm of head of pancreas
157.1	Malignant neoplasm of body of pancreas

157.2	Malignant neoplasm of tail of pancreas
157.3	Malignant neoplasm of pancreatic duct
157.4	Malignant neoplasm of islets of Langerhans
157.8	Malignant neoplasm of other specified sites of pancreas
157.9	Malignant neoplasm of pancreas, part unspecified
158.0	Malignant neoplasm of retroperitoneum
158.8	Malignant neoplasm of specified parts of peritoneum
158.9	Malignant neoplasm of peritoneum, unspecified
159.0	Malignant neoplasm of intestinal tract, part unspecified
159.1	Malignant neoplasm of spleen, not elsewhere classified
159.8	Malignant neoplasm of other sites of digestive system and intra-abdominal organs
159.9	Malignant neoplasm of ill-defined sites within the digestive organs and peritoneum
160.0	Malignant neoplasm of nasal cavities
160.1	Malignant neoplasm of auditory tube, middle ear, and mastoid air cells
160.2	Malignant neoplasm of maxillary sinus
160.3	Malignant neoplasm of ethmoidal sinus
160.4	Malignant neoplasm of frontal sinus
160.5	Malignant neoplasm of sphenoidal sinus
160.8	Malignant neoplasm of other accessory sinuses
160.9	Malignant neoplasm of accessory sinus, unspecified
161.0	Malignant neoplasm of glottis
161.1	Malignant neoplasm of supraglottis
161.2	Malignant neoplasm of subglotitis
161.3	Malignant neoplasm of laryngeal cartilages
161.8	Malignant neoplasm of other specified sites of larynx
161.9	Malignant neoplasm of larynx, unspecified
162.0	Malignant neoplasm of trachea
162.2	Malignant neoplasm of main bronchus
162.3	Malignant neoplasm of upper lobe, bronchus or lung
162.4	Malignant neoplasm of middle lobe, bronchus or lung
162.5	Malignant neoplasm of lower lobe, bronchus or lung
162.8	Malignant neoplasm of other parts of bronchus or lung
162.9	Malignant neoplasm of bronchus long, unspecified
163.0	Malignant neoplasm of parietal pleura
163.1	Malignant neoplasm of visceral pleura
163.8	Malignant neoplasm of other specified sites of pleura
163.9	Malignant neoplasm of pleura, unspecified

164.0	Malignant neoplasm of thymus
164.1	Malignant neoplasm of heart
164.2	Malignant neoplasm of anterior mediastinum
164.3	Malignant neoplasm of posterior mediastinum
164.8	Malignant neoplasm of other parts of mediastinum
164.9	Malignant neoplasm of mediastinum, part unspecified
165.0	Malignant neoplasm of upper respiratory tract, part unspecified
165.8	Malignant neoplasm of other sites within the respiratory system and intrathoracic organs
165.9	Malignant neoplasm of ill-defined sites within the respiratory system
170.0	Malignant neoplasm of bones of skull and face, except mandible
170.1	Malignant neoplasm of mandible
170.2	Malignant neoplasm of vertebral column, excluding sacrum and coccyx
170.3	Malignant neoplasm of ribs, sternum, and clavicle
170.4	Malignant neoplasm of scapula and long bones of upper limb
170.5	Malignant neoplasm of short bones of upper limb
170.6	Malignant neoplasm of pelvic bones, sacrum, and coccyx
170.7	Malignant neoplasm of long bones of lower limb
170.8	Malignant neoplasm of short bones of lower limb
170.9	Malignant neoplasm of bone and articular cartilage, site unspecified
171.0	Malignant neoplasm of connective and other soft tissue of head, face, and neck
171.2	Malignant neoplasm of connective and other soft tissue of upper limb, including shoulder
171.3	Malignant neoplasm of connective and other soft tissue of lower limb, including hip
171.4	Malignant neoplasm of connective and other soft tissue of thorax
171.5	Malignant neoplasm of connective and other soft tissue of abdomen
171.6	Malignant neoplasm of connective and other soft tissue of pelvis
171.7	Malignant neoplasm of connective and other soft tissue of trunk, unspecified
171.8	Malignant neoplasm of other specified sites of connective and other soft tissue
171.9	Malignant neoplasm of connective and other soft tissue, site unspecified
172.0	Malignant melanoma of skin of lip
172.1	Malignant melanoma of skin of eyelid, including canthus
172.2	Malignant melanoma of skin of ear and external auditory canal
172.3	Malignant melanoma of skin of other and unspecified parts of face
172.4	Malignant melanoma of skin of scalp and neck
172.5	Malignant melanoma of skin of trunk, except scrotum
172.6	Malignant melanoma of skin of upper limb, including shoulder
172.7	Malignant melanoma of skin of lower limb, including hip

172.8	Malignant melanoma of other specified sites of skin
172.9	Malignant melanoma of skin, site unspecified
173.00	Unspecified malignant neoplasm of skin of lip
173.01	Basal cell carcinoma of skin of lip
173.02	Squamous cell carcinoma of skin of lip
173.09	Other specified malignant neoplasm of skin of lip
173.10	Unspecified malignant neoplasm of eyelid, including canthus
173.11	Basal cell carcinoma of eyelid, including canthus
173.12	Squamous cell carcinoma of eyelid, including canthus
173.19	Other specified malignant neoplasm of eyelid, including canthus
173.20	Unspecified malignant neoplasm of skin of ear and external auditory canal
173.21	Basal cell carcinoma of skin of ear and external auditory canal
173.22	Squamous cell carcinoma of skin of ear and external auditory canal
173.29	Other specified malignant neoplasm of skin of ear and external auditory canal
173.30	Unspecified malignant neoplasm of skin of other and unspecified parts of face
173.31	Basal cell carcinoma of skin of other and unspecified parts of face
173.32	Squamous cell carcinoma of skin of other and unspecified parts of face
173.39	Other specified malignant neoplasm of skin of lip other and unspecified parts of face
173.40	Unspecified malignant neoplasm of scalp and skin of neck
173.41	Basal cell carcinoma of scalp and skin of neck
173.42	Squamous cell carcinoma of scalp and skin of neck
173.49	Other specified malignant neoplasm of scalp and skin of neck
173.50	Unspecified malignant neoplasm of skin of trunk, except scrotum
173.51	Basal cell carcinoma of skin of trunk, except scrotum
173.52	Squamous cell carcinoma of skin of trunk, except scrotum
173.59	Other specified malignant neoplasm of skin of trunk, except scrotum
173.60	Unspecified malignant neoplasm of skin of upper limb, including shoulder
173.61	Basal cell carcinoma of skin of upper limb, including shoulder
173.62	Squamous cell carcinoma of skin of upper limb, including shoulder
173.69	Other specified malignant neoplasm of skin of upper limb, including shoulder
173.70	Unspecified malignant neoplasm of skin of lower limb, including hip
173.71	Basal cell carcinoma of skin of lower limb, including hip
173.72	Squamous cell carcinoma of skin of lower limb, including hip
173.79	Other specified malignant neoplasm of skin of lower limb, including hip
173.80	Unspecified malignant neoplasm of skin of other specified sites of skin
173.81	Basal cell carcinoma of skin of other specified sites of skin
173.82	Squamous cell carcinoma of skin of other specified sites of skin
173.89	Other specified malignant neoplasm of skin of other specified sites of skin

173.90	Unspecified malignant neoplasm of skin, site unspecified
173.91	Basal cell carcinoma of skin of skin, site unspecified
173.92	Squamous cell carcinoma of skin of skin, site unspecified
173.99	Other specified malignant neoplasm of skin of skin, site unspecified
174.0	Malignant neoplasm of nipple and areola of female breast
174.1	Malignant neoplasm of central portion of female breast
174.2	Malignant neoplasm of upper-inner quadrant of female breast
174.3	Malignant neoplasm of lower-inner quadrant of female breast
174.4	Malignant neoplasm of upper-outer quadrant of female breast
174.5	Malignant neoplasm of lower-outer quadrant of female breast
174.6	Malignant neoplasm of axillary tail of female breast
174.8	Malignant neoplasm of other specified sites of female breast
174.9	Malignant neoplasm of breast (female), unspecified
176.0	Kaposi’s sarcoma, skin
176.1	Kaposi’s sarcoma, soft tissue
176.2	Kaposi’s sarcoma, palate
176.3	Kaposi’s sarcoma, gastrointestinal sites
176.4	Kaposi’s sarcoma, lung
176.5	Kaposi’s sarcoma, lymph nodes
176.8	Kaposi’s sarcoma, other specified sites
176.9	Kaposi’s sarcoma, unspecified site
179	Malignant neoplasm of uterus, part unspecified
180.0	Malignant neoplasm of endocervix
180.1	Malignant neoplasm of exocervix
180.8	Malignant neoplasm of other specified sites of cervix
180.9	Malignant neoplasm of cervix uteri, unspecified site
181	Malignant neoplasm of placenta
182.0	Malignant neoplasm of corpus uteri, except isthmus
182.1	Malignant neoplasm of isthmus
182.8	Malignant neoplasm of other specified sites of body of uterus
183.0	Malignant neoplasm of ovary
183.2	Malignant neoplasm of fallopian tub
183.3	Malignant neoplasm of broad ligament of uterus
183.4	Malignant neoplasm of parametrium
183.5	Malignant neoplasm of round ligament of uterus
183.8	Malignant neoplasm of other specified sites of uterine adnexa
183.9	Malignant neoplasm of uterine adnexa, unspecified site
184.0	Malignant neoplasm of vagina

184.1	Malignant neoplasm of labia majora
184.2	Malignant neoplasm of labia minora
184.3	Malignant neoplasm of clitoris
184.4	Malignant neoplasm of vulva, unspecified site
184.8	Malignant neoplasm of other specified sites of female genital organs
184.9	Malignant neoplasm of female genital organ, site unspecified
188.0	Malignant neoplasm of trigone of urinary bladder
188.1	Malignant neoplasm of dome of urinary bladder
188.2	Malignant neoplasm of lateral wall of urinary bladder
188.3	Malignant neoplasm of anterior wall of urinary bladder
188.4	Malignant neoplasm of posterior wall of urinary bladder
188.5	Malignant neoplasm of bladder neck
188.6	Malignant neoplasm of ureteric orifice
188.7	Malignant neoplasm of urachus
188.8	Malignant neoplasm of other specified sites of bladder
188.9	Malignant neoplasm of bladder, part unspecified
189.0	Malignant neoplasm of kidney, except pelvis
189.1	Malignant neoplasm of renal pelvis
189.2	Malignant neoplasm of ureter
189.3	Malignant neoplasm of urethra
189.4	Malignant neoplasm of paraurethral glands
189.8	Malignant neoplasm of other specified sites of urinary organs
189.9	Malignant neoplasm of urinary organ, site unspecified
190.0	Malignant neoplasm of eyeball, except conjunctiva, cornea, retina, and choroid
190.1	Malignant neoplasm of orbit
190.2	Malignant neoplasm of lacrimal gland
190.3	Malignant neoplasm of conjunctiva
190.4	Malignant neoplasm of cornea
190.5	Malignant neoplasm of retina
190.6	Malignant neoplasm of choroid
190.7	Malignant neoplasm of lacrimal duct
190.8	Malignant neoplasm of other specified sites of eye
190.9	Malignant neoplasm of eye, part unspecified
191.0	Malignant neoplasm of cerebrum, except lobes and ventricles
191.1	Malignant neoplasm of frontal lobe
191.2	Malignant neoplasm of temporal lobe
191.3	Malignant neoplasm of parietal lobe
191.4	Malignant neoplasm of occipital lobe

191.5	Malignant neoplasm of ventricles
191.6	Malignant neoplasm of cerebellum nos
191.7	Malignant neoplasm of brain stem
191.8	Malignant neoplasm of other parts of brain
191.9	Malignant neoplasm of brain, unspecified
192.0	Malignant neoplasm of cranial nerves
192.1	Malignant neoplasm of cerebral meninges
192.2	Malignant neoplasm of spinal cord
192.3	Malignant neoplasm of spinal meninges
192.8	Malignant neoplasm of other specified sites of nervous system
192.9	Malignant neoplasm of nervous system, part unspecified
193	Malignant neoplasm of thyroid gland
194.0	Malignant neoplasm of adrenal gland
194.1	Malignant neoplasm of parathyroid gland
194.3	Malignant neoplasm of pituitary gland and craniopharyngeal duct
194.4	Malignant neoplasm of pineal gland
194.5	Malignant neoplasm of carotid body
194.6	Malignant neoplasm of aortic body and other paraganglia
194.8	Malignant neoplasm of other endocrine gland and related structures
194.9	Malignant neoplasm of endocrine gland, site unspecified
195.0	Malignant neoplasm of head, face, and neck
195.1	Malignant neoplasm of thorax
195.2	Malignant neoplasm of abdomen
195.3	Malignant neoplasm of pelvis
195.4	Malignant neoplasm of upper limb
195.5	Malignant neoplasm of lower limn
195.8	Malignant neoplasm of other specified sites
196.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face, and neck
196.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
196.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
196.3	Secondary and unspecified malignant neoplasm of lymph nodes of axilla and upper limb
196.5	Secondary and unspecified malignant neoplasm of lymph nodes of inguinal region and lower limb
196.6	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
196.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple sites
196.9	Secondary and unspecified malignant neoplasm of lymph nodes, site unspecified
197.0	Secondary malignant neoplasm of lung

197.1	Secondary malignant neoplasm of mediastinum
197.2	Secondary malignant neoplasm of pleura
197.3	Secondary malignant neoplasm of other respiratory organs
197.4	Secondary malignant neoplasm of small intestine including duodenum
197.5	Secondary malignant neoplasm of large intestine and rectum
197.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
197.7	Secondary malignant neoplasm of liver, secondary
197.8	Secondary malignant neoplasm of other digestive organs and spleen
198.0	Secondary malignant neoplasm of kidney
198.1	Secondary malignant neoplasm of other urinary organs
198.2	Secondary malignant neoplasm of skin
198.3	Secondary malignant neoplasm of brain and spinal cord
198.4	Secondary malignant neoplasm of other parts of nervous system
198.5	Secondary malignant neoplasm of bone and bone marrow
198.6	Secondary malignant neoplasm of ovary
198.7	Secondary malignant neoplasm of adrenal gland
198.81	Secondary malignant neoplasm of breast
198.82	Secondary malignant neoplasm of genital organs
198.89	Secondary malignant neoplasm of other specified sites
199.0	Disseminated malignant neoplasm without specification of site
199.1	Other malignant neoplasm without specification of site
199.2	Malignant neoplasm associated with transplant organ
200.00	Reticulosarcoma, unspecified site, extranodal and solid organ sites
200.01	Reticulosarcoma, lymph nodes of head, face, and neck
200.02	Reticulosarcoma, intrathoracic lymph nodes
200.03	Reticulosarcoma, intra-abdominal lymph nodes
200.04	Reticulosarcoma, lymph nodes of axilla and upper limb
200.05	Reticulosarcoma, lymph nodes of inguinal region and lower limb
200.06	Reticulosarcoma, intrapelvic lymph nodes
200.07	Reticulosarcoma, spleen
200.08	Reticulosarcoma, lymph nodes of multiple sites
200.10	Lymphoscarcoma, unspecified site, extranodal and solid organ sites
200.11	Lymphoscarcoma, lymph nodes of head, face, and neck
200.12	Lymphoscarcoma, intrathoracic lymph nodes
200.13	Lymphoscarcoma, intra-abdominal lymph nodes
200.14	Lymphoscarcoma, lymph nodes of axilla and upper limb
200.15	Lymphoscarcoma, lymph nodes of inguinal region and lower limb
200.16	Lymphoscarcoma, intrapelvic lymph nodes
200.17	Lymphoscarcoma, spleen

200.18	Lymphoscarcoma, lymph nodes of multiple sites
200.20	Burkitt's tumor or lymphoma, unspecified site, extranodal and solid organ sites
200.21	Burkitt's tumor or lymphoma, lymph nodes of head, face, and neck
200.22	Burkitt's tumor or lymphoma, intrathoracic lymph nodes
200.23	Burkitt's tumor or lymphoma, intra-abdominal lymph nodes
200.24	Burkitt's tumor or lymphoma, lymph nodes of axilla and upper limb
200.25	Burkitt's tumor or lymphoma, lymph nodes of inguinal region and lower limb
200.26	Burkitt's tumor or lymphoma, intrapelvic lymph nodes
200.27	Burkitt's tumor or lymphoma, spleen
200.28	Burkitt's tumor or lymphoma, lymph nodes of multiple sites
200.30	Marginal zone lymphoma, unspecified site, extranodal and solid organ sites
200.31	Marginal zone lymphoma, lymph nodes of head, face, and neck
200.32	Marginal zone lymphoma, intrathoracic lymph nodes
200.33	Marginal zone lymphoma, intra-abdominal lymph nodes
200.34	Marginal zone lymphoma, lymph nodes of axilla and upper limb
200.35	Marginal zone lymphoma, lymph nodes of inguinal region and lower limb
200.36	Marginal zone lymphoma, intrapelvic lymph nodes
200.37	Marginal zone lymphoma, spleen
200.38	Marginal zone lymphoma, lymph nodes of multiple sites
200.40	Mantle cell lymphoma, unspecified site, extranodal and solid organ sites
200.41	Mantle cell lymphoma, lymph nodes of head, face, and neck
200.42	Mantle cell lymphoma, intrathoracic lymph nodes
200.43	Mantle cell lymphoma, intra-abdominal lymph nodes
200.44	Mantle cell lymphoma, lymph nodes of axilla and upper limb
200.45	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
200.46	Mantle cell lymphoma, intrapelvic lymph nodes
200.47	Mantle cell lymphoma, spleen
200.48	Mantle cell lymphoma, lymph nodes of multiple sites
200.50	Primary central nervous system lymphoma, unspecified site, extranodal and solid organ sites
200.51	Primary central nervous system lymphoma, lymph nodes of head, face, and neck
200.52	Primary central nervous system lymphoma, intrathoracic lymph nodes
200.53	Primary central nervous system lymphoma, intra-abdominal lymph nodes
200.54	Primary central nervous system lymphoma, lymph nodes of axilla and upper limb
200.55	Primary central nervous system lymphoma, lymph nodes of inguinal region and lower limb
200.56	Primary central nervous system lymphoma, intrapelvic lymph nodes
200.57	Primary central nervous system lymphoma, spleen

200.58	Primary central nervous system lymphoma, lymph nodes of multiple sites
200.60	Anaplastic large cell lymphoma, unspecified site, extranodal and solid organ sites
200.61	Anaplastic large cell lymphoma, lymph nodes of head, face, and neck
200.62	Anaplastic large cell lymphoma, intrathoracic lymph nodes
200.63	Anaplastic large cell lymphoma, intra-abdominal lymph nodes
200.64	Anaplastic large cell lymphoma, lymph nodes of axilla and upper limb
200.65	Anaplastic large cell lymphoma, lymph nodes of inguinal region and lower limb
200.66	Anaplastic large cell lymphoma, intrapelvic lymph nodes
200.67	Anaplastic large cell lymphoma, spleen
200.68	Anaplastic large cell lymphoma, lymph nodes of multiple sites
200.70	Large cell lymphoma, unspecified site, extranodal and solid organ sites
200.71	Large cell lymphoma, lymph nodes of head, face, and neck
200.72	Large cell lymphoma, intrathoracic lymph nodes
200.73	Large cell lymphoma, intra-abdominal lymph nodes
200.74	Large cell lymphoma, lymph nodes of axilla and upper limb
200.75	Large cell lymphoma, lymph nodes of inguinal region and lower limb
200.76	Large cell lymphoma, intrapelvic lymph nodes
200.77	Large cell lymphoma, spleen
200.78	Large cell lymphoma, lymph nodes of multiple sites
200.80	Other named variants of lymphosarcoma and reticulosarcoma, unspecified site, extranodal and solid organ sites
200.81	Other named variants of lymphosarcoma and reticulosarcoma, lymph nodes of head, face, and neck
200.82	Other named variants of lymphosarcoma and reticulosarcoma, intrathoracic lymph nodes
200.83	Other named variants of lymphosarcoma and reticulosarcoma, intra-abdominal lymph nodes
200.84	Other named variants of lymphosarcoma and reticulosarcoma, lymph nodes of axilla and upper limb
200.85	Other named variants of lymphosarcoma and reticulosarcoma, lymph nodes of inguinal region and lower limb
200.86	Other named variants of lymphosarcoma and reticulosarcoma, intrapelvic lymph nodes
200.87	Other named variants of lymphosarcoma and reticulosarcoma, spleen
200.88	Other named variants of lymphosarcoma and reticulosarcoma, lymph nodes of multiple sites
201.00	Hodgkin’s paragranuloma, unspecified site, extranodal and solid organ sites
201.01	Hodgkin’s paragranuloma, lymph nodes of head, face, and neck
201.02	Hodgkin’s paragranuloma, intrathoracic lymph nodes
201.03	Hodgkin’s paragranuloma, intra-abdominal lymph nodes

201.04	Hodgkin’s paragranuloma, lymph nodes of axilla and upper limb
201.05	Hodgkin’s paragranuloma, lymph nodes of inguinal region and lower limb
201.06	Hodgkin’s paragranuloma, intrapelvic lymph nodes
201.07	Hodgkin’s paragranuloma, spleen
201.08	Hodgkin’s paragranuloma, lymph nodes of multiple sites
201.10	Hodgkin’s granuloma, unspecified site, extranodal and solid organ sites
201.11	Hodgkin’s granuloma, lymph nodes of head, face, and neck
201.12	Hodgkin’s granuloma, intrathoracic lymph nodes
201.13	Hodgkin’s granuloma, intra-abdominal lymph nodes
201.14	Hodgkin’s granuloma, lymph nodes of axilla and upper limb
201.15	Hodgkin’s granuloma, lymph nodes of inguinal region and lower limb
201.16	Hodgkin’s granuloma, intrapelvic lymph nodes
201.17	Hodgkin’s granuloma, spleen
201.18	Hodgkin’s granuloma, lymph nodes of multiple sites
201.20	Hodgkin’s sarcoma, unspecified site, extranodal and solid organ sites
201.21	Hodgkin’s sarcoma, lymph nodes of head, face, and neck
201.22	Hodgkin’s sarcoma, intrathoracic lymph nodes
201.23	Hodgkin’s sarcoma, intra-abdominal lymph nodes
201.24	Hodgkin’s sarcoma, lymph nodes of axilla and upper limb
201.25	Hodgkin’s sarcoma, lymph nodes of inguinal region and lower limb
201.26	Hodgkin’s sarcoma, intrapelvic lymph nodes
201.27	Hodgkin’s sarcoma, spleen
201.28	Hodgkin’s sarcoma, lymph nodes of multiple sites
201.40	Hodgkin’s disease, lymphocytic-histiocytic predominancy, unspecified site, extranodal and solid organ sites
201.41	Hodgkin’s disease, lymphocytic-histiocytic predominancy, lymph nodes of head, face, and neck
201.42	Hodgkin’s disease, lymphocytic-histiocytic predominancy, intrathoracic lymph nodes
201.43	Hodgkin’s disease, lymphocytic-histiocytic predominancy, intra-abdominal lymph nodes
201.44	Hodgkin’s disease, lymphocytic-histiocytic predominancy, lymph nodes of axilla and upper limb
201.45	Hodgkin’s disease, lymphocytic-histiocytic predominancy, lymph nodes of inguinal region and lower limb
201.46	Hodgkin’s disease, lymphocytic-histiocytic predominancy, intrapelvic lymph nodes
201.47	Hodgkin’s disease, lymphocytic-histiocytic predominancy, spleen
201.48	Hodgkin’s disease, lymphocytic-histiocytic predominancy, lymph nodes of multiple sites
201.50	Hodgkin’s disease, nodular sclerosis, unspecified site, extranodal and solid organ

	sites
201.51	Hodgkin’s disease, nodular sclerosis, lymph nodes of head, face, and neck
201.52	Hodgkin’s disease, nodular sclerosis, intrathoracic lymph nodes
201.53	Hodgkin’s disease, nodular sclerosis, intra-abdominal lymph nodes
201.54	Hodgkin’s disease, nodular sclerosis, lymph nodes of axilla and upper limb
201.55	Hodgkin’s paragranuloma, lymph nodes of inguinal region and lower limb disease, nodular sclerosis
201.56	Hodgkin’s disease, nodular sclerosis, intrapelvic lymph nodes
201.57	Hodgkin’s disease, nodular sclerosis, spleen
201.58	Hodgkin’s disease, nodular sclerosis, lymph nodes of multiple sites
201.60	Hodgkin’s disease, mixed cellularity, unspecified site, extranodal and solid organ sites
201.61	Hodgkin’s disease, mixed cellularity, lymph nodes of head, face, and neck
201.62	Hodgkin’s disease, mixed cellularity, intrathoracic lymph nodes
201.63	Hodgkin’s disease, mixed cellularity, intra-abdominal lymph nodes
201.64	Hodgkin’s disease, mixed cellularity, lymph nodes of axilla and upper limb
201.65	Hodgkin’s disease, mixed cellularity, lymph nodes of inguinal region and lower limb
201.66	Hodgkin’s disease, mixed cellularity, intrapelvic lymph nodes
201.67	Hodgkin’s disease, mixed cellularity, spleen
201.68	Hodgkin’s disease, mixed cellularity, lymph nodes of multiple sites
201.70	Hodgkin’s disease, lymphocytic depletion, unspecified site, extranodal and solid organ sites
201.71	Hodgkin’s disease, lymphocytic depletion, lymph nodes of head, face, and neck
201.72	Hodgkin’s disease, lymphocytic depletion, intrathoracic lymph nodes
201.73	Hodgkin’s disease, lymphocytic depletion, intra-abdominal lymph nodes
201.74	Hodgkin’s disease, lymphocytic depletion, lymph nodes of axilla and upper limb
201.75	Hodgkin’s disease, lymphocytic depletion, lymph nodes of inguinal region and lower limb
201.76	Hodgkin’s disease, lymphocytic depletion, intrapelvic lymph nodes
201.77	Hodgkin’s disease, lymphocytic depletion, spleen
201.78	Hodgkin’s disease, lymphocytic depletion, lymph nodes of multiple sites
201.90	Hodgkin’s disease, unspecified type, unspecified site, extranodal and solid organ sites
201.91	Hodgkin’s disease, unspecified type, lymph nodes of head, face, and neck
201.92	Hodgkin’s disease, unspecified type, intrathoracic lymph nodes
201.93	Hodgkin’s disease, unspecified type, intra-abdominal lymph nodes
201.94	Hodgkin’s disease, unspecified type, lymph nodes of axilla and upper limb
201.95	Hodgkin’s disease, unspecified type, lymph nodes of inguinal region and lower limb

201.96	Hodgkin’s disease, unspecified type, intrapelvic lymph nodes
201.97	Hodgkin’s disease, unspecified type, spleen
201.98	Hodgkin’s disease, unspecified type, lymph nodes of multiple sites
202.00	Nodular lymphoma, unspecified site, extranodal and solid organ sites
202.01	Nodular lymphoma, lymph nodes of head, face, and neck
202.02	Nodular lymphoma, intrathoracic lymph nodes
202.03	Nodular lymphoma, intra-abdominal lymph nodes
202.04	Nodular lymphoma, lymph nodes of axilla and upper limb
202.05	Nodular lymphoma, lymph nodes of inguinal region and lower limb
202.06	Nodular lymphoma, intrapelvic lymph nodes
202.07	Nodular lymphoma, spleen
202.08	Nodular lymphoma, lymph nodes of multiple sites
202.10	Mycosis fungoides, unspecified site, extranodal and solid organ sites
202.11	Mycosis fungoides, lymph nodes of head, face, and neck
202.12	Mycosis fungoides, intrathoracic lymph nodes
202.13	Mycosis fungoides, intra-abdominal lymph nodes
202.14	Mycosis fungoides, lymph nodes of axilla and upper limb
202.15	Mycosis fungoides, lymph nodes of inguinal region and lower limb
202.16	Mycosis fungoides, intrapelvic lymph nodes
202.17	Mycosis fungoides, spleen
202.18	Mycosis fungoides, lymph nodes of multiple sites
202.20	Sezary’s disease, unspecified site, extranodal and solid organ sites
202.21	Sezary’s disease, lymph nodes of head, face, and neck
202.22	Sezary’s disease, intrathoracic lymph nodes
202.23	Sezary’s disease, intra-abdominal lymph nodes
202.24	Sezary’s disease, lymph nodes of axilla and upper limb
202.25	Sezary’s disease, lymph nodes of inguinal region and lower limb
202.26	Sezary’s disease, intrapelvic lymph nodes
202.27	Sezary’s disease, spleen
202.28	Sezary’s disease, lymph nodes of multiple sites
202.30	Malignant histiocytosis, unspecified site, extranodal and solid organ sites
202.31	Malignant histiocytosis, lymph nodes of head, face, and neck
202.32	Malignant histiocytosis, intrathoracic lymph nodes
202.33	Malignant histiocytosis, intra-abdominal lymph nodes
202.34	Malignant histiocytosis, lymph nodes of axilla and upper limb
202.35	Malignant histiocytosis, lymph nodes of inguinal region and lower limb
202.36	Malignant histiocytosis, intrapelvic lymph nodes
202.37	Malignant histiocytosis, spleen
202.38	Malignant histiocytosis, lymph nodes of multiple sites

202.40	Leukemic reticuloendotheliosis, unspecified site, extranodal and solid organ sites
202.41	Leukemic reticuloendotheliosis, lymph nodes of head, face, and neck
202.42	Leukemic reticuloendotheliosis, intrathoracic lymph nodes
202.43	Leukemic reticuloendotheliosis, intra-abdominal lymph nodes
202.44	Leukemic reticuloendotheliosis, lymph nodes of axilla and upper limb
202.45	Leukemic reticuloendotheliosis, lymph nodes of inguinal region and lower limb
202.46	Leukemic reticuloendotheliosis, intrapelvic lymph nodes
202.47	Leukemic reticuloendotheliosis, spleen
202.48	Leukemic reticuloendotheliosis, lymph nodes of multiple sites
202.50	Letterer-siwe disease, unspecified site, extranodal and solid organ sites
202.51	Letterer-siwe disease, lymph nodes of head, face, and neck
202.52	Letterer-siwe disease, intrathoracic lymph nodes
202.53	Letterer-siwe disease, intra-abdominal lymph nodes
202.54	Letterer-siwe disease, lymph nodes of axilla and upper limb
202.55	Letterer-siwe disease, lymph nodes of inguinal region and lower limb
202.56	Letterer-siwe disease, intrapelvic lymph nodes
202.57	Letterer-siwe disease, spleen
202.58	Letterer-siwe disease, lymph nodes of multiple sites
202.60	Malignant mast cell tumors, unspecified site, extranodal and solid organ sites
202.61	Malignant mast cell tumors, lymph nodes of head, face, and neck
202.62	Malignant mast cell tumors, intrathoracic lymph nodes
202.63	Malignant mast cell tumors, intra-abdominal lymph nodes
202.64	Malignant mast cell tumors, lymph nodes of axilla and upper limb
202.65	Malignant mast cell tumors, lymph nodes of inguinal region and lower limb
202.66	Malignant mast cell tumors, intrapelvic lymph nodes
202.67	Malignant mast cell tumors, spleen
202.68	Malignant mast cell tumors, lymph nodes of multiple sites
202.70	Peripheral T cell lymphoma, extranodal and solid organ sites
202.71	Peripheral T cell lymphoma, lymph nodes of head, face, and neck
202.72	Peripheral T cell lymphoma, intrathoracic lymph nodes
202.73	Peripheral T cell lymphoma, intra-abdominal lymph nodes
202.74	Peripheral T cell lymphoma, lymph nodes of axilla and upper limb
202.75	Peripheral T cell lymphoma, lymph nodes of inguinal region and lower limb
202.76	Peripheral T cell lymphoma, intrapelvic lymph nodes
202.77	Peripheral T cell lymphoma, spleen
202.78	Peripheral T cell lymphoma, lymph nodes of multiple sites
202.80	Other malignant lymphomas, unspecified site, extranodal and solid organ sites
202.81	Other malignant lymphomas, lymph nodes of head, face, and neck
202.82	Other malignant lymphomas, intrathoracic lymph nodes

202.83	Other malignant lymphomas, intra-abdominal lymph nodes
202.84	Other malignant lymphomas, lymph nodes of axilla and upper limb
202.85	Other malignant lymphomas, lymph nodes of inguinal region and lower limb
202.86	Other malignant lymphomas, intrapelvic lymph nodes
202.87	Other malignant lymphomas, spleen
202.88	Other malignant lymphomas, lymph nodes of multiple sites
202.90	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, unspecified site, extranodal and solid organ sites
202.91	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, lymph nodes of head, face, and neck
202.92	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, intrathoracic lymph nodes
202.93	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, intra-abdominal lymph nodes
202.94	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, lymph nodes of axilla and upper limb
202.95	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, lymph nodes of inguinal region and lower limb
202.96	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, intrapelvic lymph nodes
202.97	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, spleen
202.98	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, lymph nodes of multiple sites
203.00	Multiple myeloma, without mention of having achieved remission
203.01	Multiple myeloma, in remission
203.02	Multiple myeloma, in relapse
203.10	Plasma cell leukemia, without mention of having achieved remission
203.11	Plasma cell leukemia, in remission
203.12	Plasma cell leukemia, in relapse
203.80	Other immunoproliferative neoplasms, without mention of having achieved remission
203.81	Other immunoproliferative neoplasms, in remission
203.82	Other immunoproliferative neoplasms, in relapse
204.00	Acute lymphoid leukemia, without mention of having achieved remission
204.01	Acute lymphoid leukemia, in remission
204.02	Acute lymphoid leukemia, in relapse
204.10	Chronic lymphoid leukemia, without mention of having achieved remission
204.11	Chronic lymphoid leukemia, in remission
204.12	Chronic lymphoid leukemia, in relapse
204.20	Subacute lymphoid leukemia, without mention of having achieved remission

204.21	Subacute lymphoid leukemia, in remission
204.22	Subacute lymphoid leukemia, in relapse
204.80	Other lymphoid leukemia, without mention of having achieved remission
204.81	Other lymphoid leukemia, in remission
204.82	Other lymphoid leukemia, in relapse
204.90	Unspecified lymphoid leukemia, without mention of having achieved remission
204.91	Unspecified lymphoid leukemia, in remission
204.92	Unspecified lymphoid leukemia, in relapse
205.00	Acute myeloid leukemia, without mention of having achieved remission
205.01	Acute myeloid leukemia, in remission
205.02	Acute myeloid leukemia, in relapse
205.10	Chronic myeloid leukemia, without mention of having achieved remission
205.11	Chronic myeloid leukemia, in remission
205.12	Chronic myeloid leukemia, in relapse
205.20	Subacute myeloid leukemia, without mention of having achieved remission
205.21	Subacute myeloid leukemia, in remission
205.22	Subacute myeloid leukemia, in relapse
205.30	Myeloid sarcoma, without mention of having achieved remission
205.31	Myeloid sarcoma in remission
205.32	Myeloid sarcoma, in relapse
205.80	Other myeloid leukemia, without mention of having achieved remission
205.81	Other myeloid leukemia, in remission
205.82	Other myeloid leukemia, in relapse
205.90	Unspecified myeloid leukemia, without mention of having achieved remission
205.91	Unspecified myeloid leukemia, in remission
205.92	Unspecified myeloid leukemia, in relapse
206.00	Acute monocytic leukemia, without mention of having achieved remission
206.01	Acute monocytic leukemia, in remission
206.02	Acute monocytic leukemia, in relapse
206.10	Chronic monocytic leukemia, without mention of having achieved remission
206.11	Chronic monocytic leukemia, in remission
206.12	Chronic monocytic leukemia, in relapse
206.20	Subacute monocytic leukemia, without mention of having achieved remission
206.21	Subacute monocytic leukemia, in remission
206.22	Subacute monocytic leukemia, in relapse
206.80	Other monocytic leukemia, without mention of having achieved remission
206.81	Other monocytic leukemia, in remission
206.82	Other monocytic leukemia, in relapse
206.90	Unspecified monocytic leukemia, without mention of having achieved remission

206.91	Unspecified monocytic leukemia, in remission
206.92	Unspecified monocytic leukemia, in relapse
207.00	Acute erythremia and erythroleukemia, without mention of having achieved remission
207.01	Acute erythremia and erythroleukemia, in remission
207.02	Acute erythremia and erythroleukemia, in relapse
207.10	Chronic erythremia, without mention of having achieved remission
207.11	Chronic erythremia, in remission
207.12	Chronic erythremia, in relapse
207.20	Megakaryocytic leukemia, without mention of having achieved remission
207.21	Megakaryocytic leukemia, in remission
207.22	Megakaryocytic leukemia, in relapse
207.80	Other specified leukemia, without mention of having achieved remission
207.81	Other specified leukemia, in remission
207.82	Other specified leukemia, in relapse
208.00	Acute leukemia of unspecified type, without mention of having achieved remission
208.01	Acute leukemia of unspecified cell type, in remission
208.02	Acute leukemia of unspecified cell type, in relapse
208.10	Chronic leukemia of unspecified cell type, without mention of having achieved remission
208.11	Chronic leukemia of unspecified cell type, in remission
208.12	Chronic leukemia of unspecified cell type, in relapse
208.20	Subacute leukemia of unspecified cell type, without mention of having achieved remission
208.21	Subacute leukemia of unspecified cell type, in remission
208.22	Subacute leukemia of unspecified cell type, in relapse
208.80	Other leukemia of unspecified cell type, without mention of having achieved remission
208.81	Other leukemia of unspecified cell type, in remission
208.82	Other leukemia of unspecified cell type, in relapse
208.90	Unspecified leukemia, without mention of having achieved remission
208.91	Unspecified leukemia, in remission
208.92	Unspecified leukemia, in relapse
209.00	Malignant carcinoid tumor of the small intestine, unspecified portion
209.01	Malignant carcinoid tumor of the duodenum
209.02	Malignant carcinoid tumor of the jejunum
209.03	Malignant carcinoid tumor of the ileum
209.10	Malignant carcinoid tumor of the large intestine, unspecified portion
209.11	Malignant carcinoid tumor of the appendix

209.12	Malignant carcinoid tumor of the cecum
209.13	Malignant carcinoid tumor of the ascending colon
209.14	Malignant carcinoid tumor of the transverse colon
209.15	Malignant carcinoid tumor of the descending colon
209.16	Malignant carcinoid tumor of the sigmoid colon
209.17	Malignant carcinoid tumor of the rectum
209.20	Malignant carcinoid tumor of unknown primary site
209.21	Malignant carcinoid tumor of the bronchus and lung
209.22	Malignant carcinoid tumor of the thymus
209.23	Malignant carcinoid tumor of the stomach
209.24	Malignant carcinoid tumor of the kidney
209.25	Malignant carcinoid tumor of foregut, not otherwise specified
209.26	Malignant carcinoid tumor of midgut, not otherwise specified
209.27	Malignant carcinoid tumor of hindgut, not otherwise specified
209.29	Malignant carcinoid tumor of other sites
209.30	Malignant poorly differentiated neuroendocrine carcinoma, any site
209.31	Merkel cell carcinoma of the face
209.32	Merkel cell carcinoma of the scalp and neck
209.33	Merkel cell carcinoma of the upper limb
209.34	Merkel cell carcinoma of the lower limb
209.35	Merkel cell carcinoma of the trunk
209.36	Merkel cell carcinoma of other sites
209.70	Secondary neuroendocrine tumor, unspecified site
209.71	Secondary neuroendocrine tumor of distant lymph nodes
209.72	Secondary neuroendocrine tumor of liver
209.73	Secondary neuroendocrine tumor of bone
209.74	Secondary neuroendocrine tumor of peritoneum
209.75	Secondary Merkel cell carcinoma
209.79	Secondary neuroendocrine tumor of other sites
ICD-10	
C00.0	Malignant neoplasm of external upper lip
C00.1	Malignant neoplasm of external lower lop
C00.2	Malignant neoplasm of external lip, unspecified
C00.3	Malignant neoplasm of upper lip, inner aspect
C00.4	Malignant neoplasm of lower lip, inner aspect
C00.5	Malignant neoplasm of lip, unspecified, inner aspect
C00.6	Malignant neoplasm of commissure of lip, unspecified
C00.8	Malignant neoplasm of overlapping sites of lip
C00.9	Malignant neoplasm of lip, unspecified

C01	Malignant neoplasm of base of tongue
C02.0	Malignant neoplasm of dorsal surface of tongue
C02.1	Malignant neoplasm of border of tongue
C02.2	Malignant neoplasm of ventral surface of tongue
C02.3	Malignant neoplasm of anterior two-thirds of tongue, part unspecified
C02.4	Malignant neoplasm of lingual tonsil
C02.8	Malignant neoplasm of overlapping sites of tongue
C02.9	Malignant neoplasm of tongue, unspecified
C03.0	Malignant neoplasm of upper gum
C03.1	Malignant neoplasm of lower gum
C03.9	Malignant neoplasm of gum, unspecified
C04.0	Malignant neoplasm of anterior floor of mouth
C04.1	Malignant neoplasm of lateral floor of mouth
C04.8	Malignant neoplasm of overlapping sites of floor of mouth
C04.9	Malignant neoplasm of floor of mouth, unspecified
C05.0	Malignant neoplasm of hard palate
C05.1	Malignant neoplasm of soft palate
C05.2	Malignant neoplasm of uvula
C05.8	Malignant neoplasm of overlapping sites of palate
C05.9	Malignant neoplasm of palate, unspecified
C06.0	Malignant neoplasm of cheek mucosa
C06.1	Malignant neoplasm of vestibule of mouth
C06.2	Malignant neoplasm of retromolar area
C06.80	Malignant neoplasm of overlapping sites of unspecified parts of mouth
C06.89	Malignant neoplasm of overlapping sites of other parts of mouth
C06.9	Malignant neoplasm of mouth, unspecified
C07	Malignant neoplasm of parotid gland
C08.0	Malignant neoplasm of submandibular gland
C08.1	Malignant neoplasm of sublingual gland
C08.9	Malignant neoplasm of major salivary gland, unspecified
C09.0	Malignant neoplasm of tonsillar fossa
C09.1	Malignant neoplasm of tonsillar pillar (anterior) (posterior)
C09.8	Malignant neoplasm of overlapping sites of tonsil
C09.9	Malignant neoplasm of tonsil, unspecified
C10.0	Malignant neoplasm of vallecular
C10.1	Malignant neoplasm of anterior surface of epiglottis
C10.2	Malignant neoplasm of lateral wall of oropharynx
C10.3	Malignant neoplasm of posterior wall of oropharynx

C10.4	Malignant neoplasm of branchial cleft
C10.8	Malignant neoplasm of overlapping sites of oropharynx
C10.9	Malignant neoplasm of oropharynx, unspecified
C11.0	Malignant neoplasm of superior wall of nasopharynx
C11.1	Malignant neoplasm of posterior wall of nasopharynx
C11.2	Malignant neoplasm of lateral wall of nasopharynx
C11.3	Malignant neoplasm of anterior wall of nasopharynx
C11.8	Malignant neoplasm of overlapping sites of nasopharynx
C11.9	Malignant neoplasm of nasopharynx, unspecified
C12	Malignant neoplasm of pyriform sinus
C13.0	Malignant neoplasm of postcricoid region
C13.1	Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
C13.2	Malignant neoplasm of posterior wall of hypopharynx
C13.8	Malignant neoplasm of overlapping sites of hypopharynx
C13.9	Malignant neoplasm of hypopharynx, unspecified
C14.0	Malignant neoplasm of pharynx, unspecified
C14.2	Malignant neoplasm of Waldeyer’s ring
C14.8	Malignant neoplasm of overlapping sites of lip, oral cavity and pharynx
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Merckel’s diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum

C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.2	Hepatoblastoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.1	Malignant neoplasm of ampulla of Vater
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C26.0	Malignant neoplasm of intestinal tract, part unspecified
C26.1	Malignant neoplasm of spleen
C26.9	Malignant neoplasm of ill-defined sites within the digestive system

C30.0	Malignant neoplasm of nasal cavity
C30.1	Malignant neoplasm of middle ear
C31.0	Malignant neoplasm of maxillary sinus
C31.1	Malignant neoplasm of ethmoidal sinus
C31.2	Malignant neoplasm of frontal sinus
C31.3	Malignant neoplasm of sphenoid sinus
C31.8	Malignant neoplasm of overlapping sites of accessory sinuses
C31.9	Malignant neoplasm of sinus, unspecified
C32.0	Malignant neoplasm of glottis
C32.1	Malignant neoplasm of supraglottis
C32.2	Malignant neoplasm of subglottis
C32.3	Malignant neoplasm of laryngeal cartilage
C32.8	Malignant neoplasm of overlapping sites of larynx
C32.9	Malignant neoplasm of larynx, unspecified
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C37	Malignant neoplasm of thymus
C38.0	Malignant neoplasm of heart
C38.1	Malignant neoplasm of anterior mediastinum
C38.2	Malignant neoplasm of posterior mediastinum
C38.3	Malignant neoplasm of mediastinum, part unspecified
C38.4	Malignant neoplasm of pleura
C38.8	Malignant neoplasm of overlapping sites of heart, mediastinum and pleura
C39.0	Malignant neoplasm of upper respiratory tract, part unspecified

C39.9	Malignant neoplasm of lower respiratory tract, part unspecified
C40.00	Malignant neoplasm of scapula and long bones of unspecified upper limb
C40.01	Malignant neoplasm of scapula and long bones of right upper limb
C40.02	Malignant neoplasm of scapula and long bones of left upper limb
C40.10	Malignant neoplasm of short bones of unspecified upper limb
C40.11	Malignant neoplasm of short bones of right upper limb
C40.12	Malignant neoplasm of short bones of left upper limb
C40.20	Malignant neoplasm of long bones of unspecified lower limb
C40.21	Malignant neoplasm of long bones of right lower limb
C40.22	Malignant neoplasm of long bones of left lower limb
C40.30	Malignant neoplasm of short bones unspecified lower limb
C40.31	Malignant neoplasm of short bones of right lower limb
C40.32	Malignant neoplasm of short bones of left lower limb
C40.80	Malignant neoplasm of overlapping sites of bone and articular cartilage of unspecified limb
C40.81	Malignant neoplasm of overlapping sites of bone and articular cartilage of right limb
C40.82	Malignant neoplasm of overlapping sites of bone and articular cartilage of left limb
C40.90	Malignant neoplasm of unspecified bones and articular cartilage of unspecified limb
C40.91	Malignant neoplasm of unspecified bones and articular cartilage of right limb
C40.92	Malignant neoplasm of unspecified bones and articular cartilage of left limb
C41.0	Malignant neoplasm of bones of skull and face
C41.1	Malignant neoplasm of mandible
C41.2	Malignant neoplasm of vertebral column
C41.3	Malignant neoplasm of ribs, sternum and clavicle
C41.4	Malignant neoplasm of pelvic bones, sacrum and coccyx
C41.9	Malignant neoplasm of bone and articular cartilage, unspecified
C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.11	Malignant melanoma of right eyelid, including canthus
C43.12	Malignant melanoma of left eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face

C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C4A.0	Merkel cell carcinoma of lip
C4A.10	Merkel cell carcinoma of unspecified eyelid, including canthus
C4A.11	Merkel cell carcinoma of right eyelid, including canthus
C4A.12	Merkel cell carcinoma of left eyelid, including canthus
C4A.20	Merkel cell carcinoma of unspecified ear and external auricular canal
C4A.21	Merkel cell carcinoma of right ear and external auricular canal
C4A.22	Merkel cell carcinoma of left ear and external auricular canal
C4A.30	Merkel cell carcinoma of unspecified part of face
C4A.31	Merkel cell carcinoma of nose
C4A.39	Merkel cell carcinoma of other parts of face
C4A.4	Merkel cell carcinoma ma of scalp and neck
C4A.51	Merkel cell carcinoma of anal skin
C4A.52	Merkel cell carcinoma of skin of breast
C4A.59	Merkel cell carcinoma of other part of trunk
C4A.60	Merkel cell carcinoma of unspecified upper limb, including shoulder
C4A.61	Merkel cell carcinoma of right upper limb, including shoulder
C4A.62	Merkel cell carcinoma of left upper limb, including shoulder
C4A.70	Merkel cell carcinoma of unspecified lower limb, including hip
C4A.71	Merkel cell carcinoma of right lower limb, including hip
C4A.72	Merkel cell carcinoma of left lower limb, including hip
C4A.8	Merkel cell carcinoma of overlapping sites of skin
C4A.9	Merkel cell carcinoma of skin, unspecified
C44.00	Unspecified malignant neoplasm of skin of lip
C44.01	Basal cell carcinoma of skin of lip
C44.02	Squamous cell carcinoma of skin of lip
C44.09	Other specified malignant neoplasm of skin of lip

C44.101	Unspecified malignant neoplasm of skin of unspecified eyelid, including canthus
C44.102	Unspecified malignant neoplasm of skin of right eyelid, including canthus
C44.109	Unspecified malignant neoplasm of skin of left eyelid, including canthus
C44.111	Basal cell carcinoma of skin of unspecified eyelid, including canthus
C44.112	Basal cell carcinoma of skin of right eyelid, including canthus
C44.119	Basal cell carcinoma of skin of left eyelid, including canthus
C44.121	Squamous cell carcinoma of skin of unspecified eyelid, including canthus
C44.122	Squamous cell carcinoma of skin of right eyelid, including canthus
C44.129	Squamous cell carcinoma of skin of left eyelid, including canthus
C44.191	Other specified malignant neoplasm of skin of unspecified eyelid, including canthus
C44.192	Other specified malignant neoplasm of skin of right eyelid, including canthus
C44.199	Other specified malignant neoplasm of skin of left eyelid, including canthus
C44.201	Unspecified malignant neoplasm of skin of unspecified ear and external auricular canal
C44.202	Unspecified malignant neoplasm of skin of right ear and external auricular canal
C44.209	Unspecified malignant neoplasm of skin of left ear and external auricular canal
C44.211	Basal cell carcinoma of skin of unspecified ear and external auricular canal
C44.212	Basal cell carcinoma of skin of right ear and external auricular canal
C44.219	Basal cell carcinoma of skin of left ear and external auricular canal
C44.221	Squamous cell carcinoma of skin of unspecified ear and external auricular canal
C44.222	Squamous cell carcinoma of skin of right ear and external auricular canal
C44.229	Squamous cell carcinoma of skin of left ear and external auricular canal
C44.291	Other specified malignant neoplasm of skin of unspecified ear and external auricular canal
C44.292	Other specified malignant neoplasm of skin of right ear and external auricular canal
C44.299	Other specified malignant neoplasm of skin of left ear and external auricular canal
C44.300	Unspecified malignant neoplasm of skin of unspecified part of face
C44.301	Unspecified malignant neoplasm of skin of nose
C44.309	Unspecified malignant neoplasm of skin of other parts of face
C44.310	Basal cell carcinoma of skin of unspecified part of face
C44.311	Basal cell carcinoma of skin of nose
C44.319	Basal cell carcinoma of skin of other parts of face
C44.320	Squamous cell carcinoma of skin of unspecified part of face
C44.321	Squamous cell carcinoma of skin of nose
C44.329	Squamous cell carcinoma of skin of other parts of face
C44.390	Other specified malignant neoplasm of skin of unspecified part of face
C44.391	Other specified malignant neoplasm of skin of nose

C44.399	Other specified malignant neoplasm of skin of other parts of face
C44.40	Unspecified malignant neoplasm of skin of scalp and neck
C44.41	Basal cell carcinoma of skin of scalp and neck
C44.42	Squamous cell carcinoma of skin of scalp and neck
C44.49	Other specified malignant neoplasm of skin of scalp and neck
C44.500	Unspecified malignant neoplasm of anal skin
C44.501	Unspecified malignant neoplasm of skin of breast
C44.509	Unspecified malignant neoplasm of skin of other part of trunk
C44.510	Basal cell carcinoma of anal skin
C44.511	Basal cell carcinoma of skin of breast
C44.519	Basal cell carcinoma of skin of other part of trunk
C44.520	Squamous cell carcinoma of anal skin
C44.521	Squamous cell carcinoma of skin of breast
C44.529	Squamous cell carcinoma of skin of other part of trunk
C44.590	Other specified malignant neoplasm of anal skin
C44.591	Other specified malignant neoplasm of skin of breast
C44.599	Other specified malignant neoplasm of skin of other part of trunk
C44.601	Unspecified malignant neoplasm of skin of unspecified upper limb, including shoulder
C44.602	Unspecified malignant neoplasm of skin of right upper limb, including shoulder
C44.609	Unspecified malignant neoplasm of skin of left upper limb, including shoulder
C44.611	Basal cell carcinoma of skin of unspecified upper limb, including shoulder
C44.612	Basal cell carcinoma of skin of right upper limb, including shoulder
C44.619	Basal cell carcinoma of skin of left upper limb, including shoulder
C44.621	Squamous cell carcinoma of skin of unspecified upper limb, including shoulder
C44.622	Squamous cell carcinoma of skin of right upper limb, including shoulder
C44.629	Squamous cell carcinoma of skin of left upper limb, including shoulder
C44.691	Other specified malignant neoplasm of skin of unspecified upper limb, including shoulder
C44.692	Other specified malignant neoplasm of skin of right upper limb, including shoulder
C44.699	Other specified malignant neoplasm of skin of left upper limb, including shoulder
C44.701	Unspecified malignant neoplasm of skin of unspecified lower limb, including hip
C44.702	Unspecified malignant neoplasm of skin of right lower limb, including hip
C44.709	Unspecified malignant neoplasm of skin of left lower limb, including hip
C44.711	Basal cell carcinoma of skin of unspecified lower limb, including hip
C44.712	Basal cell carcinoma of skin of right lower limb, including hip
C44.719	Basal cell carcinoma of skin of left lower limb, including hip
C44.721	Squamous cell carcinoma of skin of unspecified lower limb, including hip

C44.722	Squamous cell carcinoma of skin of right lower limb, including hip
C44.729	Squamous cell carcinoma of skin of left lower limb, including hip
C44.791	Other specified malignant neoplasm of skin of unspecified lower limb, including hip
C44.792	Other specified malignant neoplasm of skin of right lower limb, including hip
C44.799	Other specified malignant neoplasm of skin of left lower limb, including hip
C44.80	Unspecified malignant neoplasm of overlapping sites of skin
C44.81	Basal cell carcinoma of skin of overlapping sites of skin
C44.82	Squamous cell carcinoma of skin of overlapping sites of skin
C44.89	Other specified malignant neoplasm of skin, unspecified
C44.90	Unspecified malignant neoplasm of skin, unspecified
C44.91	Basal cell carcinoma of skin of skin, unspecified
C44.92	Squamous cell carcinoma of skin of skin, unspecified
C44.99	Other specified malignant neoplasm of skin, unspecified
C45.0	Mesothelioma of pleura
C45.1	Mesothelioma of peritoneum
C45.2	Mesothelioma of pericardium
C45.7	Mesothelioma of other sites
C45.9	Mesothelioma, unspecified
C46.0	Kaposi’s sarcoma of skin
C46.1	Kaposi’s sarcoma of soft tissue
C46.2	Kaposi’s sarcoma of palate
C46.3	Kaposi’s sarcoma of lymph nodes
C46.4	Kaposi’s sarcoma of gastrointestinal sites
C46.50	Kaposi’s sarcoma of unspecified lung
C46.51	Kaposi’s sarcoma of right lung
C46.52	Kaposi’s sarcoma of left lung
C46.7	Kaposi’s sarcoma of other sites
C46.9	Kaposi’s sarcoma, unspecified
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck
C47.10	Malignant neoplasm of peripheral nerves of unspecified upper limb, including shoulder
C47.11	Malignant neoplasm of peripheral nerves of right upper limb, including shoulder
C47.12	Malignant neoplasm of peripheral nerves of left upper limb, including shoulder
C47.20	Malignant neoplasm of peripheral nerves of unspecified lower limb, including hip
C47.21	Malignant neoplasm of peripheral nerves of right lower limb, including hip
C47.22	Malignant neoplasm of peripheral nerves of left lower limb, including hip
C47.3	Malignant neoplasm of peripheral nerves of thorax

C47.4	Malignant neoplasm of peripheral nerves of abdomen
C47.5	Malignant neoplasm of peripheral nerves of pelvis
C47.6	Malignant neoplasm of peripheral nerves of trunk, unspecified
C47.8	Malignant neoplasm of overlapping sites of peripheral nerves and autonomic nervous system
C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system, unspecified
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C49.10	Malignant neoplasm of connective and soft tissue of unspecified upper limb, including shoulder
C49.11	Malignant neoplasm of connective and soft tissue of right upper limb, including shoulder
C49.12	Malignant neoplasm of connective and soft tissue of left upper limb, including shoulder
C49.20	Malignant neoplasm of connective and soft tissue of unspecified lower limb, including hip
C49.21	Malignant neoplasm of connective and soft tissue of right lower limb, including hip
C49.22	Malignant neoplasm of connective and soft tissue of left lower limb, including hip
C49.3	Malignant neoplasm of connective and soft tissue of thorax
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.5	Malignant neoplasm of connective and soft tissue of pelvis
C49.6	Malignant neoplasm of connective and soft tissue of trunk, unspecified
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C49.A0	Gastrointestinal stromal tumor, unspecified site
C49.A1	Gastrointestinal stromal tumor of esophagus
C49.A2	Gastrointestinal stromal tumor of stomach
C49.A3	Gastrointestinal stromal tumor of small intestine
C49.A4	Gastrointestinal stromal tumor of large intestine
C49.A5	Gastrointestinal stromal tumor of rectum
C49.A9	Gastrointestinal stromal tumor of other sites
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.111	Malignant neoplasm of central portion of right female breast

C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C51.0	Malignant neoplasm of labium majus
C51.1	Malignant neoplasm of labium minus
C51.2	Malignant neoplasm of clitoris
C51.8	Malignant neoplasm of overlapping sites of vulva
C51.9	Malignant neoplasm of vulva, unspecified
C52	Malignant neoplasm of vagina
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C53.8	Malignant neoplasm of overlapping sites of cervix uteri
C53.9	Malignant neoplasm of cervix uteri, unspecified
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified

C55	Malignant neoplasm of uterus, part unspecified
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.10	Malignant neoplasm of unspecified broad ligament
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.20	Malignant neoplasm of unspecified round ligament
C57.21	Malignant neoplasm of right round ligament
C57.22	Malignant neoplasm of left round ligament
C57.3	Malignant neoplasm of parametrium
C57.4	Malignant neoplasm of uterine adnexa, unspecified
C57.7	Malignant neoplasm of other specified female genital organs
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C57.9	Malignant neoplasm of female genital organ, unspecified
C58	Malignant neoplasm of placenta
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C66.1	Malignant neoplasm of right ureter
C66.2	Malignant neoplasm of left ureter
C66.9	Malignant neoplasm of unspecified ureter
C67.0	Malignant neoplasm of trigone of bladder
C67.1	Malignant neoplasm of dome of bladder
C67.2	Malignant neoplasm of lateral wall of bladder
C67.3	Malignant neoplasm of anterior wall of bladder
C67.4	Malignant neoplasm of posterior wall of bladder
C67.5	Malignant neoplasm of bladder neck
C67.6	Malignant neoplasm of ureteric orifice
C67.7	Malignant neoplasm of urachus
C67.8	Malignant neoplasm of overlapping sites of bladder
C67.9	Malignant neoplasm of bladder, unspecified

C68.0	Malignant neoplasm of urethra
C68.1	Malignant neoplasm of paraurethral glands
C68.8	Malignant neoplasm of overlapping sites of urinary organs
C68.9	Malignant neoplasm of urinary organ, unspecified
C69.00	Malignant neoplasm of unspecified conjunctiva
C69.01	Malignant neoplasm of right conjunctiva
C69.02	Malignant neoplasm of left conjunctiva
C69.10	Malignant neoplasm of unspecified cornea
C69.11	Malignant neoplasm of right cornea
C69.12	Malignant neoplasm of left cornea
C69.20	Malignant neoplasm of unspecified retina
C69.21	Malignant neoplasm of right retina
C69.22	Malignant neoplasm of left retina
C69.30	Malignant neoplasm of unspecified retina
C69.31	Malignant neoplasm of right retina
C69.32	Malignant neoplasm of left retina
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.50	Malignant neoplasm of unspecified lacrimal gland and duct
C69.51	Malignant neoplasm of right lacrimal gland and duct
C69.52	Malignant neoplasm of left lacrimal gland and duct
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C69.80	Malignant neoplasm of overlapping sites unspecified eye and adnexa
C69.81	Malignant neoplasm of overlapping sites right eye and adnexa
C69.82	Malignant neoplasm of overlapping sites left eye and adnexa
C69.90	Malignant neoplasm of unspecified site of unspecified eye
C69.91	Malignant neoplasm of unspecified site of right conjunctiva
C69.92	Malignant neoplasm of unspecified site of left conjunctiva
C70.0	Malignant neoplasm of cerebral meninges
C70.1	Malignant neoplasm of spinal meninges
C70.9	Malignant neoplasm of meninges, unspecified
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe

C71.5	Malignant neoplasm of cerebral lobe
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C72.20	Malignant neoplasm of unspecified olfactory nerve
C72.21	Malignant neoplasm of right olfactory nerve
C72.22	Malignant neoplasm of left olfactory nerve
C72.30	Malignant neoplasm of unspecified optic nerve
C72.31	Malignant neoplasm of right optic nerve
C72.32	Malignant neoplasm of left optic nerve
C72.40	Malignant neoplasm of unspecified acoustic nerve
C72.41	Malignant neoplasm of right acoustic nerve
C72.42	Malignant neoplasm of left acoustic nerve
C72.50	Malignant neoplasm of unspecified cranial nerve
C72.59	Malignant neoplasm of other cranial nerves
C72.9	Malignant neoplasm of central nervous system, unspecified
C73	Malignant neoplasm of thyroid gland
C74.00	Malignant neoplasm of cortex of unspecified adrenal gland
C74.01	Malignant neoplasm of cortex of right adrenal gland
C74.02	Malignant neoplasm of cortex of left adrenal gland
C74.10	Malignant neoplasm of medulla of unspecified adrenal gland
C74.11	Malignant neoplasm of medulla of right adrenal gland
C74.12	Malignant neoplasm of medulla of left adrenal gland
C74.90	Malignant neoplasm of unspecified part of unspecified adrenal gland
C74.91	Malignant neoplasm of unspecified part of right adrenal gland
C74.92	Malignant neoplasm of unspecified part of left adrenal gland
C75.0	Malignant neoplasm of parathyroid gland
C75.1	Malignant neoplasm of pituitary gland
C75.2	Malignant neoplasm of craniopharyngeal duct
C75.3	Malignant neoplasm of pineal gland
C75.4	Malignant neoplasm of carotid body
C75.5	Malignant neoplasm of aortic body and other paraganglia
C75.8	Malignant neoplasm with pluriglandular involvement, unspecified
C75.9	Malignant neoplasm of endocrine gland, unspecified
C7A.00	Malignant carcinoid tumor of unspecified site

C7A.010	Malignant carcinoid tumor of the duodenum
C7A.011	Malignant carcinoid tumor of the jejunum
C7A.012	Malignant carcinoid tumor of the ileum
C7A.019	Malignant carcinoid tumor of the small intestine, unspecified portion
C7A.020	Malignant carcinoid tumor of the appendix
C7A.021	Malignant carcinoid tumor of the cecum
C7A.022	Malignant carcinoid tumor of the ascending colon
C7A.023	Malignant carcinoid tumor of the transverse colon
C7A.024	Malignant carcinoid tumor of the descending colon
C7A.025	Malignant carcinoid tumor of the sigmoid colon
C7A.026	Malignant carcinoid tumor of the rectum
C7A.029	Malignant carcinoid tumor of the large intestine, unspecified portion
C7A.090	Malignant carcinoid tumor of the bronchus and lung
C7A.091	Malignant carcinoid tumor of the thymus
C7A.092	Malignant carcinoid tumor of the stomach
C7A.093	Malignant carcinoid tumor of the kidney
C7A.094	Malignant carcinoid tumor of the foregut, unspecified
C7A.095	Malignant carcinoid tumor of the midgut, unspecified
C7A.096	Malignant carcinoid tumor of the hindgut, unspecified
C7A.098	Malignant carcinoid tumor of other sites
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7A.8	Other malignant neuroendocrine tumors
C7B.00	Secondary carcinoid tumors, unspecified site
C7B.01	Secondary carcinoid tumors of distant lymph nodes
C7B.02	Secondary carcinoid tumors of liver
C7B.03	Secondary carcinoid tumors of bone
C7B.04	Secondary carcinoid tumors of peritoneum
C7B.09	Secondary carcinoid tumors of other sites
C7B.1	Secondary Merkel cell carcinoma
C7B.8	Other secondary neuroendocrine tumors
C76.0	Malignant neoplasm of head, face and neck
C76.1	Malignant neoplasm of thorax
C76.2	Malignant neoplasm of abdomen
C76.3	Malignant neoplasm of pelvis
C76.40	Malignant neoplasm of unspecified upper limb
C76.41	Malignant neoplasm of right upper limb
C76.42	Malignant neoplasm of left upper limb
C76.50	Malignant neoplasm of unspecified lower limb

C76.51	Malignant neoplasm of right lower limb
C76.52	Malignant neoplasm of left lower limb
C76.8	Malignant neoplasm of other specified ill-defined sites
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C77.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
C77.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
C77.3	Secondary and unspecified malignant neoplasm of axilla and upper limb lymph nodes
C77.4	Secondary and unspecified malignant neoplasm of inguinal and lower limb lymph nodes
C77.5	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
C77.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions
C77.9	Secondary and unspecified malignant neoplasm of lymph node, unspecified
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.1	Secondary malignant neoplasm of mediastinum
C78.2	Secondary malignant neoplasm of pleura
C78.30	Secondary malignant neoplasm of unspecified respiratory organs
C78.39	Secondary malignant neoplasm of other respiratory organs
C78.4	Secondary malignant neoplasm of small intestine
C78.5	Secondary malignant neoplasm of large intestine and rectum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of intrahepatic bile duct
C78.80	Secondary malignant neoplasm of unspecified digestive organ
C78.89	Secondary malignant neoplasm of other digestive organs
C79.00	Secondary malignant neoplasm of unspecified kidney and renal pelvis
C79.01	Secondary malignant neoplasm of right kidney and renal pelvis
C79.02	Secondary malignant neoplasm of left kidney and renal pelvis
C79.10	Secondary malignant neoplasm of unspecified urinary organs
C79.11	Secondary malignant neoplasm of bladder
C79.19	Secondary malignant neoplasm of other urinary organs
C79.2	Secondary malignant neoplasm of skin
C79.31	Secondary malignant neoplasm of brain
C79.32	Secondary malignant neoplasm of cerebral meninges
C79.40	Secondary malignant neoplasm of unspecified part of nervous system
C79.49	Secondary malignant neoplasm of other parts of nervous system
C79.51	Secondary malignant neoplasm of bone

C79.52	Secondary malignant neoplasm of bone marrow
C79.60	Secondary malignant neoplasm of unspecified ovary
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.70	Secondary malignant neoplasm of unspecified adrenal gland
C79.71	Secondary malignant neoplasm of right adrenal gland
C79.72	Secondary malignant neoplasm of left adrenal gland
C79.81	Secondary malignant neoplasm of breast
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
C79.9	Secondary malignant neoplasm of unspecified site
C80.0	Disseminated malignant neoplasm, unspecified
C80.1	Malignant (primary) neoplasm, unspecified
C80.2	Malignant neoplasm associated with transplanted organ
C81.00	Nodular lymphocyte predominant Hodgkin lymphoma, unspecified site
C81.01	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.02	Nodular lymphocyte predominant Hodgkin lymphoma, intrathoracic lymph nodes
C81.03	Nodular lymphocyte predominant Hodgkin lymphoma, intra-abdominal lymph nodes
C81.04	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.05	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.06	Nodular lymphocyte predominant Hodgkin lymphoma, intrapelvic lymph nodes
C81.07	Nodular lymphocyte predominant Hodgkin lymphoma, spleen
C81.08	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of multiple sites
C81.09	Nodular lymphocyte predominant Hodgkin lymphoma, extranodal and solid organ sites
C81.10	Nodular sclerosis Hodgkin lymphoma, unspecified site
C81.11	Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.12	Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes
C81.13	Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph nodes
C81.14	Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.15	Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.16	Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes
C81.17	Nodular sclerosis Hodgkin lymphoma, spleen
C81.18	Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites

C81.19	Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites
C81.20	Mixed cellularity Hodgkin lymphoma, unspecified site
C81.21	Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.22	Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes
C81.23	Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes
C81.24	Mixed cellularity Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.25	Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.26	Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes
C81.27	Mixed cellularity Hodgkin lymphoma, spleen
C81.28	Mixed cellularity Hodgkin lymphoma, lymph nodes of multiple sites
C81.29	Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites
C81.30	Lymphocyte depleted Hodgkin lymphoma, unspecified site
C81.31	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.32	Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes
C81.33	Lymphocyte depleted Hodgkin lymphoma, intra-abdominal lymph nodes
C81.34	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.35	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.36	Lymphocyte depleted Hodgkin lymphoma, intrapelvic lymph nodes
C81.37	Lymphocyte depleted Hodgkin lymphoma, spleen
C81.38	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of multiple sites
C81.39	Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites
C81.40	Lymphocyte-rich Hodgkin lymphoma, unspecified site
C81.41	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.42	Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes
C81.43	Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes
C81.44	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.45	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.46	Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes
C81.47	Lymphocyte-rich Hodgkin lymphoma, spleen
C81.48	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites
C81.49	Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites
C81.70	Other Hodgkin lymphoma, unspecified site
C81.71	Other Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.72	Other Hodgkin lymphoma, intrathoracic lymph nodes
C81.73	Other Hodgkin lymphoma, intra-abdominal lymph nodes
C81.74	Other Hodgkin lymphoma, lymph nodes of axilla and upper limb

C81.75	Other Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.76	Other Hodgkin lymphoma, intrapelvic lymph nodes
C81.77	Other Hodgkin lymphoma, spleen
C81.78	Other Hodgkin lymphoma, lymph nodes of multiple sites
C81.79	Other Hodgkin lymphoma, extranodal and solid organ sites
C81.90	Hodgkin lymphoma, unspecified, unspecified site
C81.91	Hodgkin lymphoma, unspecified lymph nodes of head, face, and neck
C81.92	Hodgkin lymphoma, unspecified intrathoracic lymph nodes
C81.93	Hodgkin lymphoma, unspecified intra-abdominal lymph nodes
C81.94	Hodgkin lymphoma, unspecified lymph nodes of axilla and upper limb
C81.95	Hodgkin lymphoma, unspecified lymph nodes of inguinal region and lower limb
C81.96	Hodgkin lymphoma, unspecified intrapelvic lymph nodes
C81.97	Hodgkin lymphoma, unspecified spleen
C81.98	Hodgkin lymphoma, unspecified lymph nodes of multiple sites
C81.99	Hodgkin lymphoma, unspecified extranodal and solid organ sites
C82.00	Follicular lymphoma grade I, unspecified site
C82.01	Follicular lymphoma grade I, lymph nodes of head, face, and neck
C82.02	Follicular lymphoma grade I, intrathoracic lymph nodes
C82.03	Follicular lymphoma grade I, intra-abdominal lymph nodes
C82.04	Follicular lymphoma grade I, lymph nodes of axilla and upper limb
C82.05	Follicular lymphoma grade I, lymph nodes of inguinal region and lower limb
C82.06	Follicular lymphoma grade I, intrapelvic lymph nodes
C82.07	Follicular lymphoma grade I, spleen
C82.08	Follicular lymphoma grade I, lymph nodes of multiple sites
C82.09	Follicular lymphoma grade I, extranodal and solid organ sites
C82.10	Follicular lymphoma grade II, unspecified site
C82.11	Follicular lymphoma grade II, lymph nodes of head, face, and neck
C82.12	Follicular lymphoma grade II, intrathoracic lymph nodes
C82.13	Follicular lymphoma grade II, intra-abdominal lymph nodes
C82.14	Follicular lymphoma grade II, lymph nodes of axilla and upper limb
C82.15	Follicular lymphoma grade II, lymph nodes of inguinal region and lower limb
C82.16	Follicular lymphoma grade II, intrapelvic lymph nodes
C82.17	Follicular lymphoma grade II, spleen
C82.18	Follicular lymphoma grade II, lymph nodes of multiple sites
C82.19	Follicular lymphoma grade II, extranodal and solid organ sites
C82.20	Follicular lymphoma grade III, unspecified, unspecified site
C82.21	Follicular lymphoma grade III, l unspecified, ymph nodes of head, face, and neck
C82.22	Follicular lymphoma grade III, unspecified, intrathoracic lymph nodes
C82.23	Follicular lymphoma grade III, unspecified, intra-abdominal lymph nodes

C82.24	Follicular lymphoma grade III, unspecified, lymph nodes of axilla and upper limb
C82.25	Follicular lymphoma grade III, unspecified, lymph nodes of inguinal region and lower limb
C82.26	Follicular lymphoma grade III, unspecified, intrapelvic lymph nodes
C82.27	Follicular lymphoma grade III, unspecified, spleen
C82.28	Follicular lymphoma grade III, unspecified, lymph nodes of multiple sites
C82.29	Follicular lymphoma grade III, unspecified, extranodal and solid organ sites
C82.30	Follicular lymphoma grade IIIa, unspecified site
C82.31	Follicular lymphoma grade IIIa, lymph nodes of head, face, and neck
C82.32	Follicular lymphoma grade IIIa, intrathoracic lymph nodes
C82.33	Follicular lymphoma grade IIIa, intra-abdominal lymph nodes
C82.34	Follicular lymphoma grade IIIa, lymph nodes of axilla and upper limb
C82.35	Follicular lymphoma grade IIIa, lymph nodes of inguinal region and lower limb
C82.36	Follicular lymphoma grade IIIa, intrapelvic lymph nodes
C82.37	Follicular lymphoma grade IIIa, spleen
C82.38	Follicular lymphoma grade IIIa, lymph nodes of multiple sites
C82.39	Follicular lymphoma grade IIIa, extranodal and solid organ sites
C82.40	Follicular lymphoma grade IIIb, unspecified site
C82.41	Follicular lymphoma grade IIIb, lymph nodes of head, face, and neck
C82.42	Follicular lymphoma grade IIIb, intrathoracic lymph nodes
C82.43	Follicular lymphoma grade IIIb, intra-abdominal lymph nodes
C82.44	Follicular lymphoma grade IIIb, lymph nodes of axilla and upper limb
C82.45	Follicular lymphoma grade IIIb, lymph nodes of inguinal region and lower limb
C82.46	Follicular lymphoma grade IIIb, intrapelvic lymph nodes
C82.47	Follicular lymphoma grade IIIb, spleen
C82.48	Follicular lymphoma grade IIIb, lymph nodes of multiple sites
C82.49	Follicular lymphoma grade IIIb, extranodal and solid organ sites
C82.50	Diffuse follicle center lymphoma, unspecified site
C82.51	Diffuse follicle center lymphoma, lymph nodes of head, face, and neck
C82.52	Diffuse follicle center lymphoma, intrathoracic lymph nodes
C82.53	Diffuse follicle center lymphoma, intra-abdominal lymph nodes
C82.54	Diffuse follicle center lymphoma, lymph nodes of axilla and upper limb
C82.55	Diffuse follicle center lymphoma, lymph nodes of inguinal region and lower limb
C82.56	Diffuse follicle center lymphoma, intrapelvic lymph nodes
C82.57	Diffuse follicle center lymphoma, spleen
C82.58	Diffuse follicle center lymphoma, lymph nodes of multiple sites
C82.59	Diffuse follicle center lymphoma, extranodal and solid organ sites

C82.60	Cutaneous follicle center lymphoma, unspecified site
C82.61	Cutaneous follicle center lymphoma, lymph nodes of head, face, and neck
C82.62	Cutaneous follicle center lymphoma, intrathoracic lymph nodes
C82.63	Cutaneous follicle center lymphoma, intra-abdominal lymph nodes
C82.64	Cutaneous follicle center lymphoma, lymph nodes of axilla and upper limb
C82.65	Cutaneous follicle center lymphoma, lymph nodes of inguinal region and lower limb
C82.66	Cutaneous follicle center lymphoma, intrapelvic lymph nodes
C82.67	Cutaneous follicle center lymphoma, spleen
C82.68	Cutaneous follicle center lymphoma, lymph nodes of multiple sites
C82.69	Cutaneous follicle center lymphoma, extranodal and solid organ sites
C82.80	Other types of follicular lymphoma, unspecified site
C82.81	Other types of follicular lymphoma, lymph nodes of head, face, and neck
C82.82	Other types of follicular lymphoma, intrathoracic lymph nodes
C82.83	Other types of follicular lymphoma, intra-abdominal lymph nodes
C82.84	Other types of follicular lymphoma, lymph nodes of axilla and upper limb
C82.85	Other types of follicular lymphoma, lymph nodes of inguinal region and lower limb
C82.86	Other types of follicular lymphoma, intrapelvic lymph nodes
C82.87	Other types of follicular lymphoma, spleen
C82.88	Other types of follicular lymphoma, lymph nodes of multiple sites
C82.89	Other types of follicular lymphoma, extranodal and solid organ sites
C82.90	Follicular lymphoma, unspecified, unspecified site
C82.91	Follicular lymphoma, unspecified, lymph nodes of head, face, and neck
C82.92	Follicular lymphoma, unspecified, intrathoracic lymph nodes
C82.93	Follicular lymphoma, unspecified, intra-abdominal lymph nodes
C82.94	Follicular lymphoma, unspecified, lymph nodes of axilla and upper limb
C82.95	Follicular lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C82.96	Follicular lymphoma, unspecified, intrapelvic lymph nodes
C82.97	Follicular lymphoma, unspecified, spleen
C82.98	Follicular lymphoma, unspecified, lymph nodes of multiple sites
C82.99	Follicular lymphoma, unspecified, extranodal and solid organ sites
C83.00	Small cell B-cell lymphoma, unspecified site
C83.01	Small cell B-cell lymphoma, lymph nodes of head, face, and neck
C83.02	Small cell B-cell lymphoma, intrathoracic lymph nodes
C83.03	Small cell B-cell lymphoma, intra-abdominal lymph nodes
C83.04	Small cell B-cell lymphoma, lymph nodes of axilla and upper limb
C83.05	Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb

C83.06	Small cell B-cell lymphoma, intrapelvic lymph nodes
C83.07	Small cell B-cell lymphoma, spleen
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.09	Small cell B-cell lymphoma, extranodal and solid organ sites
C83.10	Mantle cell lymphoma, unspecified site
C83.11	Mantle cell lymphoma, lymph nodes of head, face, and neck
C83.12	Mantle cell lymphoma, intrathoracic lymph nodes
C83.13	Mantle cell lymphoma, intra-abdominal lymph nodes
C83.14	Mantle cell lymphoma, lymph nodes of axilla and upper limb
C83.15	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
C83.16	Mantle cell lymphoma, intrapelvic lymph nodes
C83.17	Mantle cell lymphoma, spleen
C83.18	Mantle cell lymphoma, lymph nodes of multiple sites
C83.19	Mantle cell lymphoma, extranodal and solid organ sites
C83.30	Diffuse large B-cell lymphoma, unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma, intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma, intra-abdominal lymph nodes
C83.34	Diffuse large B-cell lymphoma, lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.36	Diffuse large B-cell lymphoma, intrapelvic lymph nodes
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma, lymph nodes of multiple sites
C83.39	Diffuse large B-cell lymphoma, extranodal and solid organ sites
C83.50	Lymphoblastic (diffuse) lymphoma, unspecified site
C83.51	Lymphoblastic (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.52	Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes
C83.53	Lymphoblastic (diffuse) lymphoma, intra-abdominal lymph nodes
C83.54	Lymphoblastic (diffuse) lymphoma, lymph nodes of axilla and upper limb
C83.55	Lymphoblastic (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.56	Lymphoblastic (diffuse) lymphoma, intrapelvic lymph nodes
C83.57	Lymphoblastic (diffuse) lymphoma, spleen
C83.58	Lymphoblastic (diffuse) lymphoma, lymph nodes of multiple sites
C83.59	Lymphoblastic (diffuse) lymphoma, extranodal and solid organ sites
C83.70	Burkitt lymphoma, unspecified site
C83.71	Burkitt lymphoma, lymph nodes of head, face, and neck
C83.72	Burkitt lymphoma, intrathoracic lymph nodes
C83.73	Burkitt lymphoma, intra-abdominal lymph nodes

C83.74	Burkitt lymphoma, lymph nodes of axilla and upper limb
C83.75	Burkitt lymphoma, lymph nodes of inguinal region and lower limb
C83.76	Burkitt lymphoma, intrapelvic lymph nodes
C83.77	Burkitt lymphoma, spleen
C83.78	Burkitt lymphoma, lymph nodes of multiple sites
C83.79	Burkitt lymphoma, extranodal and solid organ sites
C83.80	Other non-follicular lymphoma, unspecified site
C83.81	Other non-follicular lymphoma, lymph nodes of head, face, and neck
C83.82	Other non-follicular lymphoma, intrathoracic lymph nodes
C83.83	Other non-follicular lymphoma, intra-abdominal lymph nodes
C83.84	Other non-follicular lymphoma, lymph nodes of axilla and upper limb
C83.85	Other non-follicular lymphoma, lymph nodes of inguinal region and lower limb
C83.86	Other non-follicular lymphoma, intrapelvic lymph nodes
C83.87	Other non-follicular lymphoma, spleen
C83.88	Other non-follicular lymphoma, lymph nodes of multiple sites
C83.89	Other non-follicular lymphoma, extranodal and solid organ sites
C83.90	Non-follicular (diffuse) lymphoma, unspecified site
C83.91	Non-follicular (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.92	Non-follicular (diffuse) lymphoma, intrathoracic lymph nodes
C83.93	Non-follicular (diffuse) lymphoma, intra-abdominal lymph nodes
C83.94	Non-follicular (diffuse) lymphoma, lymph nodes of axilla and upper limb
C83.95	Non-follicular (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.96	Non-follicular (diffuse) lymphoma, intrapelvic lymph nodes
C83.97	Non-follicular (diffuse) lymphoma, spleen
C83.98	Non-follicular (diffuse) lymphoma, lymph nodes of multiple sites
C83.99	Non-follicular (diffuse) lymphoma, extranodal and solid organ sites
C84.00	Mycosis fungoides, unspecified site
C84.01	Mycosis fungoides, lymph nodes of head, face, and neck
C84.02	Mycosis fungoides, intrathoracic lymph nodes
C84.03	Mycosis fungoides, intra-abdominal lymph nodes
C84.04	Mycosis fungoides, lymph nodes of axilla and upper limb
C84.05	Mycosis fungoides, lymph nodes of inguinal region and lower limb
C84.06	Mycosis fungoides, intrapelvic lymph nodes
C84.07	Mycosis fungoides, spleen
C84.08	Mycosis fungoides, lymph nodes of multiple sites
C84.09	Mycosis fungoides, extranodal and solid organ sites
C84.10	Sezary disease, unspecified site
C84.11	Sezary disease, lymph nodes of head, face, and neck

C84.12	Sezary disease, intrathoracic lymph nodes
C84.13	Sezary disease, intra-abdominal lymph nodes
C84.14	Sezary disease, lymph nodes of axilla and upper limb
C84.15	Sezary disease, lymph nodes of inguinal region and lower limb
C84.16	Sezary disease, intrapelvic lymph nodes
C84.17	Sezary disease, spleen
C84.18	Sezary disease, lymph nodes of multiple sites
C84.19	Sezary disease, extranodal and solid organ sites
C84.40	Peripheral T-cell lymphoma, not classified, unspecified site
C84.41	Peripheral T-cell lymphoma, not classified, lymph nodes of head, face, and neck
C84.42	Peripheral T-cell lymphoma, not classified, intrathoracic lymph nodes
C84.43	Peripheral T-cell lymphoma, not classified, intra-abdominal lymph nodes
C84.44	Peripheral T-cell lymphoma, not classified, lymph nodes of axilla and upper limb
C84.45	Peripheral T-cell lymphoma, not classified, lymph nodes of inguinal region and lower limb
C84.46	Peripheral T-cell lymphoma, not classified, intrapelvic lymph nodes
C84.47	Peripheral T-cell lymphoma, not classified, spleen
C84.48	Peripheral T-cell lymphoma, not classified, lymph nodes of multiple sites
C84.49	Peripheral T-cell lymphoma, not classified, extranodal and solid organ sites
C84.60	Anaplastic large cell lymphoma, ALK-positive, unspecified site
C84.61	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of head, face, and neck
C84.62	Anaplastic large cell lymphoma, ALK-positive, intrathoracic lymph nodes
C84.63	Anaplastic large cell lymphoma, ALK-positive, intra-abdominal lymph nodes
C84.64	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of axilla and upper limb
C84.65	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of inguinal region and lower limb
C84.66	Anaplastic large cell lymphoma, ALK-positive, intrapelvic lymph nodes
C84.67	Anaplastic large cell lymphoma, ALK-positive, spleen
C84.68	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of multiple sites
C84.69	Anaplastic large cell lymphoma, ALK-positive, extranodal and solid organ sites
C84.70	Anaplastic large cell lymphoma, ALK-negative, unspecified site
C84.71	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of head, face, and neck
C84.72	Anaplastic large cell lymphoma, ALK-negative, intrathoracic lymph nodes
C84.73	Anaplastic large cell lymphoma, ALK-negative, intra-abdominal lymph nodes
C84.74	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of axilla and upper limb
C84.75	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of inguinal region

	and lower limb
C84.76	Anaplastic large cell lymphoma, ALK-negative, intrapelvic lymph nodes
C84.77	Anaplastic large cell lymphoma, ALK-negative, spleen
C84.78	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of multiple sites
C84.79	Anaplastic large cell lymphoma, ALK-negative, extranodal and solid organ sites
C84.A0	Cutaneous T-cell lymphoma, unspecified, unspecified site
C84.A1	Cutaneous T-cell lymphoma, unspecified, lymph nodes of head, face, and neck
C84.A2	Cutaneous T-cell lymphoma, unspecified, intrathoracic lymph nodes
C84.A3	Cutaneous T-cell lymphoma, unspecified, intra-abdominal lymph nodes
C84.A4	Cutaneous T-cell lymphoma, unspecified, lymph nodes of axilla and upper limb
C84.A5	Cutaneous T-cell lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C84.A6	Cutaneous T-cell lymphoma, unspecified, intrapelvic lymph nodes
C84.A7	Cutaneous T-cell lymphoma, unspecified, spleen
C84.A8	Cutaneous T-cell lymphoma, unspecified, lymph nodes of multiple sites
C84.A9	Cutaneous T-cell lymphoma, unspecified, extranodal and solid organ sites
C84.Z0	Other mature T/NK-cell lymphomas, unspecified site
C84.Z1	Other mature T/NK-cell lymphomas, lymph nodes of head, face, and neck
C84.Z2	Other mature T/NK-cell lymphomas, intrathoracic lymph nodes
C84.Z3	Other mature T/NK-cell lymphomas, intra-abdominal lymph nodes
C84.Z4	Other mature T/NK-cell lymphomas, lymph nodes of axilla and upper limb
C84.Z5	Other mature T/NK-cell lymphomas, lymph nodes of inguinal region and lower limb
C84.Z6	Other mature T/NK-cell lymphomas, intrapelvic lymph nodes
C84.Z7	Other mature T/NK-cell lymphomas, spleen
C84.Z8	Other mature T/NK-cell lymphomas, lymph nodes of multiple sites
C84.Z9	Other mature T/NK-cell lymphomas, extranodal and solid organ sites
C84.90	Mature T/NK-cell lymphomas, unspecified, unspecified site
C84.91	Mature T/NK-cell lymphomas, unspecified, lymph nodes of head, face, and neck
C84.92	Mature T/NK-cell lymphomas, unspecified, intrathoracic lymph nodes
C84.93	Mature T/NK-cell lymphomas, unspecified, intra-abdominal lymph nodes
C84.94	Mature T/NK-cell lymphomas, unspecified, lymph nodes of axilla and upper limb
C84.95	Mature T/NK-cell lymphomas, unspecified, lymph nodes of inguinal region and lower limb
C84.96	Mature T/NK-cell lymphomas, unspecified, intrapelvic lymph nodes
C84.97	Mature T/NK-cell lymphomas, unspecified, spleen
C84.98	Mature T/NK-cell lymphomas, unspecified, lymph nodes of multiple sites
C84.99	Mature T/NK-cell lymphomas, unspecified, extranodal and solid organ sites
C85.10	Unspecified B-cell lymphoma, unspecified site

C85.11	Unspecified B-cell lymphoma, lymph nodes of head, face, and neck
C85.12	Unspecified B-cell lymphoma, intrathoracic lymph nodes
C85.13	Unspecified B-cell lymphoma, intra-abdominal lymph nodes
C85.14	Unspecified B-cell lymphoma, lymph nodes of axilla and upper limb
C85.15	Unspecified B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.16	Unspecified B-cell lymphoma, intrapelvic lymph nodes
C85.17	Unspecified B-cell lymphoma, spleen
C85.18	Unspecified B-cell lymphoma, lymph nodes of multiple sites
C85.19	Unspecified B-cell lymphoma, extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma, unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face, and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites
C85.80	Other specified types of non-Hodgkin lymphoma, unspecified site
C85.81	Other specified types of non-Hodgkin lymphoma, lymph nodes of head, face, and neck
C85.82	Other specified types of non-Hodgkin lymphoma, intrathoracic lymph nodes
C85.83	Other specified types of non-Hodgkin lymphoma, intra-abdominal lymph nodes
C85.84	Other specified types of non-Hodgkin lymphoma, lymph nodes of axilla and upper limb
C85.85	Other specified types of non-Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C85.86	Other specified types of non-Hodgkin lymphoma, intrapelvic lymph nodes
C85.87	Other specified types of non-Hodgkin lymphoma, spleen
C85.88	Other specified types of non-Hodgkin lymphoma, lymph nodes of multiple sites
C85.89	Other specified types of non-Hodgkin lymphoma, extranodal and solid organ sites
C85.90	Non-Hodgkin lymphoma, unspecified, unspecified site
C85.91	Non-Hodgkin lymphoma, unspecified, lymph nodes of head, face, and neck
C85.92	Non-Hodgkin lymphoma, unspecified, intrathoracic lymph nodes
C85.93	Non-Hodgkin lymphoma, unspecified, intra-abdominal lymph nodes

C85.94	Non-Hodgkin lymphoma, unspecified, lymph nodes of axilla and upper limb
C85.95	Non-Hodgkin lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C85.96	Non-Hodgkin lymphoma, unspecified, intrapelvic lymph nodes
C85.97	Non-Hodgkin lymphoma, unspecified, spleen
C85.98	Non-Hodgkin lymphoma, unspecified, lymph nodes of multiple sites
C85.99	Non-Hodgkin lymphoma, unspecified, extranodal and solid organ sites
C86.0	Extranodal NK/T-cell lymphoma, nasal type
C86.1	Hepatosplenic T-cell lymphoma
C86.2	Enteropathy-type (intestinal) T-cell lymphoma
C86.3	Subcutaneous panniculitis-like T-cell lymphoma
C86.4	Blastic NK-cell lymphoma
C86.5	Angioimmunoblastic T-cell lymphoma
C86.6	Primary cutaneous CD30-positive T-cell proliferation
C88.0	Waldenstrom macroglobulinemia
C88.2	Heavy chain disease
C88.3	Immunoproliferative small intestinal disease
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma)
C88.8	Other malignant immunoproliferative diseases
C88.9	Malignant immunoproliferative disease, unspecified
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.11	Plasma cell leukemia in remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.21	Extramedullary plasmacytoma in remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.31	Solitary plasmacytoma in remission
C90.32	Solitary plasmacytoma in relapse
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia in remission
C91.02	Acute lymphoblastic leukemia in relapse
C91.10	Chronic lymphoblastic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphoblastic leukemia of B-cell type in remission
C91.12	Chronic lymphoblastic leukemia of B-cell type in relapse

C91.30	Prolymphocytic leukemia of B-cell type not having achieved remission
C91.31	Prolymphocytic leukemia of B-cell type in remission
C91.32	Prolymphocytic leukemia of B-cell type in relapse
C91.40	Hairy cell leukemia not having achieved remission
C91.41	Hairy cell leukemia in remission
C91.42	Hairy cell leukemia in relapse
C91.50	Adult T-cell lymphoma/leukemia (HTLV-1-associated) not having achieved remission
C91.51	Adult T-cell lymphoma/leukemia (HTLV-1-associated) in remission
C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated) in relapse
C91.60	Prolymphocytic leukemia of T-cell type not having achieved remission
C91.61	Prolymphocytic leukemia of T-cell type in remission
C91.62	Prolymphocytic leukemia of T-cell type in relapse
C91.A0	Mature B-cell leukemia Burkitt-type not having achieved remission
C91.A1	Mature B-cell leukemia Burkitt-type in remission
C91.A2	Mature B-cell leukemia Burkitt-type in relapse
C91.Z0	Other lymphoid leukemia not having achieved remission
C91.Z1	Other lymphoid leukemia in remission
C91.Z2	Other lymphoid leukemia in relapse
C91.90	Lymphoid leukemia, unspecified, not having achieved remission
C91.91	Lymphoid leukemia, unspecified, leukemia in remission
C91.92	Lymphoid leukemia, unspecified, leukemia in relapse
C92.00	Acute myeloblastic leukemia not having achieved remission
C92.01	Acute myeloblastic leukemia in remission
C92.02	Acute myeloblastic leukemia in relapse
C92.10	Chronic myeloblastic leukemia, BCR/ABL-positive not having achieved remission
C92.11	Chronic myeloblastic leukemia, BCR/ABL-positive in remission
C92.12	Chronic myeloblastic leukemia, BCR/ABL-positive in relapse
C92.20	Atypical chronic myeloid leukemia, BCR/ABL-negative not having achieved remission
C92.21	Atypical chronic myeloid leukemia, BCR/ABL-negative in remission
C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative in relapse
C92.30	Myeloid sarcoma not having achieved remission
C92.31	Myeloid sarcoma in remission
C92.32	Myeloid sarcoma in relapse
C92.40	Acute promyelocytic leukemia not having achieved remission
C92.41	Acute promyelocytic leukemia in remission
C92.42	Acute promyelocytic leukemia in relapse

C92.50	Acute myelomonocytic leukemia not having achieved remission
C92.51	Acute myelomonocytic leukemia in remission
C92.52	Acute myelomonocytic leukemia in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.61	Acute myeloid leukemia with 11q23-abnormality in remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia not having achieved remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia in remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia in relapse
C92.Z0	Other myeloid leukemia not having achieved remission
C92.Z1	Other myeloid leukemia in remission
C92.Z2	Other myeloid leukemia in relapse
C92.90	Myeloid leukemia, unspecified, not having achieved remission
C92.91	Myeloid leukemia, unspecified, in remission
C92.92	Myeloid leukemia, unspecified, in relapse
C93.00	Acute monoblastic/monocytic leukemia not having achieved remission
C93.01	Acute monoblastic/monocytic leukemia in remission
C93.02	Acute monoblastic/monocytic leukemia in relapse
C93.10	Chronic myelomonocytic leukemia not having achieved remission
C93.11	Chronic myelomonocytic leukemia in remission
C93.12	Chronic myelomonocytic leukemia in relapse
C93.30	Juvenile myelomonocytic leukemia not having achieved remission
C93.31	Juvenile myelomonocytic leukemia in remission
C93.32	Juvenile myelomonocytic leukemia in relapse
C93.Z0	Other monocytic leukemia not having achieved remission
C93.Z1	Other monocytic leukemia in remission
C93.Z2	Other monocytic leukemia in relapse
C93.90	Monocytic leukemia, unspecified, not having achieved remission
C93.91	Monocytic leukemia, unspecified, in remission
C93.92	Monocytic leukemia, unspecified, in relapse
C94.00	Acute erythroid leukemia, not having achieved remission
C94.01	Acute erythroid leukemia, in remission
C94.02	Acute erythroid leukemia, in relapse
C94.20	Acute megakaryoblastic leukemia, not having achieved remission
C94.21	Acute megakaryoblastic leukemia, in remission
C94.22	Acute megakaryoblastic leukemia, in relapse
C94.30	Mast cell leukemia, not having achieved remission
C94.31	Mast cell leukemia, in remission

C94.32	Mast cell leukemia, in relapse
C94.40	Acute panmyelosis with myelofibrosis, not having achieved remission
C94.41	Acute panmyelosis with myelofibrosis, in remission
C94.42	Acute panmyelosis with myelofibrosis, in relapse
C94.80	Other specified leukemias, not having achieved remission
C94.81	Other specified leukemias, in remission
C94.82	Other specified leukemias, in relapse
C95.00	Acute leukemia of unspecified cell type, not having achieved remission
C95.01	Acute leukemia of unspecified cell type, in remission
C95.02	Acute leukemia of unspecified cell type, in relapse
C95.10	Chronic leukemia of unspecified cell type, not having achieved remission
C95.11	Chronic leukemia of unspecified cell type, in remission
C95.12	Chronic leukemia of unspecified cell type, in relapse
C95.90	Leukemia, unspecified, not having achieved remission
C95.91	Leukemia, unspecified, in remission
C95.92	Leukemia, unspecified, in relapse
C96.0	Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
C96.20	Malignant mast cell neoplasm, unspecified
C96.21	Aggressive systemic mastocytosis
C96.22	Mast cell sarcoma
C96.29	Other malignant mast cell neoplasm
C96.4	Sarcoma of dendritic cells (accessory cells)
C96.5	Multifocal and unisystemic Langerhans-cell histiocytosis
C96.6	Unifocal Langerhans-cell histiocytosis
C96.A	Histiocytic sarcoma
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified