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.