NON-INTERVENTIONAL/LOW-INTERVENTIONAL STUDY TYPE 1 STUDY REPORT ABSTRACT

Title: A Comparative Observational Study Evaluating the Incidence Rate of Endometrial Cancer in Women Aged 50 Years and Over Who Use Low Dose Vaginal Estrogen Unopposed by a Progestogen: A Post-Authorization Safety Study in the United States and Sweden

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Rationale and background: Systemic estrogen use is associated with increased risk of endometrial cancer (EC). It is unknown whether vaginal estrogen, which is administered locally rather than orally also increases the risk of EC. This non-interventional study was designed as a Post-Authorization Safety Study (PASS) that was conducted in the United States (US) and Sweden to fulfill a post-marketing requirement (PMR) to the U.S Food and Drug Administration (FDA).

Research question and objectives: What is the incidence rate (IR) of endometrial cancer (EC) in postmenopausal women with a uterus who use low-dose vaginal estrogen (LDVE) unopposed by a progestogen compared to non-users and compared to users of estrogen and progestogen combination hormone therapy (E+P HT)?

Primary Objectives:

1. To estimate and compare the IR of EC in postmenopausal women aged ≥50 years, with a uterus, regardless of prior use of hormone therapy (defined as any estrogen, progestin, E+P HT, or other opposed estrogen hormone therapy), in the following groups:
   a. New users of low-dose vaginal estrogen (LDVE) versus non-users of vaginal estrogen.
   b. New users of moderate-dose vaginal estrogen (MDVE) versus non-users of vaginal estrogen.
   c. New users of high-dose Premarin Vaginal Cream (HDVC) versus non-users of vaginal estrogen (HIRD only, as Premarin VC is not available in Sweden).
2. To estimate and compare the IR of EC separately among the LDVE, MDVE, and HDVC new users (HIRD only) aged ≥50 years, with a uterus, and regardless of prior use of hormone therapy relative to non-users of vaginal estrogen stratified by prior use of hormone therapy including unopposed estrogen, unopposed progestin, single-entity or combination progestin-opposed estrogen hormone therapy, other opposed estrogen hormone therapy or no prior hormone use.

3. To estimate and compare the IR of EC separately among new users of LDVE, MDVE, and HDVC (HIRD only) aged >50 years, with a uterus, and regardless of prior use of hormone therapy relative to non-users of vaginal estrogen stratified by duration of use, index formulation, active ingredient at index, number of dispensings, and number of dispensings per index formulation.

Secondary Objective:

1. To estimate and compare the IR of EC among women aged ≥50 years, with a uterus, and without prior hormone therapy use, in the following groups:
   a. LDVE new users versus E+P HT new users of hormone therapy.
   b. MDVE new users versus E+P HT new users of hormone therapy.
   c. HDVC new users versus E+P HT new users of hormone therapy (HIRD only).

Study design: This was a non-interventional longitudinal cohort study among women who were at least 50 years old conducted with secondary data from a US healthcare claims data source (the Healthcare Integrated Research Database) and longitudinal data collected from five Swedish National Registers. The three exposed cohorts were new users of vaginal estrogen grouped into 3 dose categories: LDVE, MDVE, and HDVC (HIRD only). These patients had no prior use of any vaginal estrogen but could have prior use of other types of hormone therapies such as E+P HT. The primary comparator group included patients visiting a gynecologist with no history of vaginal estrogen use (non-users) but could have used other hormone therapies. The secondary active comparator group included E+P HT new users with no prior use of any hormone therapies indicated for post-menopausal symptoms. These patients were compared to the subset of vaginal estrogen patients who also had no prior use of any hormone therapies.

Setting:
The study period was 01 January 2006 through 31 December 2021 in the HIRD, and 01 January 1997 through 31 December 2019 in the Swedish registers. Ascertainment of exposure was from 01 January 2007 through 31 December 2021 in the HIRD, to allow for a 12-month baseline period. Ascertainment of exposure in the Swedish Prescribed Drug Register (SPDR) was assessed from 01 July 2007 through 31 December 2019. The index date was the date of initiating a study drug for vaginal estrogen or E+P HT new users. The index date for the non-user cohort was the date of a gynecological visit.

Because cancer can take time to develop after an exposure, it was considered unlikely that a cancer diagnosis within six months of starting a new drug would be attributable to that drug. Therefore, follow-up (i.e., accrual of person-time) started 6 months after index for vaginal estrogen new users and E+P HT new users. Non-users did not start any treatment on index, so it was assumed their risk of EC was constant over time. For those patients, follow-up started the day after index. For all patients, follow-up continued until they started a different hormone therapy, switched to a different vaginal estrogen dose, had a hysterectomy, were diagnosed with endometrial cancer, ended their continuous health plan eligibility (HIRD only), emigrated from Sweden (Swedish Registers only), died, or until the study period ended.

Subjects and study size, including dropouts: The exposure of interest was new use of low, moderate, or high-dose vaginal estrogen. Patients using these vaginal estrogens were compared to non-users of vaginal estrogen, who were women ≥50 who had a gynecologist visit. They were also compared to women using oral, transdermal, or injectable E+P HT. Study eligible patients in the HIRD needed to have at least 1 year of continuous health plan enrollment prior to their index date (the baseline period) and Swedish patients needed at least 2 years of baseline time prior to their index date. Patients were excluded if they had a history of hysterectomy, a history of endometrial cancer, prior fills of vaginal estrogen, a fill of two or more different vaginal estrogen medication fills on index or were missing data on urbanicity or region.

Variables and data sources: The HIRD was used to create the US study population and the Swedish Registers were used to create the Swedish study population.

Low dose vaginal estrogen (LDVE) was defined as daily doses[(1)] ≤10 mcg estradiol or ≤0.3 mg conjugated estrogen at cohort entry.[(1)] Moderate dose vaginal estrogen (MDVE) was defined as daily doses >10 mcg to ≤25 mcg estradiol or >0.3 mg to ≤0.45 mg conjugated estrogen (HIRD only) at cohort entry. High-dose vaginal estrogen only consisted of high-dose Premarin Vaginal Cream (HDVC) and was only studied in the HIRD. It was defined as a Premarin VC daily dose >0.45 mg conjugated estrogen. Premarin VC was also included in the LDVE and MDVE cohorts when used in those dosages.

The outcome of this study was endometrial cancer (EC). The Swedish Cancer Register was used to identify Swedish patients with EC. In Sweden, the registration of newly detected tumors is based on compulsory reports from all health care providers, both public and private. Most cancers are reported twice, and the completeness of the register is close to 100%. In the HIRD, EC was defined using an algorithm, which was developed and validated in a separate validation study.

Hazard ratios of EC were estimated using Cox proportional hazards models adjusted for demographic characteristics and medical and prescription history using propensity score matching (PSM) or inverse probability weighting (IPW) methods. Incidence rates (IR) and 95% confidence intervals (CI) of EC were also calculated. A subgroup analysis was conducted among vaginal estrogen users compared to non-users by history of hormone therapy use (unopposed estrogen, unopposed progestin, progestin opposed estrogen hormone therapy, other opposed estrogen therapy, or no prior use). A second subgroup analysis was conducted among vaginal estrogen users compared to non-users by vaginal estrogen active ingredient at index, formulation at index, number of dispensings over follow-up, duration of use over follow-up, and number of dispensings over follow-up by formulation at index.

Several sensitivity analyses were conducted. The first varied the induction period for LDVE users (no induction period, 3 months, or 12 months) or applied a 6-month induction period for non-users to test the impact of the induction period and to determine whether the EC IR was constant for non-users. The second restricted analyses to only the first treatment episode to evaluate the possibility of informed censoring and selection in the analysis. The third was an intent-to-treat analysis removing all censoring for use of other hormone therapies or switching treatment groups to evaluate the impact of informed censoring. A

similar analysis was conducted for similar reasons removing the censoring for starting progestin. A fifth sensitivity analysis was conducted extending the minimum HIRD baseline period from 12 months to 18 months to evaluate the possible impact of missing information on medical history. An analysis was conducted by stratifying the comparative analyses by patients' history of cancer. An additional analysis in the HIRD explored whether HDVC users with >2 fills per year (higher than the intended average daily dose) and HDVC users with ≤2 fills per year had a higher risk of EC compared to non-users. Another HIRD analysis compared HDVC new users to LDVE new users to determine if patients using the higher dose had a higher risk of EC than patients using low doses.

Finally, a probabilistic QBA was done to assess the impact of missing baseline data on hysterectomy on the analyses comparing LDVE users to non-users and E+P HT new users. A second QBA was done to assess the impact of EC algorithm PPV and sensitivity on outcome misclassification on the analyses comparing LDVE, MDVE and HDVC users to non-users and E+P HT new users.

Results:

HIRD: In the primary analysis the study population consisted of 235,399 LDVE users, 17,558 MDVE users, 107,969 HDVC users, and 2,488,416 non-users of vaginal estrogen. In the secondary analysis the study population, a subset of the primary population without prior use of hormone therapy, consisted of 175,101 LDVE new users, 12,847 MDVE new users, 83,162 HDVC new users of hormone therapy, and 45,323 E+P HT new users.

The average age of women in the HIRD cohorts ranged from 58 to 63 years. Women in the HIRD had a median baseline period ranging from 2 to 3 years and were followed for approximately 1 to 2 years. Women in the LDVE and HDVC cohorts had index dates throughout the study period. Index dates for MDVE users were primarily between 2007 and 2010 due to Vagifem® 25 mcg leaving the market. Hyperlipidemia, hypertension, osteoarthritis, and depression were common baseline comorbidities across cohorts. Antidepressants, lipid lowering agents, immunosuppressants, and corticosteroids were common prescription medications filled (~40% of patients) across cohorts during baseline.

In the HIRD, the main analysis comparing LDVE users to non-users (HIRD Table 5a) showed an inverse association with EC (HR = 0.48, 95% CI = 0.43—0.53). A sensitivity analysis that started follow-up after 6 months for non-users resulted in a higher, though still inverse association with EC (HR = 0.87, 95% CI = 0.78—0.97) (HIRD Table 5b). This analysis suggested that selection bias may be present, over-estimating the incidence of EC in non-users. Missing baseline data on hysterectomy was corrected using a Monte Carlo quantitative bias simulation and resulted in a final IRR comparing LDVE users to non-users of 1.05 (95% CI = 0.68—1.58) (HIRD Table 11).

The main analysis comparing MDVE users to non-users showed no association with EC (Table 5a, HR = 1.19, 95% CI = 0.58—1.68). Starting follow-up after six months for non-users increased the HR (Table 5b, HR = 1.68, 95% CI = 1.17—2.42). Further correcting this HR for outcome misclassification decreased the HR from 1.68 to 1.29 (95% CI = 0.56—1.84). An ITT analysis of the association was added because the MDVE users switched to LDVE, HDVC or other estrogen treatments after Vagifem 25 mcg left the market and this showed a decrease in the original HR from 1.19 to 1.09 (95% CI = 0.86—1.39).

The main analysis HR comparing HDVC users to non-users was 0.46 (95% CI = 0.40—0.53). Correcting for selection bias (HIRD Table 5b) increased the HR to 0.76 (95% CI = 0.65—0.88). Outcome misclassification corrections did not affect the association. Per the protocol, other sensitivity analyses were not performed in this cohort.

The bias seen in non-users was not present in the secondary analyses, but those analyses were missing baseline data on hysterectomy. The secondary analysis comparing LDVE new users to E+P HT new users was HR = 0.74 (0.63—0.87). After correcting for missing baseline data on hysterectomy, the IRR of EC comparing LDVE new users to E+P HT new users was 0.87 (0.58—1.31). Corrections for outcome misclassification decreased the IRR (0.59, 95% CI = 0.33—0.87).

The comparative analysis of MDVE new users to E+P HT new users showed an association with EC (HR = 1.95, 95% CI = 1.12—3.41). The ITT analysis of MDVE new users and E+P HT new user decreased the association to 1.83 (1.14—2.94). Correcting this estimate for outcome misclassification increased the HR to 2.06 (95% CI = 0.87—3.20).

The comparative analysis of HDVC new users to E+P HT new users showed a slight inverse association (HR = 0.84, 0.67—1.05). Outcome misclassification did not affect this cohort.

Subgroup analyses by history of hormone therapy use, duration of use, number of fills, index formulation, index active ingredient and number of fills by index formulation did not show any heterogeneity.

Finally, some differences were seen in comparative analyses by patients' history of cancer especially in the secondary analyses. Among patients with a history of cancer, the HR of EC comparing LDVE new users to E+P HT new users was 1.23 (95% CI = 0.95—1.60) while among patients without a history of cancer the HR = 0.51 (95% CI = 0.41—0.64). Similar trends were seen in the analyses comparing MDVE and HDVC new users to E+P HT patients where positive associations were found among patients with a history of cancer and inverse associations were found among patients without a history of cancer.

Sweden: In the primary analysis the study population consisted of 191,392 LDVE users, 120,881 MDVE users, and 395,490 non-users. In the secondary analysis the study population, a subset of the primary study population without prior use of any hormone therapy, consisted of 139,717 LDVE new users, 94,783 MDVE new users, and 40,870 E+P HT new users.

The average age of women in the Swedish cohorts ranged from 61 to 65 years. Women in Sweden had a mean baseline period of 17 years in the LDVE analyses and 12 years in the MDVE analyses and were followed for approximately 2 to 6 years depending on the cohort. The distributions of index dates for these cohorts were similar to the distribution in the HIRD. Hypertension, postmenopausal atrophic vaginitis, and vasomotor symptoms were the most common (N~15-20%) baseline comorbidities diagnosed by a specialist. Before and after PSM, non-users had a higher prevalence of cancer, especially breast and ovarian cancer. Sedatives/hypnotics (N>20%), lipid lowering agents (N~15-20%), and antidepressants (~20%) were the most common medications used in the two years prior to index.

The HR of EC comparing LDVE users to non-users was HR = 0.73 (95% CI = 0.65—0.81). Sensitivity analyses starting follow-up after 6 months in the non-user cohort showed an 80% drop in the number of non-user cases. This increased the HR to 2.81 (95% CI = 2.35—3.37). The incidence rate (per 10,000 PY) in the non-users changed from 10.66 (95% CI = 9.98-11.37) to 2.63 (95% CI = 2.27—3.02).

Comparing MDVE users to non-users, the HR of EC was 0.95 (95% CI = 0.83—1.09). Per the protocol, the only sensitivity analysis done for this cohort added a censoring criterion at the restart of the index drug, which produced a lower HR (0.33, 95% CI = 0.25—0.44).

The secondary analyses had much smaller sample sizes and were based on fewer cases due to 1:4 propensity score matching a larger vaginal estrogen population (139,717 LDVE and 94,783 MDVE new users) to a small (N=40,870) E+P HT population. As a result, estimates from these analyses were imprecise. The association between LDVE and EC compared to E+P HT was HR= 1.34 (95% CI = 0.84—2.13). When patients were censored after restarting the index drug the HR increased to 1.93 (95% CI = 0.77—4.87).

The HR between MDVE and EC compared to E+P HT was HR=1.15 (95% CI = 0.73—1.83). When patients were censored after restarting the index drug the HR increased to 4.38 (95% CI = 0.90—21.19).

As with the HIRD results, for Sweden, no trends were seen by history of hormone therapy, duration of use, number of fills, index formulation, index active ingredient, or number of fills by index formulation. The effect modification by history of cancer was not present in the Swedish analyses.

Pooled Analyses: Pooled analyses of the main results (adjusted for confounding, but uncorrected for any other biases) comparing LDVE to non-users (HR = 0.59, 95% CI = 0.54—0.63) and E+P HT (HR = 0.67, 95% CI = 0.59—0.77) both found inverse associations with EC. MDVE users compared to non-users were not no associated with EC (HR = 0.98, 95% CI = 0.87—1.12). The analysis comparing MDVE new users to E+P HT new users showed a strong positive association with EC (HR = 1.52, 95% CI = 1.08—2.15), likely driven by the HIRD results. Subgroups by history of hormone therapy in the pooled ITT analysis produced estimates ranging from 0.59 to 1.08 with wide CIs consistent with one another.

Discussion: The primary analysis results comparing LDVE users to non-users in both study populations showed inverse associations with EC, but these results were unexpected and were due, in part, to selection biases that manifested differently in the HIRD and Swedish Registers. In the HIRD this selection bias was due to capturing women presenting at the gynecologist on index for symptoms of EC. These prevalent EC cases could be removed by starting follow-up after six months thus correcting for the bias. In Sweden, the prevalent cases could be removed, but the non-user cohort was also missing data on most healthy women at risk of EC. Women in Sweden receive routine gynecological care and screenings in primary care and are referred to the gynecologist for more complicated gynecological conditions. Since no primary care registry exists in Sweden, it was not possible to estimate an unbiased incidence of EC in the non-user population in the Swedish Register cohort. Therefore, the bias could not be corrected in the Swedish Registers' primary analyses.

In the HIRD, after addressing selection bias, missing data on hysterectomy, and adjusting for confounding, no association was found between low dose or high dose vaginal estrogen and endometrial cancer when compared to no use and compared to use of E+P HT.

The main analysis found MDVE use was not associated with increased risk of EC compared to non-users (HR = 0.98, 95% CI = 0.87—1.12). However, in the HIRD analysis, after correcting for selection bias, an increased risk of EC was found. Analyses comparing MDVE new users to E+P HT new users found no association in the Swedish registers; but an increased risk of EC was observed for the same comparison in the HIRD. The HIRD results could partly be explained by MDVE patients switching to LDVE, HDVC, or other estrogen medications after Vagifem® 25mcg (used by 77% of MDVE patients) went off the market in 2010. The positive association in the HIRD's secondary analyses may also be due to a higher proportion of breast cancer patients in the MDVE cohort than the comparator cohorts.

No trends by history of hormone therapy or by duration of use, number of dispensings, active ingredient at index, index formulation, or number of dispensings by index formulation were found. In the HIRD, among patients *with* a history of cancer, vaginal estrogen was associated with EC, while among patients *without* a history of cancer, vaginal estrogen was inversely associated with EC compared to E+P HT. This may be caused by baseline breast cancers in the vaginal estrogen cohorts. This effect modification was not seen in the Swedish database; however, this could be due to small sample size and different code lists.

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