## **Supplemental Table 2**: Prospective, Interventional Studies (n = 8) of Endometrial Histology with Vaginal Estrogen Use in Menopausal Women

| **Reference** | **Treatment(s)** | **Study design and population** | **Endometrial cancer or hyperplasia** |
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| Ulrich et al, 201030  Study VAG-1748  Duration: 52 weeks | * Vaginal E2 tablets 10 µg [Vagifem] (n = 336) * Daily for 2 weeks, then twice weekly for 50 weeks | * Prospective, open-label study conducted at 40 sites in 7 countries * Healthy, non-hysterectomized, postmenopausal women (≥45 years) with moderate-to-severe urogenital symptoms * Women had to have endometrial thickness <4 mm (by ultrasound) * Endometrial biopsy at baseline and week 52/end of treatment taken (Pipelle) to determine hyperplasia rate | * No cases of endometrial hyperplasia or cancer were found * One biopsy was scored as a polyp of hyperplastic type, which appears to be reported as a case of complex hyperplasia without atypia in the Vagifem prescribing information47 * The incidence of endometrial hyperplasia or cancer was 0 (95% CI, 0–0.011) |
| Yumru et al, 200932  Duration: 12 weeks | * Vaginal E2 tablets 25 μg (n = 35) * Given daily for 2 weeks, then twice weekly for 10 weeks | * Prospective data from 1 center in Turkey * Non-hysterectomized postmenopausal women (46–67 years) with symptomatic vaginal atrophy * Endometrial biopsies (Pipelle) were performed in women with endometrial thickness ≥5 mm | * No cases of endometrial hyperplasia or cancer reported |
| Mainini et al, 200528  Duration: 24 weeks | * Vaginal E2 tablets 25 µg [Vagifem] daily for 2 weeks, and twice a week for 22 weeks (n = 325) | * Prospective data from a single site * Postmenopausal women (51–67 years) with symptomatic vaginal atrophy * No endometrial study entry criteria were reported * Incidence of endometrial hyperplasia with or without uterine bleeding was the safety endpoint * Endometrial biopsy performed if thickness >4 mm at end of treatment | * No endometrial cancer was reported * 2/266 simple glandular hyperplasia * 1/266 cystic hyperplasia |
| Santen et al, 200226  Duration: 12 weeks | * Vaginal E2 cream 10 µg/g [dilution of 100 µg/g Estrace®, Allergan Pharmaceutical International Limited, Madison, NJ] (n = 7) * Daily for 3 weeks, then twice weekly for 9 weeks | * Prospectively collected data * Postmenopausal women with symptoms of estrogen-deficiency, signs of urogenital atrophy, and without a history of breast cancer * Endometrial biopsy taken (Pipelle) at baseline and again at 12 weeks to determine any stimulation of endometrial proliferation | * No endometrial hyperplasia or cancer reported |
| Manonai et al, 200129  Duration: 12 weeks | * Vaginal E2 tablets 25 μg (n = 27) * Given daily for 2 weeks, then twice weekly for 10 weeks | * Prospective data from 1 center in Thailand * Healthy, non-hysterectomized, postmenopausal women (47–65 years) with urogenital symptoms * Endometrial biopsy performed with vaginal bleeding | * No cases of endometrial hyperplasia or cancer reported |
| van Haaften et al, 199731  Duration: 3 weeks (prior to operation) | * Vaginal ovules   + E2 0.05 mg/day (n = 9)   + Estriol 0.5 mg/day (n = 8) * Untreated (n = 12) | * Postmenopausal women (49–82 years) scheduled to undergo hysterectomy due to uterine prolapse or myomatosus * Endometria obtained after hysterectomy were processed and viewed under light microscopy by a blinded pathologist * Endometrial assessment prior to giving estrogen was not mentioned | * No cases of endometrial cancer or hyperplasia reported |
| Handa et al, 199425  Duration: 24 weeks | * CEE cream 0.3 mg (0.5 g of 0.625 mg) [Premarin] (n = 20) * Daily for 2 weeks, then 3 times weekly for 22 weeks | * Prospective data from a single site * Postmenopausal women with symptomatic vaginal atrophy and atrophic endometrium (by endometrial biopsy; if not possible, endometrial thickness ≤5 mm) * Endometrial biopsies taken (Pipelle) at baseline and week 24 | * No endometrial hyperplasia or cancer reported |
| Semmens et al, 198527  Duration: 24 months | * CEE 0.625 mg/day [Premarin] was administered orally (n = 9 per group) or CEE 0.625 mg/day vaginally (n = 5) for 25 days followed by 5 days without medication; the cycle was then repeated | * Prospectively collected data from a single site * Postmenopausal, amenorrheic women (51–70 years) with climacteric symptoms * Endometrial biopsies by curettage were performed when vaginal bleeding occurred | * No endometrial hyperplasia or cancer reported |

HT, hormone therapy; HR, hazard ratio; CI, confidence interval; CE, conjugated estrogens; E2, 17β-estradiol; LOCF, last observation carried forward.