## **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, 201030Study VAG-1748Duration: 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)
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| Yumru et al, 200932Duration: 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
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| Mainini et al, 200528Duration: 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
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| Santen et al, 200226Duration: 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
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| Manonai et al, 200129Duration: 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
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| van Haaften et al, 199731Duration: 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
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| Handa et al, 199425Duration: 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
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| Semmens et al, 198527Duration: 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
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HT, hormone therapy; HR, hazard ratio; CI, confidence interval; CE, conjugated estrogens; E2, 17β-estradiol; LOCF, last observation carried forward.