Bleeding Patterns and Endometrial Safety with a 1-Year, Segesterone Acetate*/Ethinyl Estradiol Contraceptive Vaginal System

David F Archer, MD[1**]; Kurt T Barnhart, MD, MSCE[2]; Anita L Nelson, MD[3]; Mitchell D Creinin, MD[4]; Jeffrey T Jensen, MD, MPH[5]; Sebastian Mirkin, MD[6]; Ruth B Merkatz, PhD[7]

[1]Eastern Virginia Medical School, Norfolk, VA; [2]University of Pennsylvania, Philadelphia, PA; [3]Essential Access Health, Los Angeles, CA; [4]University of California, Davis; Sacramento, CA; [5]Oregon Health & Science University, Portland, OR; [6]TherapeuticsMD, Boca Raton, FL; [7]Population Council, New York, NY

**EVMS Eastern Virginia Medical School

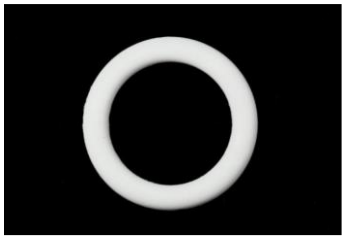
*Formerly known as Nestorone®

Disclosures

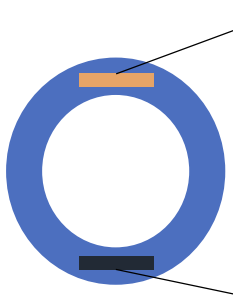
Dr. Archer	• Consultant: AbbVie, Actavis, Agile Therapeutics, Bayer Healthcare, Endoceutics, Exeltis, InnovaGyn, Merck, Pfizer, Radius Health, Sermonix, Shionogi, Teva Women's Healthcare, and TherapeuticsMD • Research support: Actavis, Bayer Healthcare, Endoceutics, Glenmark, Merck, Radius Health, Shionogi, and TherapeuticsMD
Dr. Barnhart	• Consultant: AbbVie and Bayer Healthcare
Dr. Nelson	• Advisory board/Consultant: Agile Therapeutics, AMAG, American Regent, Bayer Healthcare, Merck, and Sebela • Research support: Estetra, EvoFem, FHI (MonaLisa), Sebela, and Mithra • Speaker's bureau: Bayer Healthcare, Cooper Surgical and Merck
Dr. Creinin	• Advisory board: Lupin and Merck • Consultant: Danco, Estetra, Exeltis, and Medicines360 • Research support: Dare Bioscience, Fidelity Charitable, HRA Pharma, Medicines360, Sebela, NIH/NICHD and the Society of Family Planning
Dr. Jensen	• Advisory board: AbbVie, Bayer Healthcare, Merck, Population Council, and Sebela • Research support: AbbVie, Bayer Healthcare, Dare Bioscience, Estetra SPRL, Medicines360, Merck, NIH, and NICHD
Dr. Mirkin	• Employer: TherapeuticsMD with stock/stock options
Dr. Merkatz	• Employer: Population Council, a not-for-profit research organization

SA/EE 1-Year Contraceptive Vaginal System (CVS)

- A novel 1-year, ring-shaped CVS combining segesterone acetate (SA) and ethinyl estradiol (EE)
  - Reusable for 13 cycles (one year) on a 21-day in/7-day out regimen
  - Does not require refrigeration before first use or during cyclical periods of nonuse
- Approved by the FDA as Annovera™ in August 2018
  - Licensed to TherapeuticsMD, Boca Raton, FL



Delivers SA 0.15 mg/EE 0.013 mg per day 13 cycles: 3 weeks on/1 week off



8.4 mm (3/8”) in cross section

58 mm (2 1/4”) in diameter

Objectives

- To analyze the bleeding patterns and endometrial safety of the CVS (SA 0.15 mg/ EE 0.013 mg) for up to 13 cycles of use

CVS: contraceptive vaginal system; EE: ethinyl estradiol; SA: segesterone acetate

Phase 3 Trials: Study Design

- Two multicenter, single-arm, open-label, pivotal, phase 3 studies evaluated the efficacy and safety of a single SA/EE CVS used on a 21-day in/7-day out regimen for up to 13 cycles
  - 300A (CCN006) study at 15 US study sites, supported by NICHD
  - 300B study at 12 international study sites, supported by USAID & WHO
    - Brazil, Chile, Dominican Republic, Finland, Hungary, Sweden, Australia, and US (5 sites)
- Basic entry requirements
  - Healthy
  - Sexually active
  - 18–40 years

NICHD: National Institute of Child Health and Human Development; USAID: United States Agency for International Development; WHO: World Health Organization.

Bleeding Data

- All phase 3 participants recorded in paper diaries the occurrence of vaginal bleeding and spotting daily for each 28-day cycle
- Bleeding data by 28-day cycles were summarized for
  - Scheduled (occurring on cycle days 22–28)
  - Unscheduled (occurring on cycle days 1 to 21)
- Factors associated with unscheduled bleeding/spotting (B/S) from the first 4 cycles of CVS use were identified using Pearson's χ^2 test and evaluated with multiple logistic regression analyses
  - The first 4 cycles were used for this analysis
    - To avoid bias due to the varied length of time women participated in the trial
    - Early bleeding patterns can influence contraceptive discontinuation

Vieira CS, et al. *Contraception.* 2019 [Epub ahead of print, Aug6].

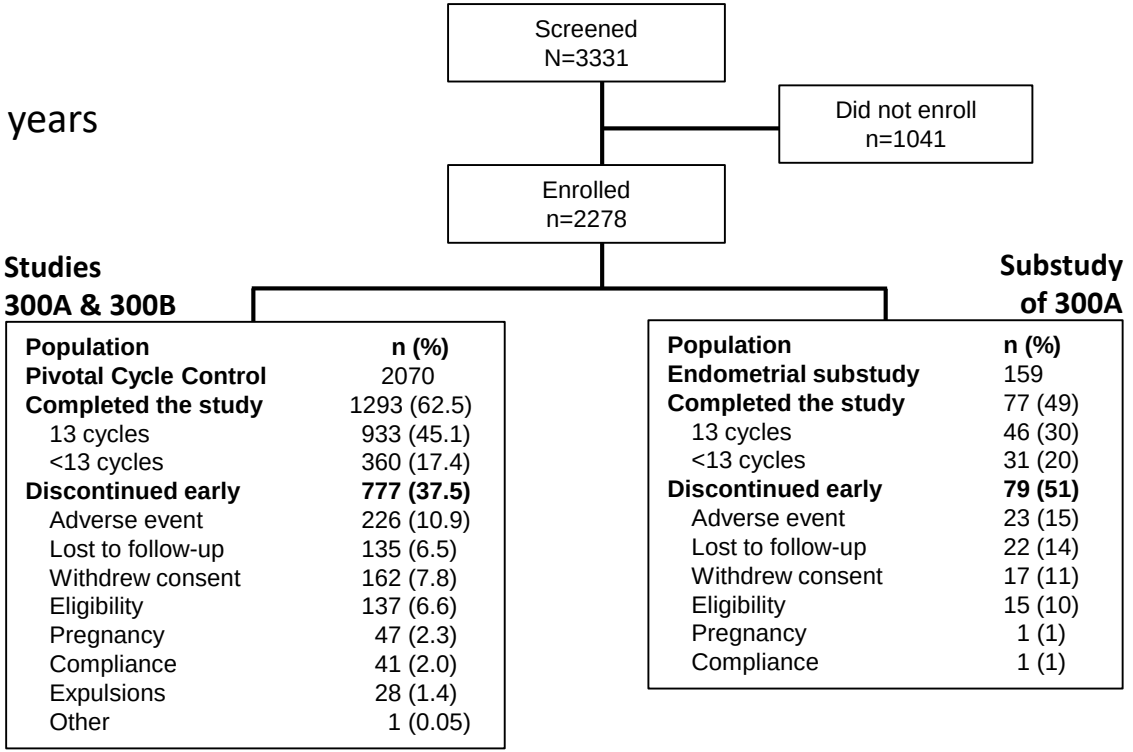
Endometrial Safety Substudy

- Women consented to join an endometrial safety substudy at five 300A study sites[1]
  - All had to have normal baseline endometrial biopsies
  - First 25 women reaching cycle 6 had repeat biopsies
  - Remaining had biopsies at cycles 12–13 or at early termination
- Biopsies evaluated by three blinded pathologists
  - If diagnoses by pathologists differed, the most severe diagnosis was used
  - Histologic changes were evaluated in women with both screening and follow-up biopsies

1. Gemzell-Danielsson K, et al. *Contraception.* 2019;99:323-328.

Disposition and Demographics (300A & 300B)

- Mean age: 26.7 ± 5.1 years
  - Most (70%) were 20 to 29 years
- Mean BMI: 24 ± 3.6 kg/m^2



Studies 300A & 300B

Population	n (%)
Pivotal Cycle Control	2070
Completed the study	1293 (62.5)
13 cycles	933 (45.1)
<13 cycles	360 (17.4)
Discontinued early	**777 (37.5)**
Adverse event	226 (10.9)
Lost to follow-up	135 (6.5)
Withdrew consent	162 (7.8)
Eligibility	137 (6.6)
Pregnancy	47 (2.3)
Compliance	41 (2.0)
Expulsions	28 (1.4)
Other	1 (0.05)

Substudy of 300A

Population	n (%)
Endometrial substudy	159
Completed the study	77 (49)
13 cycles	46 (30)
<13 cycles	31 (20)
Discontinued early	**79 (51)**
Adverse event	23 (15)
Lost to follow-up	22 (14)
Withdrew consent	17 (11)
Eligibility	15 (10)
Pregnancy	1 (1)
Compliance	1 (1)

Bleeding Profile

- 98% of women had scheduled B/S (during ring removal days) with a mean 4.9 days per cycle[1]
- 5%–10% of women per cycle reported unscheduled bleeding[2]
  - Mean number of unscheduled B/S days was ≤1 day per cycle
- 3%–5% of women had complete amenorrhea per cycle[1]
- Early discontinuation due to unacceptable bleeding was 1.7%[2]

B/S: bleeding or spotting; IQR: interquartile range.

1. Vieira CS, et al. *Contraception.* 2019 [Epub ahead of print, Aug6]. **2.** Annovera Prescribing Information. Population Council, New York, NY.

Demographic Factors Associated with Bleeding

- Ethnicity and race were significantly associated with unscheduled B/S
  - Black/African-American (vs White) women were more likely to report unscheduled B/S (OR 1.49; 95% CI, 1.14–1.94)
- Age, BMI, education and current smoking did not influence bleeding patterns

Risk Factors, n (%)	Unscheduled B/S			*P*-value*
	No episodes n=902	1–3 episodes n=833	≥4 episodes n=335	
Ethnicity				0.003
Hispanic	278 (30.8)	244 (29.3)	71 (21.2)	
Not Hispanic	624 (69.2)	589 (70.7)	264 (78.8)	
Race				0.01
Black	101 (11.2)	116 (13.9)	64 (19.1)	
White	672 (74.5)	601 (72.1)	227 (67.8)	
Other/Unknown	129 (14.3)	116 (13.9)	44 (13.1)	

**P*-value by Pearson Chi-Square. BMI: body mass index; B/S: bleeding or spotting; CI: confidence interval; OR: odds ratio. B/S episode = bleeding/spotting days bound on either end by 2 days of no bleeding or spotting.

Vieira CS, et al. *Contraception.* 2019 [Epub ahead of print, Aug6].

Endometrial Histology

- Of the 156 women in the endometrial safety substudy, 83 had follow-up biopsies[1]
- No cases of endometrial hyperplasia or carcinoma were identified at cycle 6 (n=24), cycles 12/13 (n=30) or at other end of therapy times (n=29)
- The most frequent histologic diagnoses were atrophic/inactive or secretory[1]

Results, n (%)	Histologic Diagnoses	Baseline[a] (n=83)	Cycle 6 (n=24)	Cycles 12-13 (n=30)	Other (n=29)
Normal	Insufficient or no tissue	4 (5)	0	3 (10)	1 (3)
	Atrophic/inactive	6 (7)	7 (29)	8 (27)	8 (28)
	Secretory	25 (30)	7 (29)	11 (37)	13 (45)
	Proliferative	33 (40)	4 (17)	2 (7)	6 (21)
	Menstrual	2 (2)	1 (4)	2 (7)	0
	Mixed	9 (11)	4 (17)	3 (10)	1 (3)
Abnormal	Hyperplasia	1 (1)[b]	0	0	0
Other	Endometritis/polyp	3 (4)	1 (4)	1 (3)	0

[a]All subjects with both a baseline (Screening, Visit 0) and follow-up biopsy.
[b]One woman with endometrial hyperplasia was allowed to continue participating in the study.

1. Gemzell-Danielsson K, et al. *Contraception.* 2019;99:323-328.

Conclusions

- Participants using the SA/EE CVS for up to 13 cycles experienced cycle control with a planned withdrawal bleed every 28 days[1]
  - Mean number of unscheduled B/S days was ≤1 day per cycle[2]
- Discontinuation rate due to unacceptable bleeding (1.7%) was very low[2]
- Endometrial histology confirmed endometrial safety[3]
- SA/EE CVS (Annovera™) is an effective,[4] convenient, easily-used,[5] new contraceptive method with an acceptable safety profile[3]

1. Vieira CS, et al. *Contraception.* 2019 [Epub ahead of print, Aug6]. **2.** Annovera Prescribing Information. Population Council, New York, NY. **3.** Gemzell-Danielsson K, et al. *Contraception.* 2019;99:323-328. **4.** Archer DF, et al. *Lancet Glob Health.* 2019:7:e1054-1064. **5.** Merkatz RB, et al. *Contraception.* 2014; 90:514-521.

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THANK YOU

To the 3000+ women volunteers from 4 continents who helped us develop Annovera

The Investigators, sub investigators, coordinators and other dedicated staff at clinical sites

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