Segesterone Acetate/Ethinyl Estradiol 1-Year Contraceptive Vaginal System Safety Evaluation

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Introduction

- Segesterone acetate (SA) 150 mcg/day and ethinyl estradiol (EE) 13 mcg/day contraceptive vaginal system (CVS)[1]
  - Annovera™ (TherapeuticsMD), US approval August 2018
  - Self inserted and used in 21/7 day cycle for up to 13 cycles (1 year)
  - Does not require refrigeration
- SA is non-orally active[2]
  - Inhibits ovulation at very low dose
  - Binds with high specificity to progesterone receptor
  - No binding or transactivation of androgen receptors

Objective

To evaluate clinical safety outcomes from nine studies, including the impact of body mass index (BMI) on adverse events (AEs)

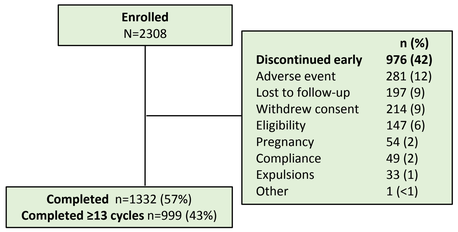
Methods

- Pooled data from four studies conducted with the final manufactured CVS
  - One-year pharmacokinetic study conducted at 3 study sites in the US (1) and Latin America (2)
  - Two identical, 1-year, phase-3, single arm, open-label multinational studies with sites in the US (20), Europe (3), Latin America (3) and Australia (1) with a 1-year extension from one of these studies
- Safety population included all women who inserted the CVS
- Safety evaluated by AE reporting, and endometrial biopsies, vaginal microbiology, and liver proteins from 3 US-based phase 3 substudy sites
- Data safety monitoring board (DSMB) recommended discontinuation and cessation of enrollment of women with BMI >29.0 kg/m^2 after 2 women with BMI >29.0 kg/m^2 had a VTE during first 6 cycles of use

Results

- Combined study population: 3052 women
  - 2308 (75.6%) received final manufactured CVS; 999 (43.3%) completed 13 cycles (**Figure 1**)
  - 209 women with BMI >29 kg/m^2 were enrolled; 36/209 (17%) completed 13 cycles
- Demographics
  - Mean age: 26.7 ± 5.1 years
  - Mean BMI: 24.1 ± 3.7 kg/m^2
  - Race: Caucasian 1638 (71%); Black 328 (14%); other 248 (11%); Asian 82 (4%); unknown 12 (<1%)

Figure 1. Safety Population: Disposition and demographics



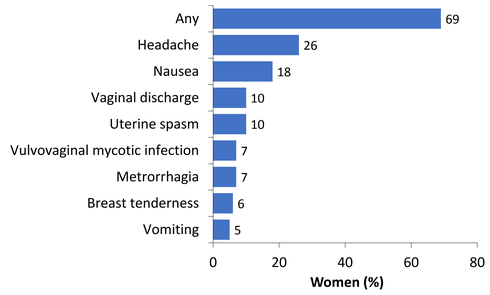
Discontinued early	n (%) 976 (42)
Adverse event	281 (12)
Lost to follow-up	197 (9)
Withdrew consent	214 (9)
Eligibility	147 (6)
Pregnancy	54 (2)
Compliance	49 (2)
Expulsions	33 (1)
Other	1 (<1)

Safety

Adverse events

- 2016 (87%) women reported ≥1 treatment-emergent adverse event (TEAE)
  - Most subjects (814 [72%]) graded as mild or moderate
- 1602 (69%) women experienced treatment-related TEAEs (**Figure 2**)

Figure 2. Most common treatment-related TEAEs (in ≥5% of women)



- Metrorrhagia leading TEAE cause of discontinuation (1.7%, n=39); <1.5% of women discontinued for the remaining common treatment-related TEAEs
- TEAEs appeared to be comparable between subjects with a BMI >29.0 kg/m^2 or <29.0 kg/m^2 (**Table 1**)

Venous thromboembolic events

- Four non-fatal cases of VTE; all women recovered (**Table 2**)
- Of the 2308 women enrolled in a phase 3 study with a BMI <29 kg/m^2, VTE rate was 10.8/10,000 women-years (95% CI, 8.9-13.1)
- No VTEs at non-US sites (1120 [48%] subjects)

Table 1. Phase 3 treatment-emergent AEs[a] overall and by BMI subgroup

	Phase 3 SA/EE CVS (N=2308) N (%)		
	All (N=2308)	BMI ≤29.0 kg/m^2 (n=2099)	BMI >29.0 kg/m^2 (N=209)
Any TEAE	2016 (87)	1861 (89)	155 (74)
Any serious TEAE[b]	43 (2)	38 (2)	5 (2)
Any TEAE leading to discontinuation	275 (12)	259 (12)	16 (8)
Any TEAE leading to death	0	0	0
Any TEAE related to CVS (adverse reaction)	1602 (69)	1498 (71)	104 (50)
Any severe TEAE	335 (15)	307 (15)	28 (13)

AE, adverse event; BMI, body mass index; CVS, contraceptive vaginal system; EE, ethinyl estradiol; SA, segesterone acetate.
[a]Treatment-emergent AE was defined as an AE that began on or after first use of the CVS and up to 14 days after final CVS use, or a pre-existing condition that worsened during the same time frame.
[b]Investigators assessed 15 of these SAEs as related to the CVS.

Table 2. Venous thromboembolic events by cycle and any relevant risk factors

Event	Cycle	Subject disposition and/or risk factors
Pulmonary embolism	2	High BMI 29 kg/m^2
Deep vein thrombosis	3	High BMI 31 kg/m^2
Deep vein thrombosis	6	Factor V Leiden mutation
Cerebral venous thrombosis	7	28-year old subject with a BMI of 25.2 kg/m^2; withdrew from study before clotting evaluation; reported smoking <10 cigarettes/day

BMI, body mass index.

CVS expulsions

- 2096 (90.8%) had evaluable diary responses on CVS expulsions
  - 1107 (52.8%) reported ≥1 complete (24.5%) or partial (44.0%) expulsion
- Expulsions occurred most frequently during the initial cycle of use

Clinical laboratory values, vital signs and physical exam

- No safety signals from standard laboratory chemistry, hematology, vital signs, or physical exams
- No clinically relevant or significant mean changes in total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, or glucose (**Table 3**)
- Small changes from baseline (all within normal range) were observed in plasma levels of factor VIII, fibrinogen and protein S (**Table 4**)
- No clinically relevant weight changes reported; 35 women reported weight increase (8%) or decrease (<1%)
- Eight women reported hypertension; one of these women discontinued

Table 3. Mean changes from baseline to end of study in lipids and glucose

	Baseline mean ± SD	End of study mean ± SD	Mean change from baseline ± SD
Total cholesterol	4.5 ± 0.8	4.7 ± 0.9	0.24 ± 0.7
HDL	1.6 ± 0.4	1.8 ± 0.4	0.16 ± 0.3
LDL	2.5 ± 0.7	2.5 ± 0.7	-0.03 ± 0.6
Triglycerides	1.0 ± 0.4	1.2 ± 0.6	0.23 ± 0.5
Glucose	4.6 ± 0.6	4.6 ± 0.8	0.07 ± 0.7

Table 4. Mean changes from baseline to cycle 13 in hepatic factors with normal ranges (n=106)[4]

	Baseline mean ± SD	Cycle 13 mean ± SD	Mean change from baseline ± SD	Normal range
Factor VIII (relative to reference)	114 ± 42	137 ± 58	20 ± 48†	50–180
Fibrinogen (g/L)	2.8 ± 0.7	3.0 ± 0.6	0.2 ± 0.6*	2.1–4.3
Protein S[a] (relative to reference)	85 ± 17	76 ± 17	-6 ± 19*	60–140

[a]n=105 at either baseline or final evaluation
*P<0.01, †P<0.001 for the mean (SD) change from baseline

Conclusions

- Safety studies showed no unexpected safety signals; the TEAEs and SAEs observed with the SA/EE CVS were similar in both type and frequency to those found with other combined hormonal contraceptives[5-8]
- 1-year SA/EE CVS has an acceptable safety profile comparable to other combined hormonal contraceptives[5-8]
- Further study is warranted in obese women as they are at higher risk for VTE
- SA/EE CVS has similar prescribing precautions to those of other combined hormonal contraceptives[5-8]

References

1. Annovera™ (segesterone acetate and ethinyl estradiol vaginal system) Prescribing Information. *Population Council*, New York, NY. **2.** Kumar N, et al. *Endocrinology*. 2017;158:170-182. **3.** Gemzell-Danielsson K, et al. *Contraception*. 2019; In press. **4.** Archer DF, et al. *Contraception*. 2016;93:58-64. **5.** Portman DJ, et al. *Contraception*. 2014;89:299-306. **6.** Lybrel® tablets (90 mcg levonorgestrel and 20 mcg ethinyl estradiol) Prescribing Information. *Wyeth Pharmaceuticals Inc.* Philadelphia, PA. **7.** Kroll R, et al. *Contraception*. 2010;81:41-44. **8.** Lo Loestrin® Fe (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) Prescribing Information. *Warner Chilcott, LLC*, Rockaway, NJ.

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