# A Novel 1-Year Contraceptive Vaginal System Delivering Segesterone Acetate and Ethinyl Estradiol: Effects on Lipids and other Hepatic Proteins

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## Introduction

- Annovera™ (TherapeuticsMD, Boca Raton FL) is an FDA-approved contraceptive vaginal system (CVS) releasing segesterone acetate (SA) 150 mcg and ethinyl estradiol (EE) 13 mcg per day
- SA is a potent progestogen when given non-orally; it inhibits ovulation and is not androgenic[1]
- Changes in lipids and coagulation factors are known to be affected by combined hormonal contraceptives (CHCs), and can be influenced by the type or dose of estrogen or progestogen, or their route of administration
- As a progestin without androgenic activity, SA is not expected to have a negative impact on lipids and coagulation factors. Specific effects of SA/EE delivered vaginally on metabolic parameters warrant further investigation.

## Objective

To assess integrated phase 3 data for an impact of the SA/EE CVS on estrogen-sensitive hepatic factors such as lipids, coagulation parameters, and glucose

## Methods

- In two identically designed, pivotal, open-label, phase 3 trials, and a pharmacokinetic (PK) study, women ages 18-40 years inserted the SA/EE CVS for 13 cycles in a 21-day in and 7-day out regimen during each 28-day cycle
  - Lipids and glucose were measured at baseline and end of study
- An hepatic factor phase 3 substudy was conducted and assessed coagulation factors (factor VIII, protein S, fibrinogen) and sex hormone-binding globulin (SHBG)[2]
  - Hepatic proteins were evaluated at baseline and cycle 13
- Changes from baseline in lipids and glucose with the SA/EE CVS were summarized descriptively. Changes in hepatic proteins from baseline to cycle 13 were evaluated by analyses of variance with a mixed effects model, and a global F test.

## Results

### Participant Characteristics

- Of the 129 women in the hepatic factor substudy, 106 women had evaluable laboratory results
- Women's demographic profile and body mass index (BMI) were similar across the phase 3 and PK studies and the hepatic factor substudy (**Table 1**)

### Lipids and Glucose

- Total cholesterol, HDL cholesterol and triglycerides increased and LDL cholesterol decreased from baseline to end of study (**Figure 1; Table 2**)
- Glucose increased from baseline to study end

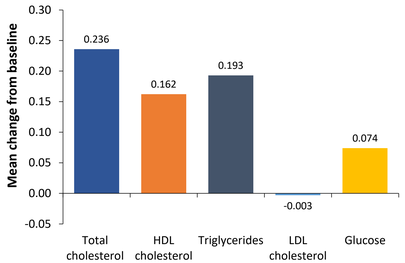
**Table 1.** Demographic characteristics from the phase 3 and PK studies and hepatic factor substudy

| Characteristic | Phase 3 and PK studies (n=2308) | Hepatic factor substudy[2] (n=129) |
|---|---|---|
| Age, mean ± SD (years) | 27 ± 5.1 | 26 ± 4.8 |
| BMI, mean ± SD (kg/m$^2$) | 24 ± 3.7 | 24 ± 3.9 |
| Race, n (%) | | |
| White | 1638 (71) | 89 (69) |
| Black | 328 (14) | 36 (28) |
| Asian | 82 (4) | 3 (2) |
| Other | 248 (11) | 3 (2) |
| Ethnicity, n (%) | | |
| Hispanic | 690 (30) | 8 (6) |
| Non-Hispanic | 1618 (70) | 121 (94) |

**Table 2.** 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 |

**Figure 1.** Mean change from baseline to end of study in lipids and glucose from the phase 3 and PK trials




### Hepatic Proteins Overall[2]

- Significant mean increases from baseline to cycle 13 were seen for fibrinogen and factor VIII activity and a significant decrease for protein S activity (**Table 3**)
- Mean SHBG levels significantly increased from baseline to end of study (**Table 3; Figure 2**)
- Mean baseline values for hepatic proteins were within normal range and stayed within normal range at cycle 13, except for SHBG (**Table 3**)

**Table 3.** Mean changes from baseline to cycle 13 in hepatic factors with normal ranges (n=106)[2]

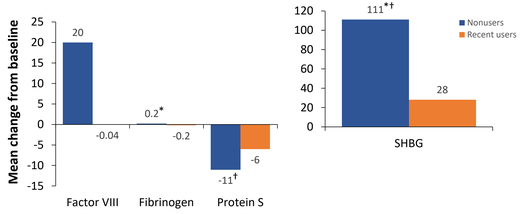
| | Baseline mean ± SD | Cycle 13 mean ± SD | Mean change from baseline ± SD | Normal range |
|---|---|---|---|---|
| Factor VIII (relative to reference) | 114 ± 42 | 137 ± 58 | 20 ± 48† | 50-180 |
| Fibrinogen (g/L) | 2.8 ± 0.7 | 3.0 ± 0.6 | 0.2 ± 0.6* | 2.1-4.3 |
| Protein S[a] (relative to reference) | 85 ± 17 | 76 ± 17 | −6 ± 19* | 60-140 |
| SHBG[a] (nmol/L) | 90 ± 62 | 187 ± 91 | 88 ± 96† | 17-124 |

[a]n=105 at either baseline or final evaluation
*$P$<0.01, †$P$<0.001, ‡$P$<0.0001 for the mean (SD) change from baseline

### Hepatic Proteins in Recent Hormonal Contraceptive Users[2]

- Changes from baseline to cycle 13 for protein S and SHBG were statistically significant (**Table 4**)
- Differences in changes from baseline between recent and never users were significant for fibrinogen and SHBG (**Table 4; Figure 2**)
- Fibrinogen, protein S, and SHBG were significantly different at baseline between women who recently used hormonal contraceptives compared with never users (**Table 4**)

**Figure 2.** Mean change from baseline in hepatic proteins by use of recent hormonal contraceptives




*$P$<0.01 for change from baseline vs recent CHC users
†$P$<0.01 for the change from baseline to cycle 6 within group

**Table 4.** Mean changes in hepatic proteins from baseline to cycle 6 for recent vs never use of hormonal contraceptives

| | Recent hormonal use[a] | Baseline mean ± SD | Cycle 6 mean ± SD | Change from baseline mean ± SD |
|---|---|---|---|---|
| Factor VIII (%) (relative to the reference standard) | No<br>Yes | 110 ± 40<br>123 ± 44 | 130 ± 64<br>119 ± 43 | 20 ± 52<br>−0.04 ± 35 |
| Fibrinogen (g/dL) | No<br>Yes | 2.7 ± 0.7*<br>3.0 ± 0.7 | 3 ± 0.7<br>3 ± 0.6 | 0.2 ± 0.7‡<br>−0.2 ± 0.6 |
| Protein S (%) (relative to the reference standard) | No<br>Yes | 90 ± 17*<br>76 ± 15 | 80 ± 22<br>69 ± 19 | −11 ± 21†<br>−6 ± 16 |
| SHBG (nmol/L) | No<br>Yes | 57 ± 25*<br>153 ± 64 | 168 ± 83<br>182 ± 50 | 111 ± 78†‡<br>28 ± 63 |

[a]Recent users were women who used hormonal contraception in the week prior to enrollment, n=36 (Yes). Nonusers were those who had not used hormonal contraception within the past 4 weeks, n=34 (No).
*$P$<0.01 for the difference at baseline between nonusers and recent CHC users
†$P$<0.01 for the change from baseline to cycle 6 within group
‡$P$<0.01 for change from baseline between nonusers and recent CHC users

## Summary and Conclusions

- Integrated safety data from two phase 3 trials, including a hepatic protein substudy, show no clinically significant impact of the SA/EE CVS on lipids, glucose, or coagulation factors. These results were not unexpected given that SA is nonandrogenic.
- Changes in lipids, glucose, and coagulation factors with the SA/EE CVS were within normal range and globally similar in direction and magnitude to those known for CHCs
- The significant increase in SHBG levels with the SA/EE CVS was expected, as such an effect is well known with CHCs, especially when paired with nonandrogenic progestins
- Previous recent use of hormonal contraceptives affected baseline levels of some coagulation factors, and may have also influenced changes from baseline
- The SA/EE CVS with a low dose of EE and the novel, nonandrogenic progestin, SA, has an acceptable metabolic profile with up to one year of use

## References

**1.** Kumar N, et al. *Endocrinology*. 2017;158:170-182. **2.** Archer DF, et al. *Contraception*. 2016;93:58-64.

## Disclosures

- DFA consults for AbbVie, Actavis, Agile Therapeutics, Bayer Healthcare, Endoceutics, Exeltis, InnovaGyn, Merck, Pfizer, Radius Health, Sermonix, Shionogi, Teva Women's Healthcare, and TherapeuticsMD; and has received research support from Actavis, Bayer Healthcare, Endoceutics, Glenmark, Merck, Radius Health, Shionogi, and TherapeuticsMD. MAT has received research support (paid to the University of Cincinnati Medical Center) from TherapeuticsMD, EvoFem, Veracept, and Medicines 360. JL consults for Allergan, Bayer Healthcare, Pfizer, and TherapeuticsMD and has received research support (paid to UH Cleveland Medical Center) from AbbVie, Allergan, Bayer Healthcare, Ferring, and Palatin. DLB is an employee of Eunice Kennedy Shriver National Institute of Child Health and Human Development. SRW, RBM, and NK are employees of Population Council, a non-profit organization. BB and SM are employees of TherapeuticsMD with stock/stock options. BB is also a Board member of TherapeuticsMD.
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