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NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	209627
Priority or Standard	Standard
Submit Date(s)	August 17, 2017
Received Date(s)	August 17, 2017
PDUFA Goal Date	August 17, 2018
Division/Office	Division of Bone Reproductive and Urologic Products (DBRUP)/Office of Drug Evaluation III (ODE III)
Review Completion Date	August 8, 2018
Established Name	Segesterone acetate and ethinyl estradiol vaginal system
(Proposed) Trade Name	Annovera
Pharmacologic Class	Combined hormonal contraceptive (CHC) (progestin + estrogen)
Applicant	Population Council
Formulation(s)	Segesterone acetate 150 µg/ethinyl estradiol 13 µg
Dose Form	Vaginal system (ring)
Dosing Regimen	Vaginal for 21 days per 28-day cycle
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy in females of reproductive potential
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as above

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CHC	combined hormonal contraceptive
CMC	chemistry, manufacturing, and controls
COC	combined oral contraceptive
CRF	case report form
CRT	clinical review template
CSR	clinical study report
CVS	contraceptive vaginal system
ECG	electrocardiogram
EE	ethinyl estradiol
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
ODE	Office of Drug Evaluation
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	Pearl Index
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SA	segesterone acetate
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event
VTE	venous thromboembolism

1. Executive Summary

1.1. Product Introduction

ANNOVERA, a segesterone acetate/ethinyl estradiol contraceptive vaginal system (SA/EE CVS or CVS) is a combined hormone contraceptive (CHC) for the prevention of pregnancy in females of reproductive potential. The CVS is a non-biodegradable, flexible, contraceptive vaginal ring that contains two hormones, a progestin, SA, and an estrogen, EE, providing daily release rates of 150 µg and 13 µg respectively.

The CVS is used for thirteen 28-day cycles (one year). The CVS is inserted into the vagina for 21 days and then removed for 7 days. The CVS is washed and stored in a provided compact case for the 7 days per cycle that it is not in use.

SA is the progestin component and is a new molecular entity (NME). This derivative of 19-norprogesterone is not orally active. The SA/EE CVS has never been marketed. (b) (4)

Figure 1 SA/EE CVS*

Source: NDA 209627, Module 2.2, CTD Introduction p 2/5
*Nesterone=SA

The (b) (4) shaped silicone elastomer ring has two channels that contain cores: one with SA only, and the other with SA and EE. (b) (4)

The applicant notes the benefits of the CVS provide user-controlled contraception that does not require daily administration or special storage conditions. Only one CVS is needed for a full year of reversible contraception.

1.2. Conclusions on the Substantial Evidence of Effectiveness

ANNOVERA is proposed for the prevention of pregnancy in females of reproductive potential. The applicant's evidence of clinical effectiveness derives from two one-year, multicenter Phase 3 trials that enrolled 2,265 females age 18-40 years who were healthy and sexually active, with regular menstrual cycles. The trials did not include control groups. Pooled data from the two trials was used to evaluate efficacy. Overall, there were 2,111 females ≤35 years old who completed 17,427 evaluable 28-day cycles (evaluable cycles for efficacy were those during which no back-up contraception was used). Efficacy was evaluated by calculation of the Pearl Index (PI). The PI for the evaluable cycles from the pooled Phase 3 trials was 2.98 (95% Confidence Interval {CI} [2.13, 4.06]) pregnancies per 100 woman-years of ANNOVERA. This PI is comparable to that of other recently approved products for the same indication. Based on the above information, we conclude that the applicant has provided substantial evidence of effectiveness of ANNOVERA for the proposed indication.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Unintended pregnancy affects millions of women in the United States each year, and has vast consequent public health effects including adverse maternal and child health outcomes as well as significant socioeconomic costs. Safe and effective contraception is, therefore, crucial to women's health. Although many contraceptive options are available—including oral tablets, intravaginal rings, implants, a transdermal patch, and depot injections—development of contraceptives with lower doses, more convenient dosing schedules, and optimal efficacy and safety profiles remains a priority. Considering that 95% of unintended pregnancies occur in women who use contraceptives inconsistently or incorrectly or women who do not use contraception at all during the year, a vaginal system with demonstrated efficacy and safety, that can be used for up to one year without the need for refrigeration prior to dispensing, would add to the armamentarium of available contraceptive products.

Segesterone acetate/ethinyl estradiol contraceptive vaginal system (SA/EE CVS), tradename ANNOVERA, is a new combined progestin-estrogen contraceptive for the prevention of pregnancy in females of reproductive potential. SA is the progestin component and is a new molecular entity; this derivative of 19-norprogesterone is not orally active. EE is a steroid hormone commonly used in contraceptive products. The SA/EE CVS has never been marketed. The CVS is inserted into the vagina for 21 days and then removed for 7 days; one CVS can be used for up to thirteen 28-day cycles (i.e. one year). It is washed and stored in a provided compact case for the 7 days per cycle that it is not in use.

Substantial evidence of effectiveness was demonstrated in two large, multicenter, uncontrolled Phase 3 trials. The Agency uses uncontrolled trials to assess the benefit risk profile of contraceptive products because decades of historical data are available to evaluate the new product in the context of the current armamentarium of approved contraceptives. Adequate efficacy was demonstrated based on the evaluable cycles from the Phase 3 trial data that enrolled a total of 2,265 females age 18-40 years who were healthy and sexually active with regular menstrual cycles. Study 300A had a PI of 3.10 (95% CI 1.87, 4.84) pregnancies per 100 woman-years. Study 300B had a PI of 2.89 (95% CI 1.79, 4.41) pregnancies per 100 woman-years. The pooled efficacy data from both Phase 3 studies demonstrated a PI of 2.98 (95% CI 2.13, 4.06). This PI is comparable to that of other recently approved products for the same indication and was sufficient to establish efficacy of the product. Other benefits of the product include the convenience of the dosing regimen: the ring is inserted for 21 days and removed for 7 days each cycle; the same ring can be used for up to 13 cycles (one year) without the need to obtain a replacement. In addition, pharmacokinetic data showed that

plasma EE exposure from the CVS is comparable or less than that of a low dose oral CHC. The CVS provides daily SA and EE release rates of 150 µg and 13 µg respectively; the product's route of administration bypasses the first-pass metabolism of the drug substances.

The safety profile of the SA/EE CVS was evaluated using a safety database of 2,308 subjects exposed to the to-be-marketed SA/EE formulation, contributing 21,590 cycles. The safety profile of EE is well-characterized. SA is an NME and the applicant provided an adequate safety database to evaluate the risks with use of this product. Known risks of CHC use include venous thromboembolism (VTE), bleeding irregularities, headache, liver enzyme elevation and depression. The clinical development program for the SA/EE CVS identified an increased risk of VTE compared to other CHCs: the VTE rate for this product is 24.1 per 10,000 woman-years (95% CI 6.6, 61.7), whereas FDA labeling reports the likelihood of developing a VTE for CHC users is 3-12 per 10,000 woman-years. Although the VTE rate estimate appears higher than other products, it is important to recognize that the estimate is associated with considerable uncertainty as evidenced by the wide confidence interval, which has a lower limit that is less than 12 per 10,000 woman-years. Also, the Phase 3 clinical trials were not powered to evaluate an uncommon event such as VTE. To address this safety concern, a post-marketing study will be required to evaluate the risk of VTE in the general population of users of ANNOVERA. Of note, two VTEs occurred in individuals with a body mass index (BMI) greater than 29 kg/m^2, prompting the applicant to stop enrollment of women in the BMI range >29 kg/m^2. (b) (4) other safety findings in the ANNOVERA clinical trials were comparable to those observed with use of other approved CHCs. Additional post-marketing requirements (PMRs) will be a clinical drug-drug interaction study and an (b) (4) study evaluating the effects of tampon use on the (b) (4) of SA and EE. The applicant has also agreed to a postmarketing commitment to conduct a study to characterize the in vivo release rate of ANNOVERA.

Based on the above considerations, we conclude that the benefits of ANNOVERA, when used according to labeling, outweigh its risks for the prevention of pregnancy in females of reproductive potential.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Unintended pregnancy affects millions of women in the United States each year with vast consequent public health effects including adverse maternal and child health outcomes as well as social and economic costs at the family and state level.	Safe and effective contraception is crucial to women's health and as many options as possible should be available to women. Development of contraceptives with lower doses, more convenient dosing schedules, and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In 2011, 45% (or 2.8 million) of the 6.1 million pregnancies in the United States were unintended.[1] Of women at risk for unintended pregnancy: o Those who use contraception consistently and correctly during any given year (68%) account for only 5% of all unintended pregnancies. o Those who use contraceptives inconsistently or incorrectly (18%) account for 41% of all unintended pregnancies o Those who do not use contraception at all or who have gaps of a month or more during the year (14%) account for 54% of all unintended pregnancies.	optimal efficacy and safety profiles is a priority. A contraceptive vaginal system (vaginal ring) with demonstrated efficacy and safety, that can be used for up to one year without the need to obtain a replacement product, would add to the armamentarium of available contraceptive products.
Current Treatment Options	• A wide range of contraceptive products are currently available in the U.S. market, including oral tablets, intravaginal rings, implants, a transdermal patch, and depot injections. • There is one other approved intravaginal ring, Nuvaring. Nuvaring is used for three weeks and then removed for a one-week break, during which a withdrawal bleed usually occurs, after which a new ring must be inserted. Nuvaring requires refrigerated storage at 2-8°C until it is dispensed to the user, and can then be stored at 25°C for up to four months.	Despite the wide range of contraceptive options, convenience of dosing is a major limiting factor to their consistent use. Daily, weekly or monthly dosing regimens may be difficult for women to consistently adhere to, or may be associated with limiting side effects (e.g. irregular bleeding and spotting). Given that only about two thirds of women at risk for unintended pregnancy use contraceptives consistently and correctly throughout any given year, an additional vaginal ring that does not require replacement for one year, and does not require refrigeration prior to dispensing, offers a convenient and desirable option.

[1] https://www.guttmacher.org/sites/default/files/factsheet/fb-unintended-pregnancy-us_0.pdf

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The drug substance EE is commonly used in contraceptive products and is well-characterized. • The progestin component of the CVS, SA, is an NME and the sponsor has provided adequate exposure in their Phase 3 program to evaluate efficacy and safety of the product. • Convenience of dosing regimen: The ring is inserted for 21 days and removed for 7 days each cycle. The same ring can be used for up to 13 cycles (one year) without the need to obtain a replacement. • First pass metabolism is bypassed, increasing the amount of parent drug(s) available systemically to produce a therapeutic response. • Pharmacokinetic data shows the plasma EE exposure with 21 days of use of the CVS is comparable (based on maximum plasma concentration) or less than (based on area under the curve) than a low-dose oral CHC. • Adequate efficacy was demonstrated based on the evaluable cycles from the Phase 3 trial data. Study 300A had a PI of 3.10 (95% CI 1.87, 4.84) pregnancies per 100 woman-years. Study 300B had a PI of 2.89 (95% CI 1.79, 4.41) pregnancies per 100 woman-years. The pooled efficacy data from both Phase 3 studies demonstrated a PI of 2.98 (95% CI 2.13, 4.06).	An additional vaginal ring providing safe and effective contraception, and that does not require patients to obtain a new ring for up to one year, provides a beneficial option to women. This option would be of particular benefit to women with limited access to healthcare providers.
Risk and Risk Management	• Previously identified risks of CHC use include venous thromboembolic events (VTEs), bleeding irregularities, headache, liver enzyme elevation and depression. • The safety profile was evaluated using 2,308 subjects exposed to the to-be-marketed SA/EE formulation, contributing 21,590 cycles. • There were no deaths among subjects who used ANNOVERA during the development program. • There were four VTEs during the clinical development program. The	The risk of VTE will be evaluated in a post-marketing trial (PMR). The study will be a long-term cohort study comprising new users of ANNOVERA and new users of other forms of contraception, and will be powered to rule out a 1.5 to 2-fold risk of VTE for ANNOVERA compared to other products. Two other PMRs will be conducted: (1) a clinical drug-drug

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	applicant noted that two of these VTEs occurred in subjecst with a BMI >29 kg/m^2 and stopped enrolling subjects in this BMI range after their (b) (4) identified this finding. ○ The VTE rate estimate for this product is 24.1 per 10,000 woman-years (95% CI 6.6, 61.7), which is higher than the reported rate in trials for other approved CHC products (3-12 per 10,000 woman-years). The VTE rate estimate for ANNOVERA has considerable uncertainty evidenced by the wide 95% CI. Of note is that the lower limit of the 95% CI is <12 per 10,000 woman-years. ○ Since the clinical trials were not powered to evaluate uncommon events such as VTE, a post-marketing study will be required to evaluate the risk of VTE in the general population of users of ANNOVERA. • All other safety findings in the ANNOVERA clinical trials were comparable to those observed with use of other approved CHCs.	interaction study to evaluate the effects of strong CYP3A induction and inhibition on the pharmacokinetics of SA and EE and (2) an (b) (4) study to evaluate the effects of tampons on the (b) (4) of SA and EE. Given that other safety findings observed in the clinical development program for ANNOVERA were comparable to that of other CHC products, we conclude that the benefits of ANNOVERA outweigh the risks.

1.4. Patient Experience Data

Table 1 Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as			
			□	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	X	Patient preference studies (e.g., submitted studies or scientific publications)			**Section 8.2.2**
□	Patient experience data that was not submitted in the application, but were considered in this review.				
	□	Input informed from participation in meetings with patient stakeholders			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
□	Patient experience data was not submitted as part of this application.				

2. Therapeutic Context

2.1. Analysis of Condition

In 2011, 45% of all pregnancies in the US were unintended[2], representing 2.8 million pregnancies[3]. The highest rates of unintended pregnancy were among women age 18-24 and women with low incomes. Among teens, 15-19 years of age, 75% of pregnancies were unintended[1].

Unintended pregnancies can place undue financial burdens on women and can result in negative health consequences for women and children. Women with unintended pregnancies are more likely that those with intended pregnancies to receive later or no prenatal care, to smoke and consume alcohol, to be depressed and/or anxious, and to experience domestic violence during pregnancy[4]. For infants, there are greater risks of birth defects, low birth weight, and poor mental and physical functioning in early childhood[5]. Unintended pregnancy ends in abortion in about 40% of cases[2].

Contraception is used to prevent pregnancy. In the most recent evaluation of unintended pregnancy in the US, Finer and Zolna[2] note a decrease in unintended pregnancy occurred at the same time the use of highly effective long-acting methods of contraception increased among women using contraception. Therefore, efforts to reduce unintended pregnancy include increasing access to contraception, particularly more effective, longer-acting reversible forms of contraception and increasing correct and consistent use of contraceptive methods[1].

2.2. Analysis of Current Treatment Options

Reversible hormonal contraception includes progestin-containing IUSs, progestin implants, progestin injections, progestin-only pills, combined hormonal pills, combined hormonal patch, and combined hormonal vaginal ring. There is one CHC patch and one CHC vaginal ring and numerous combined oral contraceptives (COC)s. COCs vary based on type and dose of progestin, type and dose of estrogen, monophasic vs multiphasic, number of day regimen (21, 24, 26 days in a 28-day cycle) or extended (84 days).

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[2] https://www.cdc.gov/reproductivehealth/contraception/unintendedpregnancy/index.htm accessed 4/20/2018. Accessed April 20, 2018

[3] Finer, L and Zolna M. Declines in Unintended Pregnancy in the United States, 2008-2011. N Engl J Med 2016; 374:843-852.

[4] Institute of Medicine. Clinical preventive services for women: Closing the gaps. Washington, DC: The National Academies Press; 2011:102-10

[5] ACOG Committee Opinion. Reproductive Life Planning to Reduce Unintended Pregnancy. Number 654, February 2016

Table 2 lists the currently marketed non-oral CHCs and four selected COCs, two recently approved (Quartette, Lo Loestrin FE), one with a 3rd generation progestin (Yasmin), and one with numerous generic products (Alesse).

Table 2. Selected CHCs

Product Name NDA #	**Approval Year**	**Route/frequency Dose**	**Efficacy based on Pearl Index (PI) (upper limit of 95% CI)**	**Excluded sub-population**
NuvaRing 21187	2001	vaginal ring/ 3wk each month 0.12mg etonogestrel/ 15µg EE	PI 1.28 (1.9) PI US 2.02 (3.4)	no women >41 yo no women with bmi ≥ 30
OrthoEvra 21180	2001	transdermal patch/weekly for 3 wk each month 0.15mg norelgestromin/ 35µg EE	PI 1.07 (1.76)	limitation of use: less effective in women ≥ 198 lbs
Quartette 204061	2013	po/daily 0.15mg levonorgestrel (LNG)/ 20,25,30,10 µg EE	PI 3.19 (4.03)	no women >40 y/o
Lo Loestrin FE 22501	2010	po/daily 1 (b)(4) mg norethindrone acetate (NETA)/10 µg EE	PI 2.92 (4.21)	no women with BMI >35 kg/m2
Yasmin 21098	2001	po/daily 3mg drospirenone/ 30 µg EE	Pregnancy rates less than 1 per 100 w-y*	no women >40 y/o
Alesse 020683	1997	po/daily 0.1mg LNG/20µg EE	Pregnancy rate less than 1 per 100 w-y*	

*w-y=women-years
Source: https://www.accessdata.fda.gov/scripts/cder/daf/

More recently, contraceptive trials have calculated the PI instead of a pregnancy rate. The PI is now calculated based on actual use (rather than perfect use) and cycles where back up contraception was used are excluded. In addition, when possible, cycles were heterosexual intercourse did not occur (not at-risk cycles) are excluded. This, in addition to better detection of pregnancy may partially explain the increasing PIs in the more recently approved contraceptives.

CHCs as a general class have several safety issues that have been well-recognized since their introduction in the United States in the 1960s. The following adverse events represent the major concerns described in contraceptive labeling:

- Vascular events, which may be fatal, including:
  - Deep venous thrombosis, pulmonary embolism, other venous thromboses
  - Myocardial infarction (especially in women >35 years who smoke)
- Liver disease
- Hypertension
- Gallbladder disease
- Headaches
- Irregular uterine bleeding, amenorrhea, oligomenorrhea
- Adverse carbohydrate and lipid metabolic effects
- Depression
- Hereditary angioedema

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

SA is an NME and is not currently marketed in the U.S. This application is for a CVS with SA and EE. (b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

The application for this CVS was opened in July 13, 1997 under IND 049980.

A pre-clinical guidance meeting occurred on January 12, 1999 for the development of SA contraceptive products including rings, (b) (4). Pre-clinical toxicology and pharmacology, pharmacokinetics, and CMC (now Office of Product Quality (OPQ)) provided comments and advise on the development program.

The applicant submitted questions for a pre-phase 3 meeting. On August 20, 2002, the Division provided written responses to the submission. Key advice included:

- General comments for contraceptive trials:
  - For contraceptive efficacy 18-35 y/o with at least 10,0000 cycles of use, 200 must complete 1-year treatment
  - For NME requirements of a minimum of 100 subjects for one year of treatment, with a total treatment of 1500 subjects
  - PI >2.0 will be a review issue
  - The Division noted the Phase 3 protocol excluded women with BMI≥31 and requested the reason for this exclusion
  - Trial design should collect data on expected menstrual bleeding
- Comments regarding product quality:
  - (b) (4) EE will not be considered a risk if it does not exceed those occurring with comparator 30 µg EE COC that has been FDA approved.
  - Request that the applicant address concerns of bacterial contamination with the ring and how ring is stored.
  - Encourage development of a validated *in vitro and in vivo* (IVIVC) to support changes in the phase 3 trial formulation and the to be marketed (TBM) formulation or any formulation changes
  - Phase 4 studies for oil-based vaginal products and different tampons on the PK/PD, efficacy and safety of the CVS may be required

On June 27, 2005, the applicant submitted their protocols for two phase 3 trials for SA/EE CVS. Written comments and recommendations were provided to the applicant on December 28, 2005 and included:

- For an NME, the Division was now requesting that the NDA include safety and efficacy data from at least 20,000 cycles of exposure and at least 400 women completing 13 cycles of use. The Division acknowledged this advice was different from the advice given in the August 20, 2002 letter.
- Large and adequately powered Phase 4 comparative safety study to define the risk of serious thrombotic and thromboembolic adverse events (AEs)
  (PE, stroke, MI, death) associated with use of the new product will be requested for applicants with hormonal contraceptive products that contain an NME.
- Label will reflect the patient population studied in the clinical trials particularly in regards to (b) (4) subjects use of enzyme inducers, (b) (4)

- Collection of data on ring expulsion and problems with (b) (4) should be recorded on diary card.

A Type C teleconference to answer the applicant's questions concerning the Division's comments and recommendation occurred on April 3, 2006. The following were agreed to:

- Advise on collection of laboratory data:
  - Laboratory parameters for 300A sites (US sites) to include full lipid panel in addition to CBC and chemistry laboratories at baseline, 6 months and termination.
  - Coagulation parameters (Factor VIII, fibrinogen, protein S activity, SHBG) to be evaluated in 100 subjects at baseline, 6 months, and termination
  - Urine pregnancy testing (UPT) at each visit
  - Endometrial safety data obtained in a subset of subjects (at least 50 who have completed one year treatment) with baseline and post treatment endometrial biopsies.

- Advice on data analysis:
  - PI and Kaplan-Meier life table analyses be submitted for all subjects and all subjects ≤35 years.
  - PI on all cycles and on all cycles for which back-up contraception was not used, as these represent the true at-risk cycles
  - Above analyses to be submitted with data from each trial; pooled data may also be submitted
  - Provide analyses of the safety and efficacy data by geographic area (US and non-US), weight, parity, and age
  - The proportion of women over 35 years old to be included in the trial is not fixed but a sample that includes 15-20% of its subjects in this age group is acceptable

A protocol for special protocol agreement (SPA) was submitted July 11, 2006 with no agreement. In a September 18, 2006 meeting to discuss the Division's August 25, 2006 response letter to the SPA, discussions included:

- Retention of population exclusions of smokers over 35 y/o, women with family history of venous thromboembolism (VTE) (b) (4) and use of enzyme inducing medications. The Division stated these were acceptable with the understanding that any approved labeling would reflect the population studied.
- Comments regarding the diary recommending that investigators should enter data gained during a clinic visit on a separate form and not complete the diary for the subject, and noted that incomplete data would be a review issue

- Reiteration that the primary efficacy endpoint is the PI for women ≤35 years of age using only cycles for which back up contraception was not used. All other subgroup analyses would be considered supportive. 95% CI for PI and life table estimates should also be presented. Each study should be analyzed separately and each should independently demonstrate efficacy.

In October 19, 2010, a Type C Teleconference was held to discuss:

- How to conduct different metabolism studies due to difficulties performing mass balance study.
- The need to conduct a thorough QT (TQT) study
- The need for DDI of CVS with concomitant use of other vaginal products

The applicant changed the manufacturer of the drug substance and manufacturing processes testing part way through development. Therefore, in September 10, 2012, February 28, 2013 and September 30, 2013, we held meetings to discuss bridging from the phase 3 CVS to the TBM CVS, focusing on the in vitro release test method and proposed protocol for discriminatory ability of the in vitro release method. This bridging was also necessary for evaluation of data from the PK/PD, DDI, and QT/QTc studies.

On November 30, 2015, a Type C guidance meeting was held. Major issues included:

- The number of evaluable cycles was 15, 647(excluding women >35 at entry and women with BMI ≥ 29, and excluding cycles in which back up or emergency contraception (EC) was used), which fell short of the required number of cycles for efficacy. However, there were 19,726 cycles evaluable for safety based on all women treated in the two pivotal phase 3 trials and 21,590 cycles evaluable for safety based on all women who used the TBM CVS in phase 3. Upon reviewing the data on cycles, in post meeting comments, the Division concurred that the number of cycles of exposure is sufficient to support NDA filing because the number of cycles evaluable for safety was acceptable. In agreeing, the Division noted, “Although the intended target population is exclusive of women with BMI ≥29 kg/m2, the Division agrees that safety data that includes a subset of women in this higher BMI range is acceptable, because it appears that there may be a more concerning safety profile in this subset of women. Thus, inclusion of this subset of women would not result in a safety profile that is likely to be more favorable than that in the target population”. The Division also requested that the applicant enumerate the number of women and number of cycles excluded from the pooled efficacy population and provide an explanation as to why the number of efficacy evaluable cycles was so much lower than the number in the safety population.
- The Division requested an efficacy analysis that includes women of all ages.
- Increased initial release rates of SA and EE depend on duration of storage time prior to use as well as the storage temperature. The Division asked the applicant to address the

impact of using aged CVS and provide a justification that the data will generalize to likely actual use situations. Phase 3 safety and efficacy data should be stratified by age of the CVS at time of first use.

- The FDA was unable to concur with the proposed bridging plan for the manufacturing process used in phase 3 to the TBM process and drug product without additional clinical data for NDA filing/review. In vitro release procedure advise was given.
- CDRH requirements for the device components of the CVS were given
- Outstanding clinical pharmacology issues for an NME were listed
- DMEPA guidance was given regarding need for risk analysis to determine whether a Human Factors study would be required.

A Type C meeting on June 2, 2016 between the FDA and the applicant discussed bridging the TBM product to the phase 3 batches, studies needed for biocompatibility and mechanical testing, and implementation of an accelerated in vitro release quality control method.

The preNDA meeting (Type B) was held January 24, 2017 with the applicant seeking FDA's concurrence on the data and format requirements. All responses depended on an appropriate bridging strategy (through CMC data) to link the phase 3 CVS formulation to the TBM formulation being performed. The Division found the studies and analyses adequate to support filing and review of the NDA and requested:

- A sensitivity analysis including as "on-treatment" any pregnancies conceived within 14 days after CVS removal
- Number of cycles in US women for each study and in the pooled data
- Subgroup analysis by region (US vs. Non-US) and race/ethnicity
- That the submission address the generalizability of trial results to the full population of CVS users, which likely will include premenopausal women over 40 years of age.

The Division agreed:

- To review studies that the applicant had conducted to assess the in vivo delivery of SA and EE using the TBM CVS and an FDA-approved EE containing oral product and assess the in vivo release of SA and EE from the TBM product to determine if the bioavailability requirements have been met.
- That a risk management plan should be described in the NDA and anticipates that if approved, the applicant would have a PMR for a large safety study to characterize the risk of VTE in CVS users regardless of weight/BMI.

The Division requested that the applicant address DDIs.

The marketing application will be a 505(b)(2) application using the FDA's finding of safety for EE exposure in the CVS (through comparative BA bridging study with a listed drug COC) and published literature.

3.3. Foreign Regulatory Actions and Marketing History

There is no marketing history for the combined SA/EE CVS. (b) (4)

(b) (4)

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations was consulted for this NDA. Two clinical sites in Study 300A and three clinical sites in Study 300B were selected for inspection. The rationale for site selection was based on high subject enrollment, adverse events of special interest (i.e. VTE), numbers of pregnancies occurring at the site, and prior inspectional history. The applicant, Population Council, was also inspected as part of a data audit inspection and a complaint related to the protocols under review for this NDA submission. In the OSI review dated May 31, 2018, the overall assessment of findings was that the investigations at these sites appear to have been conducted adequately and the data generated by these sites appear acceptable in support of the indication.

- **Site 12, Kevin Barnhart, MD; Philadelphia, PA (Study 300A)**: This site was found to have excluded a concomitant medication (clonazepam) for one subject and to have failed to

[6] NDA 209627, Sequence 0018, submitted 4.26.2018, Response to IR, Module 1.11.4 p 10/11
[7] Email communication from Cherice Holloway CDER/OSE/OCT through Miriam Chehab OMPT/CDER/OSE/OPE/DPVII May 4, 2018

review screening labs before enrollment for three subjects. In addition, three subjects were not properly reconsented for the study using an updated informed consent form (ICF). This site was classified as deviation(s) from regulations (VAI) and the clinical investigator provided a corrective action plan to OSI. The OSI reviewer's conclusion was that "the regulatory compliance violations identified are unlikely to significantly impact data reliability."

- **Site 21, Michael Thomas, MD; Cincinatti, OH (Study 300A):** This site was selected due to VTE occurrence. Two subjects at this site had VTEs. This site was classified as no deviation from regulation (NAI).
- **Site 9, Melissa Gilman, MD; Chicago, IL (Study 300B):** One subject at this site had a VTE. There were protocol deviations involving incorrect reporting of 10 subjects' heights at this site. This site was classified as no deviation from regulation (NAI).
- **Site 23, Philip Darney, MD; San Francisco, CA (Study 300B):** This site was classified as deviation(s) from regulations (VAI) due to the clinical investigator obtaining informed consent for nine subjects using an amended version of the informed consent form not yet approved by the IRB. The clinical investigator stated that this occurred due to an oversight and outlined a corrective action plan to reduce ICF version issues. The OSI reviewer's conclusion was that "the regulatory compliance violations identified are unlikely to significantly impact data reliability."
- **Site 3, Vivian Brache, Santo Domingo, DR (Study 300B):** There were a higher number of pregnancies at this site compared to other sites. The OSI investigator noted that storage conditions may have contributed to product failure due to higher-than-acceptable temperature and humidity recordings at the site, and the fact that the air conditioning was turned off overnight at this site. The Medical Director of Population Council posited that there was more user error at this site compared with other sites, but the OSI investigator did not find any documentation of rates of user error higher than that at other sites. This site was classified as no deviation from regulation (NAI).
- **Applicant, Population Council:** The inspection covered practices related to both Study 300A and 300B and addressed a complaint made by a former Population Council employee who alleged that changes in the baseline BMI definition (which was used to analyze VTE risk) were made after the safety database was locked. Specifically, the complainant alleged that the definition of baseline BMI was changed to allow use of both screening and immediate pretreatment BMI (instead of just screening BMI) to link incidence of VTE to BMI >29 kg/m^2. Baseline BMI was also used to analyze VTE risk, instead of BMI at time-of-event. After a detailed review of records, the OSI investigator did not find evidence that baseline BMI definition was changed after safety database locking. The OSI reviewer also noted that the applicant was regularly in contact with the DSMB for the studies and responsive to all DSMB documentation requests.

4.2. Product Quality

SA is a progestin chemically known as 19-norpregn-4-ene-3,20-dione, 17-hydroxy-16-methylene acetate, and as 17-hydroxy-16-methylene-19-norpregn-4-ene-3,20-dione acetate ester. The

Chemistry Manufacturing and Controls (CMC) of segesterone acetate, an NME, is adequately documented in (b) (4) Type II Device Master File (DMF) # (b) (4). EE has a long history and is a widely used component of CHCs. The CMC for EE is adequately documented in (b) (4) Type II DMF # (b) (4).

ANNOVERA Vaginal System differs from the three FDA-approved vaginal rings, NuvaRing, Estring and Femring, in several important ways. First, it is designed to be used for thirteen (b) (4) day cycles. It is removed and stored for 7-days between each (b) (4) cycle. Secondly, (b) (4)

In addition to SA and EE, ANNOVERA consists of several types of silicone elastomers (b) (4)) and titanium dioxide, which gives the ring a uniform opaque appearance. The silicone elastomer components are manufactured by (b) (4) as described in several DMFs (b) (4) These materials were previously (b) (4) silicone elastomers. (b) (4) There are no safety concerns with these materials at the levels present.

There are three essential components of the ANNOVERA vaginal system: a ring body with an overall outside diameter of 56 mm and a cross-sectional diameter of 8.4 mm, and two drug-containing rod-shaped cores. Each ring weighs a total of (b) (4) grams. The ring body has two channels approximately 3.0 mm in diameter and 27 mm in length. Two drug-loaded cores are inserted and sealed in each channel with a silicone medical adhesive. Cores are 3 mm in diameter. One of the cores is 18 mm in length (b) (4). The other core is 11 mm in length (b) (4).

The silicone elastomer ring bodies are manufactured (b) (4) Despite the complexity, the current manufacturing process and in-process controls are adequate to ensure product with the requisite quality and performance.

The essential performance characteristic of the vaginal system is the slow, controlled release of drug from the polymeric matrix. A fast release rate may result in safety concerns. Conversely, a slow release rate may result in delivery of levels of drug too low to support efficacy. To ensure the appropriate batch-to-batch performance characteristics of the product, two in vitro release tests were developed. The first, an accelerated method, was found inadequate for use. The second method measures the in vitro release of drugs over a 30-day period. The biopharmaceutics review team performed extensive analyses to establish clinically relevant acceptance criteria. To ensure that the in vitro release criteria are met throughout the shelf-life as required by the regulatory specification, acceptance criteria for in vitro release testing for batch release was also established.

The Applicant's proposed in vitro in vivo correlation (IVIVC) was found unsuitable for use in providing a bridge to support formulation and manufacturing process changes. The in vivo release rate of the active ingredients was determined by measuring residual drug levels in the rings after use for thirteen cycles. While this gives an idea of the average rate of in vivo release, it does not adequately capture the decrease in release rate over time. The Applicant has agreed to further characterize the in vivo release rate (b) (4) as a post-marketing commitment.

In addition to in vitro release testing, the product specification includes tests for identity, dimensions, mass, (b) (4) hardness (b) (4), EE assay, SA assay, content uniformity, and related substances. Although vaginal rings are not manufactured as sterile products, they must meet requirements for microbial quality, and must be free of several specific microorganisms (e.g., E. coli). To minimize microbial contamination during the 7-day storage, the removed rings should be washed with mild soap and water and rinsed and patted dry.

The reviewer from the Center for Devices and Radiological Health (CDRH) determined that the mechanical properties (e.g., (b) (4) hardness, elongation at break, compression strength) and biocompatibility of the finished combination were adequately characterized and documented, and that the vaginal ring was suitable for the intended use.

The stability of Annovera at 25°C for 18 months has been adequately demonstrated; an 18-month expiration dating period is therefore granted. (b) (4) Storage at elevated temperatures for long periods of time can adversely impact product performance. This applies to product before first use and when stored between (b) (4) cycles.

The drug substance manufacturing facilities have acceptable CGMP status. The product manufacturer, QPharma AB, Malmo, Sweden, was satisfactorily inspected for drug and medical device GMP compliance in December 2017. All ancillary facilities have acceptable CGMP status. An Overall Inspection Recommendation of Approve was issued by the Office of Process and Facilities (OPF) Division of Inspectional Assessment on April 5, 2018. The OPF review team

recommends a post-approval inspection due to the complexity of the product and the likelihood of manufacturing scale-up.

The applicant submitted a claim for a categorical exclusion from the requirement to prepare an environmental assessment (EA) for ethinyl estradiol (EE), pursuant to 21CFR25.31(a) (i.e., use will not increase) and for segesterone, per 21 CFR 25.31(b) (i.e., use will increase but the expected introduction concentration (EIC) will be <1 parts per billion), for this application. A statement regarding the applicant's knowledge of extraordinary circumstances was submitted, as required per 21 CFR 25.15(a). Based on a review of the information provided by the applicant, and additional information obtained by FDA, the claims for categorical exclusions from EAs are acceptable. FDA also noted that because approval will result in expected concentrations of segesterone acetate that could approach environmental benchmarks, and because of the potential for cumulative effects from other drugs and xenobiotics with similar mechanisms of action, FDA recommends a prudent use of label language that provides guidance regarding environmentally protective disposal practices.

The Applicant also proposed a Comparability Protocol covering minor changes (b) (4) and documentation via a CBE-30 supplement, which was acceptable to the CMC review team.

4.3. Clinical Microbiology

Clinical Microbiology review was not necessary for this application.

4.4. Devices and Companion Diagnostic Issues

CDRH was consulted for this NDA. Contraceptive vaginal systems (referred to as "contraceptive vaginal rings" or CVR in the CDRH review) are combination products for which CDER is the lead center, with CDRH providing consultation on the ring itself. In the CDRH review dated March 8, 2018, the CDRH consultant concluded that "the information provided in the NDA including the associated responses to Informational requests is sufficient to demonstrate the adequacy of the mechanical design of the CVR to function as an intravaginal ring which may be inserted and removed monthly for a time frame of 13 months. It is also sufficient to demonstrate that its mechanical function will not be adversely affected by a shelf life of (b) (4) months." The CDRH review also provided labeling recommendations to address that the CVR is compatible for use with male condoms, but not oil-based personal lubricants. These recommendations will be incorporated into the final label for the product.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

SA/EE CVS is an intravaginal ring system designed for continuous release of a synthetic progestin (SA, 150 µg/day) and a synthetic estrogen (EE, 13 µg/day) for a maximum of 13 menstrual cycles of 28 days each. The CVS is inserted at the beginning of each menstrual cycle and remains in place continuously for three weeks (21 days) followed by a one-week (7 day) ring-free interval. A single device can provide reversible contraception for one year (13 cycles).

The progestin component of this product, SA, is a new molecular entity and the estrogen component, EE, is an approved product already marketed in the U.S. The applicant is seeking approval via the 505(b)(2) pathway to rely on published literature for the nonclinical safety evaluation of EE and to inform Sections 8 and 13 of the prescription labeling. Nonclinical studies were only conducted for SA.

Segesterone acetate is a high affinity ligand of the progesterone receptor, producing a dose-dependent increase in uterus weight with significant myometrium and endometrium proliferation. Doses ≥2.8 µg/kg/day block fertilization in female rabbits, and in female rats doses ≥67 µg/kg/day completely block spontaneous ovulation and estrus cycling. SA is not an agonist of the androgen receptor in rats, but subcutaneous (SC) doses ≥33 mg/kg/day are slightly anti-androgenic. SA is a very weak agonist of the glucocorticoid receptor and has no effect on either the estrogen or mineralocorticoid receptors in rats.

Orally administered segesterone is rapidly absorbed from the gastrointestinal (GI) tract, and the rise in portal concentration is followed by an equally rapid decrease in the systemic concentration with metabolites appearing in the bile. In all nonclinical species, SA is subject to extensive first-pass metabolism by hepatic cytochrome P450 (CYP 3A4) and carbonyl reductase enzymes, producing numerous Phase I and II metabolites that can be detected in plasma, urine and feces. At free concentrations of 1 µM and above, segesterone causes metabolism-dependent inhibition of CYP3A4 *in vitro*, suggesting the formation of reactive intermediates. Hepatocyte studies indicate that liver metabolism is somewhat slower in humans than in rats, and that segesterone does not induce its own metabolism.

After subcutaneous injections or implantation of sustained release delivery systems, SA distributes to a wide variety of tissues with the highest concentrations found in the gastrointestinal tract, adrenals, liver, ovaries, uterus, reproductive tract fat, and pancreas. The fraction of segesterone bound to serum proteins is approximately 95% in humans, rats and mice. The main route of excretion following systemic administration is fecal, with approximately 50% of the dose recovered in feces within 24 hours.

In patch-clamp studies, SA inhibited the ionic current of the human ether-à-go-go-related gene (hERG) potassium channel by 24% at 10 µM free drug concentration. It also inhibited the L-type calcium channel (hCav1.2) and the hyperpolarization-activated potassium channel (hHCN4) currents by 13.5% and 14.4%, respectively at 1 µM. In telemetrized freely moving cynomolgus monkeys, subcutaneous injections of SA at a dose of 2.5 mg/kg produced no change in blood pressure, heart rate, action potential duration or QT intervals. In rats, SA did not produce any mortality, clinical signs, respiratory or neurobehavioral effects after a single dose of 10 mg/kg SC, approximately 130 times the human exposure reported in Cycle 1 of clinical study 300PK.

Segesterone acetate was investigated in mice, rats, rabbits and monkeys. None of the anticipated endocrine effects were observed following oral administration, confirming the rapid and extensive first pass metabolism across nonclinical species. Hence, the toxicological properties of SA could only be evaluated using parenteral routes of administration.

CD1® female mice administered SA as a vaginal gel of 1, 3 and 9% SA (10, 30, and 90 mg/kg/day) for 28 days only showed alteration of the vaginal morphology consistent with the pharmacology of a progestin. Similarly, the administration of SA for three months to Sprague-Dawley rats at an average daily dose of 86 µg/day (approximately 175 µg/kg/day in males and 286 µg/kg/day in females) by subdermal implant blocked the estrus cycle, inhibiting ovulation and stimulating mammary growth and milk secretion. In males, SA treatment produced a reduction in testes, epididymis, prostate and seminal vesicle weights and an increase in adrenal weights. Female CD® rats administered SA for a year by subdermal implants with release rates of 11, 15 and 48 µg/day (approximately 75, 100 and 320 µg/kg/day) presented with a combination of effects on the primary and secondary sex organs, including enlarged mammary and pituitary glands and a reduced uterus weight. Histologically, the ovaries were devoid of corpora lutea, the uterus and vagina were arrested in diestrus and the mammary glands showed little ductal or lobuloalveolar development. The no-observable adverse-effect-level (NOAEL) after a year of dosing was 48 µg/day (320 µg/kg/day) as the effects of SA were primarily pharmacological. The mean SA serum concentration at the NOAEL was 71-fold the average steady-state serum concentration (C_{ave}) in cycle 1 of clinical study 300PK (515 pmol/L).

Female New Zealand White rabbits implanted with Silastic rods continuously releasing SA at daily rates of 25, 130 or 550 µg/day (approximately 14, 72 and 306 µg/kg/day) for three months showed a decrease in uterine weight and an increase in liver weight at all doses, and a decrease in adrenal and thyroid gland weights at the highest dose. All the effects reported in this study were consequences of the pharmacology of SA and the NOAEL for three months of dosing was 550 µg/day, corresponding to 16-fold of the C_{ave} in cycle 1 of clinical study 300PK.

Segesterone acetate was administered for 1 year to female cynomolgus monkeys using subdermal Silastic implants with release rates of 30, 87 and 395 µg/day (approximately 10, 30 and 130 µg/kg/day) without indication of systemic toxicity. The menstrual cycle of all treated animals stopped within 10 days of test article implantation and a dose-related enlargement of the uterus was observed, which correlated histologically with myometrial hypertrophy,

endometrial deciduation and inhibition of endometrial gland growth. Hormonally-induced changes were also seen in the cervix and vagina. SA inhibited ovulation and the development of corpora lutea but allowed follicular growth up to the intermediate stage. All the observed effects were consequences of the pharmacology of SA and the NOAEL for 1 year of dosing in monkeys was 395 µg/day, corresponding to 18-fold of the C_{ave} in cycle 1 of clinical study 300PK.

Vaginal rings releasing SA at a rate of approximately 100 µg/day (approximately 33 µg/kg/day) were inserted in the vagina of female cynomolgus monkeys and remained in situ for 4 weeks without sign of systemic or local toxicity. The animals receiving SA exhibited morphologic differences in the vagina, the cervix and the uterus related to its pharmacology. The NOAEL in this study was 100 µg/day, corresponding to a serum concentration 4.4-fold greater than the average steady-state segesterone concentration in cycle one of clinical study 300PK.

Segesterone acetate was not mutagenic in bacterial mutation assays and did not cause chromosome aberrations in human peripheral blood lymphocyte cultures or in the bone marrow of mice. In a mouse carcinogenicity study, the daily administration of SA intravaginally for two years using gels of 0.3%, 1% and 3% SA, providing doses of 3, 10 or 30 mg/kg/day produced subchronic or chronic inflammation of the vaginal mucosa and at the highest dose per day, an increased incidence of adenocarcinoma and lobular hyperplasia in the breast. Based on the results of this 2-year study, 30 mg/kg/day SA is considered carcinogenic in female mice. A 2-year carcinogenicity study was also conducted in female rats using segesterone subdermal Silastic implants with release rates of 0, 40, 100, 200 µg/day (approximately 267, 667 and 1333 µg/kg/day). The high dose of 200 µg/day decreased the incidence of pituitary and mammary neoplasms in the rats compared to controls. The average serum concentration of SA at the end of the two-year period in female rats receiving 200 µg/day was approximately 35 times greater than the steady-state patient concentration in cycle 1 of clinical study 300PK, and 86 times the daily dose of SA based on body surface area. Exposure was not measured in the mouse carcinogenicity study, but relevant systemic exposure was measured in the 4-week dose-selection study in mice. The carcinogenic dose of 30 mg/kg/day is 10-fold greater than the AUC of SA in cycle one of clinical study 300PK, and the non-carcinogenic dose of 10 mg/kg/day is approximately 3-fold greater than the AUC of SA in cycle one of clinical study 300PK. Patients will be exposed to less than the lifetime non-carcinogenic dose in nonclinical species, and the use of ANNOVERA is, therefore, not expected to pose a significant cancer risk.

During reproductive toxicity studies, the subdermal administration of SA to female CD® rats for 90 days did not impair the return to fertility when the implants were removed. More females from the SA treatment group became pregnant after implant removal than in the vehicle control group, and prior treatment had no effect on the number of corpora lutea or the number of implantations recorded in the animals. The subcutaneous administration of SA to pregnant rats at doses up to 250 µg/kg/day during gestation days 6-15 did not cause maternal toxicity, embryotoxicity or teratogenicity. However, daily subcutaneous injections of SA at doses of 10, 50 and 250 µg/kg/day from gestational day 15 through gestational day 25 or postpartum resulted in prolonged gestation and delivery complications leading to the death of mothers

and/or pups at all three doses. In addition, feminization of male pups, as indicated by an increase of the anogenital distance, was evident in the 10 and 50 µg/kg/day dosage groups after delivery. This effect had disappeared by day 21 postpartum. A no-observable-effect-level (NOEL) for either maternal toxicity or viability and growth in the offspring could not be identified. In rabbit, daily subcutaneous injections of SA at 10, 50 and 250 µg/kg from gestational day 6 through gestational day 18 increased embryo death and litter resorptions at the highest dose, without adverse effects on the surviving fetuses. The developmental NOAEL for SA in rabbit was 50 µg/kg/day, corresponding approximately on day 18 to an exposure 1.8-fold greater than the average exposure (AUC_{0-24}) in cycle one of clinical study 300PK.

The safety of EE is well-established and documented in the published literature following many years of clinical use. Ethinyl estradiol was first approved in 1943 and has been a component in various combined hormonal contraceptives either as a pro-drug or as the drug substance since 1960. There are several approved products that contain EE as the active pharmaceutical ingredient at the same or similar doses, and for the same or similar indication as the SA/EE 150/15 CVS (e.g. Nuvaring). The applicant has shown that the patient serum concentrations of EE following administration of the vaginal ring system were very similar to those recorded with an approved oral contraceptive product (Nordette 21; Wyeth Laboratories). This NDA however is not relying on any of the previous findings of safety for Nuvaring or Nordette 21 to support the safety of use of EE as a component of the drug product and has no right of reference to either NDA.

No toxicology studies were specifically conducted to evaluate the combination of SA and EE in a vaginal ring system, though biocompatibility studies of extracts of the SA/EE to-be-marketed device have been conducted to evaluate the potential for local toxicity. The chronic safety of EE alone has already been documented in the published literature and through extensive previous approved use through vaginal application, and the 12-month monkey study using subcutaneous implants provided evidence of the long-term safety of SA. The local tolerance of a vaginal ring system releasing SA alone was evaluated in a 4-week monkey intravaginal toxicity study, with only pharmacodynamic effects observed. There were no device-related toxicities observed. In addition, clinical studies informed the pharmacokinetics of the SA/EE vaginal ring system, eliminating the need for a nonclinical study of chronic duration with the combination. To assess the biocompatibility of the drug/device combination, nonclinical studies were completed using extracts from the proposed SA/EE vaginal ring system, and reviewed by CDRH. These studies were deemed sufficient to evaluate the local toxicity of the combined drug/device product.

The safety multiples of the therapeutic dose achieved in nonclinical studies are summarized in Table 3.

Table 3. Safety multiples of the therapeutic dose of SA* based on nonclinical studies

Nonclinical Studies	Daily Doses	Exposure and BSA-corrected Dose		Multiples of	
		$AUC_{0\text{-}24h}$ (ng·hr/mL)	Human Equivalent Dose (mg/kg)	Cycle 1 Human $AUC_{0\text{-}24h}$	Human Daily Dose (BSA)
General Toxicology					
4-Week Intravaginal Toxicity Study in Female Mice (Study 1571-001	9% Gel 90 mg/kg NOAEL	1990	7.32	**132**	**2926**
3-month Subdermal Implant Toxicity Study in Rats (Study 01-ST-TOX-0682)	0.175 mg/kg (m) 0.286 mg/kg (f) NOAEL	ND	0.03 (m) 0.05 (f)	-	**11** **19**
3-month Subdermal Implant Toxicity Study in Rabbits (Study PC-ST-05-KS/89)	0.07 mg/kg NOAEL	ND	0.02	-	**9**
12-month Subdermal Implant Toxicity Study in Rats (Study PC-ST-03-KS/89	0.075 mg/kg LOAEL	ND	0.01	-	**5**
12-month Subdermal Implant Toxicity Study in Cynomolgus Monkeys (Study PC-ST-06-KS/90)	0.13 mg/kg NOAEL	ND	0.04	-	**17**
4-Week Local Toxicity Study of Vaginal Rings in Cynomolgus Monkeys (Study 6884-102)	0.04 mg/day NOAEL	ND	0.01	-	**5**
Carcinogenicity					
2-Year Intravaginal Carcinogenicity Study in Mice (Study 1571-002, GLP)	1% Gel 10 mg/kg NOAEL	39	0.81	**3**	**325**
2-Year Subdermal Implant Carcinogenicity Study in Rats (Study 6884-103)	1.33 mg/kg NOAEL	ND	0.21	-	**86**
Reproductive Toxicology					
Embryo-Fetal Toxicity and Teratogenicity Study in Pregnant Rats (Study PC-ST-07-KS/91)	0.25 mg/kg Maternal NOAEL	ND	0.04	-	**16**
	0.25 mg/kg Fetal NOAEL	ND	0.04	-	**16**
Embryo-Fetal Toxicity and Teratogenicity Study in Pregnant New Zealand White Rabbits (Study PC-ST-08-KS/91)	0.25 mg/kg Maternal NOAEL	111	0.08	**7.4**	**32**
	0.05 mg/kg Fetal NOAEL	28	0.02	**1.9**	**6**
Perinatal and Postnatal Reproduction Toxicity Study in Pregnant Rats (Study PC-ST-09-KS/92)	0.002 mg/kg Maternal LOAEL	ND	0.0003	-	**0.13**
	0.002 mg/kg Fetal LOAEL	ND	0.0003	-	**0.13**

* Daily dose of SA = 150 µg/day; 0.0025 mg/kg/day; AUC = 14.99 ng*hr/mL

5.2. Referenced NDAs, BLAs, DMFs

Reference was made to DMF (b) (4)

5.3. Pharmacology

5.3.1. Primary Pharmacology of Segesterone Acetate

Primary pharmacology studies were only conducted for SA, a novel progestin. The applicant focused on investigating two possible mechanisms explaining the contraceptive effects of SA, both linked to its binding to the progesterone receptors.

Agonist Activity of Segesterone Acetate on the Progesterone Receptor (Study *General Pharmacology 1*, *General Pharmacology 8 and General Pharmacology 3*, non-GLP)
In rat tissues, segesterone demonstrated a high binding affinity for the progesterone receptor (EC_{50} = 10.3 nM), but did not bind to either the estrogen or androgen receptor or the sex-hormone binding globulin (SHBG).

In human receptor studies, SA was a progesterone receptor full agonist with an EC_{50} = 23.7 pM. In the same assay, the endogenous ligand, progesterone, activated the receptor with an EC_{50} = 650 pM. Segesterone acetate was approximately 200-fold less potent as an agonist of the glucocorticoid receptor (EC_{50} = 4.68 nM) and had no agonist activity on the mineralocorticoid receptor. Segesterone was an androgen receptor antagonist at relatively high concentrations (EC_{50} = 500nM). Several segesterone metabolites were also weak human progesterone receptor agonists, with the most potent being 5-dihydro-segesterone (EC_{50} = 0.41 nM).

The ability of SA to activate the progesterone receptor *in vivo* was measured by its ability to promote the transformation of the endometrium from a proliferative to a secretory stage in immature female rabbits primed with 17β-estradiol. This transformation was graded histologically using the McPhail index. Female immature New Zealand White rabbits were injected subcutaneously for six days with 2.8 µg/kg/day of estradiol before receiving subcutaneous daily doses of segesterone at 0.5 and 5 µg/kg/day for five additional days. A dose-dependent increase in uterine weight was observed with significant myometrial hypertrophy, endometrial stromal cell proliferation, and branching of endometrial glands. When administered orally, SA was 100-fold less potent in promoting the pseudo gestation changes in the uterus.

Segesterone Acetate Blockage of Ovulation (Study *General Pharmacology 2,* non-GLP)
In female rats, progestins cause a decrease in the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) through a negative feedback mechanism on the hypothalamus. The surge in LH and FSH is required for ovulation and blocking their secretion

inhibits spontaneous ovulation. Mature female Sprague Dawley rats were injected subcutaneously with increasing concentrations of progesterone, levonorgestrel and segesterone on the day of diestrus and the number of ova present in the oviduct was counted two days later. Spontaneous ovulation was completely blocked by doses of 67, 133, and 6000 μg/kg of segesterone, levonorgestrel, and progesterone, respectively.

Gonadotropin-releasing hormone (GnRH) causes ovulation in female rats by stimulating the release of gonadotropins from the pituitary. Hence, the ability of exogenous GnRH to override segesterone-induced suppression of ovulation would indicate that the pituitary gland is involved. Mature female Sprague Dawley rats were treated with progesterone, levonorgestrel or segesterone as described above, and received a subcutaneous injection of 2 μg GnRH 24 hours later. The number of ova present in the oviduct was counted on day 3. GnRH fully restored ovulation in animals treated with 66 μg/kg of segesterone, partially (57%) restored ovulation blocked by 15 μg of segesterone and was unable to overcome the blockage by doses of 133 μg/kg and above. At doses equal or greater than 353 μg/kg, segesterone also completely abolished estrus cycling in female rats.

Segesterone Acetate Prevention of Pregnancy (Study *General Pharmacology 2,* non-GLP)
Although progesterone is required for the maintenance of pregnancy, exogenous progestins administered post-coitally to pregnant rats during the transit of the fertilized egg through the oviduct (day 1 - day 7) prevent pregnancy or delay implantation. In this assay, pregnant Sprague Dawley female rats received daily subcutaneous injections of segesterone (0.01, 0.03, 0.1, 0.3, 1, 3, 5, 10, 15, 30 or 50 mg/day) from day 1 through 7 of pregnancy. On day 8, the number of implantation sites were counted in each horn. Doses ≤100 mg/kg/day were ineffective in preventing implantation. At 200 and 333 mg/kg/day, 33% of the animals showed no implantation sites or embryos at the time of autopsy. By comparison, levonorgestrel, at a dose of 333 mg/kg/day, prevented pregnancy in all animals.

The ability of SA to block fertilization was also investigated in rabbits. Segesterone acetate (0.3 to 30 μg/day) and Levonorgestrel (5 to 300 μg/day) were administered subcutaneously to adult female rabbits for 8 days. On the eighth day, FSH and human chorionic gonadotropin (hCG) were administered to induce ovulation and the animals were mated. The next day the oviducts were examined for the presence of dividing ova and the number of corpora lutea in each ovary was used as an index of ova released. Doses ≥0.55 μg/kg/day SA produced a significant reduction in the number of dividing ova found in the oviducts and doses ≥2.8 μg/kg/day completely blocked fertilization. In this assay, SA was 60 to 100 times more potent than levonorgestrel.

5.3.2. Secondary Pharmacology of Segesterone Acetate

In the secondary pharmacology studies, the applicant focused on characterizing the activity of SA on other steroid nuclear receptors.

Agonist/Antagonist Activity of Segesterone Acetate on the Androgen Receptor (Study *General Pharmacology 4,* non-GLP)

The androgenic effects of SA were evaluated in immature castrated male rats. Starting one day after castration, the rats received daily subcutaneous injections of SA (1 or 4 mg/day) or testosterone (0.2 or 0.8 mg/day) for 10 days. One day after the last injection, the ventral prostate, seminal vesicles and the levator ani muscles were removed. The weights of the prostate and seminal vesicles were used as markers of androgenic activity while the weight of levator ani muscle provided a measure of the anabolic activity. Segesterone acetate at doses up to 27 mg/kg/day did not increase the weight of any of the three tissues, showing that it is not an agonist of the rat androgen receptor. In addition, coadministration of 8.7 mg/kg/day testosterone and 27 mg/kg/day SA restored the weight of the tissues back to non-castrated values, showing that SA is not an antagonist of the rat androgen receptor either. In a similar study comparing its activity to nomegestrol and medroxyprogesterone acetates, SA at 33 mg/kg/day subcutaneously was slightly antiandrogenic.

Agonist/Antagonist Activity of Segesterone Acetate on the Estrogen Receptor (Study *General Pharmacology 5,* non-GLP*)*

The estrogenic/antiestrogenic activity of SA was investigated in ovariectomized immature female Sprague Dawley rats in which estrogens stimulate uterine growth. Animals were treated with segesterone (6.7 or 33 mg/day), estradiol (0.33 µg/kg/day) or a combination of both subcutaneously for 5 days, before the uterus was removed and weighed. Estradiol (0.33 µg/kg/day) increased the weight of the uterus, but segesterone (33 mg/kg/day) did not. However, the combination of 33 mg/kg/day segesterone and 0.33 µg/kg/day estradiol did not prevent the estradiol-induced uterus weight gain, showing that segesterone is neither an agonist nor an antagonist of the rat estrogen receptor.

Agonist/Antagonist Activity of Segesterone Acetate on the Glucocorticoid Receptor (Study *R1201,* non-GLP)

The *in vitro* binding affinity of SA for the glucocorticoid receptor is approximately five times weaker than for the progesterone receptor. The potential *in vivo* activity of SA on the glucocorticoid receptor was investigated by measure of the thymus weight in surgically-sterilized immature rats, and measure of liver glycogen and tyrosine transaminase (TAT) activity in adrenalectomized female rats. Subcutaneous injections of segesterone (33 mg/kg/day) for five days caused significant thymic involution in ovariectomized females and castrated males. However, SA at 27 mg/kg/day SC for 3 days did not increase hepatic glycogen content or TAT activity and when coadministered with dexamethasone, did not prevent the glucocorticoid-induced increase in hepatic glycogen content and TAT activity. Thus, SA has agonist activity at the glucocorticoid receptor.

Agonist/Antagonist Activity of Segesterone Acetate on the Mineralocorticoid Receptor (Study *1571-023,* non-GLP)

The activity of SA at the mineralocorticoid receptor was investigated by measure of sodium and potassium urinary excretion in adrenalectomized animals. Female Sprague Dawley rats with

both adrenal glands surgically removed received a single subcutaneous injection of aldosterone (0.2 µg), SA (50 or 250 µg) or the combination of both, followed approximately 30 minutes later by an intraperitoneal administration of sodium and potassium chloride. Urine was subsequently collected for three hours and the excretion rates of sodium and potassium were compared to evaluate the mineralocorticoid-mediated reabsorption of sodium. Segesterone had no effect on the excretion rates for sodium or potassium in the presence or absence of aldosterone.

5.3.3. Safety Pharmacology of Segesterone Acetate

Effects of Segesterone Acetate on Cardiac Ion Channel (Studies *091105.QPD*, *100308.QPD,* non-GLP)
The effect of segesterone on the human ether-à-go-go-related gene (hERG) potassium channel current was investigated in human embryonic kidney (HEK293) cells stably transfected with hERG using the patch-clamp technique. Segesterone acetate inhibits the potassium current by 1.6% at 1 µM, 8% at 3 µM, 24% at 10 µM and 47% at 30 µM free concentration. Under these conditions, the positive control terfenadine inhibited the hERG current by 73% at 60 nM. By comparison, SA activates the human progesterone receptor in cell cultures with an EC_{50} = 23.7 pM.

The effects of SA on 11 other ion channels accounting for all the major ionic current in the cardiac action potential (Ca, K, Na hyperpolarization-activated, inward or outward rectifying, ATP-sensitive, ultra-rapid, delayed and slow rectifier) were investigated using automated patch clamp instrumentation. At a free drug concentration of 1 µM, the highest inhibitions recorded were 13.5% and 14.4% for the L-type calcium channel (hCav1.2) and the hyperpolarization-activated potassium channel (hHCN4).

The ability of SA to prolong the QT interval of the cardiac action potential was evaluated in wedge preparations of dog left ventricle. The isolated ventricular tissues were perfused with increasing concentrations of SA (4, 16, 64 and 256 nM) and transmembrane action potentials were recorded from epicardial and sub endocardial regions concurrently with a transmural pseudo-ECG. Segesterone acetate produced no significant change in either repolarization time or dispersion at any of the concentrations tested and caused neither spontaneous nor induced arrhythmic activity. When the wedges were pretreated with a toxin delaying sodium channels inactivation, SA increased repolarization time and transmural dispersion of repolarization in a dose-dependent manner, leading to the development of arrhythmias at or above 100 nM free drug.

Cardiovascular Effects of Segesterone Acetate in Cynomolgus Monkeys (Study *1571-003*, GLP)
The *in vivo* cardiovascular effects of SA were investigated in freely moving telemetrized cynomolgus monkeys. The animals received subcutaneous injections of SA at doses of 0.1, 0.5 and 2.5 mg/kg once each with a washout period of seven days between doses. Under these conditions, SA produced no change in blood pressure, heart rate or any of the ECG parameters measured (QRS duration and the RR, PR, and QT intervals) at any concentration during the

twenty hours of continuous monitoring post dose. No mortality, morbidity or clinical signs were observed in the study.

CNS Safety Pharmacology (Study *1571-014*, GLP)
The neurobehavioral effects of SA were investigated in rats using the Functional Observational Battery (FOB). Female Sprague Dawley rats received a single subcutaneous injection of 0.5, 2.5, or 10 mg/kg SA and FOB evaluations were conducted predose and at approximately 2 and 24 hours postdose. Segesterone acetate did not produce any neurobehavioral effects at doses up to and including 10 mg/kg.

Pulmonary Safety Pharmacology (Study *1571-013*, GLP)
The effects of SA on respiratory functions were investigated in female rats receiving a single subcutaneous injection of 0.5, 2.5 or 10 mg/kg. Pulmonary functions (respiratory rate, tidal volume, and minute volume) were monitored using plethysmograph chambers for at least 1 hour prior to dosing followed by 4 hours postdose. A separate set of animals was used to determine exposure during the study. Segesterone acetate did not produce any effects on mortality, clinical observations, or any of the respiratory parameters measured at any dose. Test article concentrations in the serum following the 10 mg/kg subcutaneous dose produced mean AUC_{last} and C_{max} of 1939 ng·hr/mL and 745 ng/mL, respectively.

5.3.4. Pharmacology of Ethinyl Estradiol

Ethinyl estradiol mimics the endocrine properties of its natural hormone counterpart estradiol. Following entry in cells, EE binds to the intracellular estrogen receptors and initiates translocation from the cytosol to the nucleus. In the nucleus, the activated estrogen receptors regulate gene expression to promote the proliferation and growth of the vaginal, uterine and mammary epithelium. In animals, the sensitivity of the various reproductive tissues to an estrogenic signal varies between species, with the monkey considered the best animal model for the prediction of human response to synthetic hormones.

5.4. ADME/PK

5.4.1. Pharmacokinetics of Segesterone Acetate

Orally administered segesterone is rapidly absorbed from the gastrointestinal (GI) tract in monkeys, rabbits, and rats. Intestinal absorption is followed by rapid disappearance of the parent from the systemic circulation with metabolites appearing in the bile, indicating extensive hepatic biotransformation.

After subcutaneous injections or implantation of sustained release delivery systems (subdermal implants or intravaginal ring), segesterone distributes to a wide variety of tissues with the highest mean concentrations found in the gastrointestinal tract, adrenals, liver, ovaries, uterus, reproductive fat, and pancreas. By contrast, the concentrations in the brain and kidneys are low. The fraction of segesterone bound to serum proteins is approximately 95% in humans, rats

and mice. The main route of excretion in rats following subcutaneous administration is fecal, with approximately 50% of the dose recovered in feces within 24 hours and 95% of the dose recovered in feces by 120 hours post-dose.

Segesterone is completely metabolized in vitro after a 60-minute incubation in rat hepatocyte suspensions, producing 5 metabolites from Phase I and II metabolic reactions. In vivo, the major metabolite is 4,5-dihydro-17α-deacetyl-segesterone, that can be found in plasma, urine and feces.

In monkeys, the biotransformation of segesterone produces 66 different metabolites, including numerous Phase I metabolites, detected in serum and urine, and some Phase II metabolites (glucuronides), detected only in the urine.

Human hepatocytes did not fully metabolize segesterone after 240 minutes, suggesting a slower rate of liver biotransformation than in rats. Eight Phase I metabolites were produced but no subsequent Phase II reactions could be observed. The intestinal metabolism of segesterone is significantly less than the hepatic metabolism.

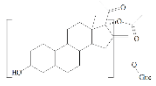
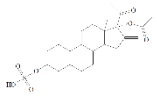
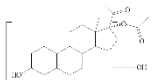
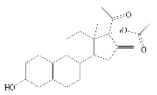
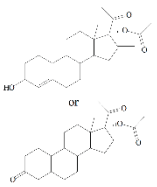
Cytochrome P450 (CYP 3A4) and carbonyl reductase enzymes are responsible for the hepatic biotransformation of segesterone. Segesterone did not induce any of the most common drug-metabolizing cytochromes (CYP 1A2, 2B6, 2C8, 2C9, 2C19 and 3A4/5) in cultures of human hepatocytes at concentrations up to 1000 nM. At concentrations of 1 µM and above, segesterone caused metabolism-dependent inhibition of CYP3A4/5, highlighting the possibility of a reactive intermediate causing metabolism-mediated inactivation of the enzyme. However, the therapeutic concentrations of free segesterone in human plasma are orders of magnitude smaller than the concentration causing enzyme inhibition *in vitro*.

Type of Study	**Major Findings**
Absorption	
Single Dose Intravenous and Oral Administration of ^{3}H-Segesterone Acetate in Male and Female Wistar Rats (Study 17247-16-220485, non-GLP)	Following a single intravenous dose of 44.5-55.7 µg/kg, the concentration of segesterone in plasma decreased in three distinctive phases: a rapid drop during the first two hours followed by near-constant level from 2 to 8 hours post dose, and finally a slow decrease for up to 32 hours. After a single oral dose of 38.5-50.0 µg/kg, the C_{max} was reached within 1 hour post-dose and the bioavailability was approximately 95%. There was no sex-related difference in the pharmacokinetics parameters.
ADME of ^{3}H- Segesterone Acetate Following a Single Subcutaneous Injection of 50 g/ g t o Female	Rat (*Females, Sprague Dawley*) T_{max} (SC): 1 h C_{max}(SC): 31.3 ng equivalents/g AUC_{inf}(SC): 240 ng equivalents•h/g

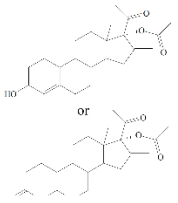
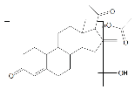
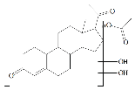
<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Sprague Dawley Rats. (Study 6884-120, GLP)</td><td></td></tr>
<tr><td>Pharmacoinetics , ADME of ^{3}H-Segesterone Acetate Following Administration of a Single Subcutaneous Dose of 500 µg/g to Female Sprague Dawley Rats (Study 6884-121, GLP)</td><td><u>Rat</u> (Females, Sprague Dawley)
T_{max} (SC): 2 h
C_{max}(SC): 95.4 ng equivalents/g
AUC_{inf}(SC): 1135 ng equivalents•h/g</td></tr>
<tr><td>Pharmacoinetic Analy sis of Segesterone Acetate in Female Cynomolgus Money s Following a Single Subcutaneous Dose of 10 mg/g (S tudy 1571-008, GLP)</td><td><u>Monkey</u> (Females, Cynomolgus)
T_{max} (SC): 2 h
$T_{½}$: 6.24 h
C_{max}(SC): 895 ng/mL
AUC_{inf}(SC): 6050 ng•h/mL</td></tr>
<tr><td>Bioavailability of Segesterone Acetate in Immature Rabbits: Comparison of Progestational Activity of Segesterone after Oral vs. Subcutaneous Administration in Immature Rabbits (Study ADME-1)</td><td><u>Rabbit</u> (Immature female)
Doses: 2.8 µg/kg/day, SC and 28 µg/kg/day, PO for 5 days.
C_{1h} SC: 895 ± 116 pmol/L
C_{1h} PO: 148 ± 16 pmol/L</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Determination of free Segesterone Acetate concentration in Female Rat, Mouse and Human sera by ultrafiltration after incubation with ^{3}H-Segesterone (Study ADME2)</td><td><u>Percentage of Free Segesterone at 37°C</u>
Human: 4.42 % ± 0.368
Rat: 4.73 % ± 0.282
Mouse: 5.45 % ± 0.158</td></tr>
<tr><td>Relative binding affinity of Segesterone Acetate to steroid hormone receptors and sex hormone binding globulin (SHBG) (Study General Pharmacology 1)</td><td>
<table>
<tr><th rowspan="2">Test Article</th><th colspan="2">Relative Binding Affinity* (nM)</th></tr>
<tr><th>PR</th><th>AR</th></tr>
<tr><td>Progesterone</td><td>20</td><td>NB</td></tr>
<tr><td>Testosterone</td><td>NB</td><td>100</td></tr>
<tr><td>Levonorgestrel</td><td>100</td><td>70</td></tr>
<tr><td>Segesterone</td><td>110</td><td>0.2</td></tr>
</table>
* Concentration of steroid competitors that reduced binding by 50%
PR=progesterone receptor; AR=androgen receptor
The binding of SA to SHBG was negligible.
</td></tr>
</table>

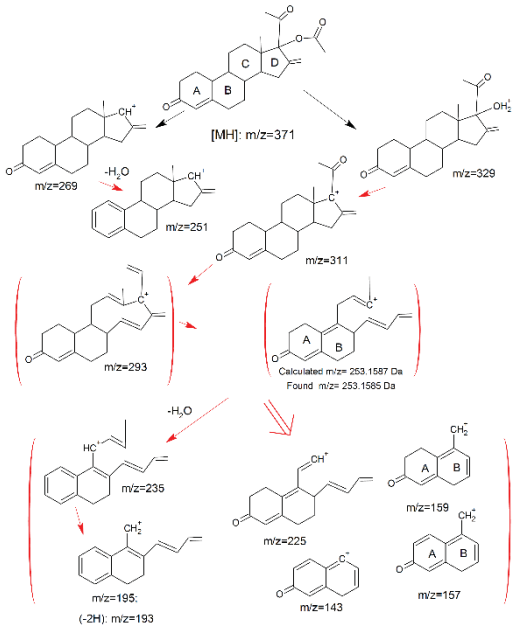
<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Determination of free Segesterone Acetate concentration in Rats, Mouse and Human sera by ultrafiltration after incubation with ^{3}H-Segesterone (Study ADME2)</td><td>
<table>
<tr><th colspan="3">% of Free Segesterone</th></tr>
<tr><th>Human</th><th>Rat</th><th>Mouse</th></tr>
<tr><td>4.42 ± 0.36</td><td>4.73 ± 0.28</td><td>5.45 ± 0.15</td></tr>
</table>
</td></tr>
<tr><td>Pharmacoinetics , Absorption, Metabolism, Distribution and Excretion Study with ^{3}H-Segesterone Acetate by single subcutaneous administration in female rats (Study 6884-121)</td><td>
<table>
<tr><th></th><th colspan="3">% of administered dose after single SC administration of 500 µg/kg</th></tr>
<tr><th></th><th>2h</th><th>24h</th><th>72h</th></tr>
<tr><td>Adrenals</td><td>0.03</td><td>0.00</td><td>0.00</td></tr>
<tr><td>Brain</td><td>0.12</td><td>0.02</td><td>0.00</td></tr>
<tr><td>Kidney</td><td>0.21</td><td>0.06</td><td>0.01</td></tr>
<tr><td>Large Intestine Tissues/Content</td><td>0.3/0.22</td><td>0.68/11</td><td>0.07/1.15</td></tr>
<tr><td>Liver</td><td>3.56</td><td>1.31</td><td>0.17</td></tr>
<tr><td>Ovaries</td><td>0.03</td><td>0.00</td><td>0.00</td></tr>
<tr><td>Pancreas</td><td>0.17</td><td>0.03</td><td>0.01</td></tr>
<tr><td>Small Intestine Tissues/content</td><td>3.74/20.1</td><td>0.72/9.17</td><td>0.33/2.13</td></tr>
<tr><td>Uterus</td><td>0.04</td><td>0.01</td><td>0.00</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
</table>

Type of Study	Major Findings
In Vitro Metabolism of Segesterone Acetate by Female Rat Hepatocytes (Study 6884-113) and Hepatic Microsomes (Study 6884-119)	See table below
Metabolic Stability and Metabolite Profiling of Segesterone Acetate in Human, Rat, and Mouse Liver S9 Fractions (Study 8POPUP1)	See tables below

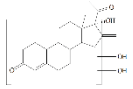
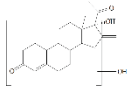
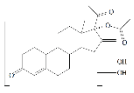
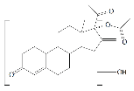
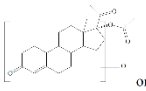
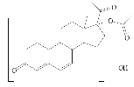
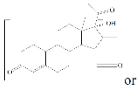
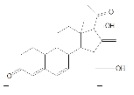
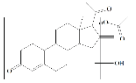
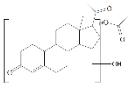
Metabolite[a]	$[M + H]^+$	Metabolite Structure from LC/MS/MS	Present in Hepatocyte Incubations	Present in Microsomal Incubations
R1	567		Yes	No
R2	455		Yes	No
R3	551		Yes	No
R4	391		Yes	No
R5	375		Yes	No
R6[b]	373		No	Yes

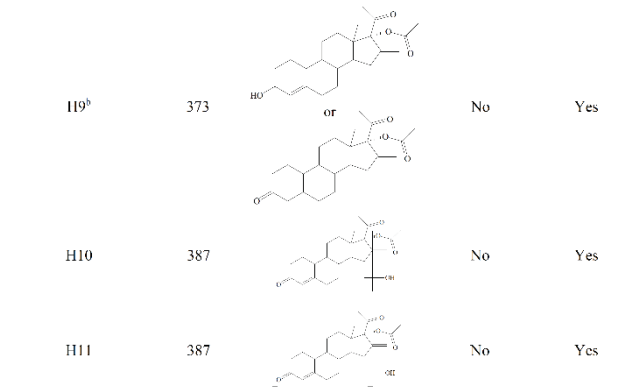
Time (min)	% of Parent Remaining		
	Human	Rat	Mouse
0	99.8	86.3	87.7
60	0.0	0.0	0.0

Metabolite Code (previous codes)[a]	$[M + H]^+$	Metabolite Structure from LC/MS/MS	Percent at 60 minutes		
			Human	Mouse	Rat
M1[b] (H9, R6)	373		8.0	0.03	ND
M2 (H4A, H4B)	387		7.7	2.4	2.9
M3 (H3)	403		14.4	8.2	25.2
M4i	405	Parent +2O +2 H	1.8	5.4	4.6
M5i	421	Parent +3O +2 H	0.7	3.6	1.7

Type of Study	Major Findings
Detection, Structure Elucidation, and Relative Quantification of Segesterone Acetate and its Metabolites in Serum and Urine Samples of Female Cynomolgus Money s after a single SC dose of 10 mg/kg (Study 9POPUP4R1)	The metabolism of segesterone in monkeys produces a complex metabolite pattern, comprised of numerous Phase I metabolites, detected in serum and urine, and Phase II metabolites (glucuronides), detected in the urine matrix only. 
In Vitro Evaluation of Segesterone Acetate as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes (Study XT105121).	The study was performed to evaluate the ability of segesterone to inhibit the metabolism of concomitantly administered probe substrates for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 in pooled human liver microsomes. Segesterone may have the potential to cause metabolism-dependent inhibition of CYP3A4 as an increase in inhibition (26%) was observed upon preincubation in the presence of NADPH at a concentration of 1 µM.
In Vitro Evaluation of Segesterone Acetate as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes (Study XT103116)	Treatment of cultured human hepatocytes from 3 separate donors with prototypical CYP inducers resulted in the anticipated increases in CYP activity. Treatment of the hepatocytes with up to 1000 nM segesterone, caused little or no change in CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4 activity.

Segesterone Concentration (nM)	% Control Activity of the P450 Enzyme			
	CYP2C9	CYP2C19	CYP2B6	CYP3A4
10	105±28	104±58	101±22	105±66
100	99±30	104±62	103±24	106±65
1000	96±32	101±55	115±38	99±58

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>An Investigation of the Potential for Segesterone Acetate to Induce Cytochrome P450 Metabolism in Cultured Human Hepatocytes (Study M1999-056)</td><td>In primary cultures of human hepatocytes from a single donor, SA did not induce CYP1A2, 2A6, 2C9, 2D6 and 3A4 at up to 100 µM. It was an inducer of CYP2C19 at 100 µM and an inhibitor of CYP3A4 above 10 µM.
<table>
<tr><th rowspan="2">Segesterone Concentration (µM)</th><th colspan="4">% Control Activity of the P450 Enzyme</th></tr>
<tr><th>CYP2C9</th><th>CYP2C19</th><th>CYP2D6</th><th>CYP3A4</th></tr>
<tr><td>1</td><td>114±4</td><td>95±24</td><td>100±9</td><td>97±3</td></tr>
<tr><td>10</td><td>107±7</td><td>97±54</td><td>111±5</td><td>33±17</td></tr>
<tr><td>100</td><td>55±18</td><td>238±52</td><td>78±15</td><td>9±10</td></tr>
</table></td></tr>
<tr><td>In Vitro Metabolism of Segesterone Acetate by Female Human Hepatocytes (Study 6884-113) and Hepatic Microsomes (Study 6884-119)</td><td>
<table>
<tr><th>Metabolite[a]</th><th>[M + H]+</th><th>Metabolite Structure from LC/MS/MS</th><th>Present in Hepatocyte Incubations</th><th>Present in Microsomal Incubations</th></tr>
<tr><td>H1</td><td>361</td><td>  </td><td>Yes</td><td>No</td></tr>
<tr><td>H2</td><td>345</td><td>  </td><td>Yes</td><td>No</td></tr>
<tr><td>H3</td><td>403</td><td>  </td><td>Yes</td><td>Yes</td></tr>
<tr><td>H4A, H4B</td><td>387</td><td>  </td><td>Yes</td><td>Yes</td></tr>
<tr><td>H5[b]</td><td>385</td><td>  or  </td><td>Yes</td><td>Yes</td></tr>
<tr><td>H6[b]</td><td>343</td><td>  or  </td><td>Yes</td><td>Yes</td></tr>
<tr><td>H7</td><td>387</td><td>  </td><td>Yes</td><td>Yes</td></tr>
<tr><td>H8</td><td>387</td><td>  </td><td>Yes</td><td>Yes</td></tr>
</table></td></tr>
</table>

Type of Study	Major Findings
	 H19[b] 373 or No Yes H10 387 No Yes H11 387 No Yes
Excretion	
Pharmacoinetics of Segesterone Acetate –Studies on Animals; Rats, Guinea Pigs, Rabbits (Study 17247-16-220485)	Excretion into bile was studied in rats by both IV and oral administration. By both routes, about 50% of the radioactivity in the dose was excreted in bile within 6–7 hours.

Time (hr)	Cumulative % of Radioactive Dose in Bile	
	50 µg/kg IV	50 µg/kg PO
2	41	-
3	-	21-38
6	50	-
7	-	40-48

Pharmacoinetics of Segesterone Acetate –Studies on Animals; Rats, Guinea Pigs, Rabbits (Study 17247-16-220485)

Absorption, Metabolism, and Excretion of ^{3}H-segesterone Acetate Following Subcutaneous Administration to Rats (Study 6884-120)

The overall recovery of radioactivity after a single intravenous, oral or subcutaneous administration of segesterone to female rats was 70-80% within 120 hours postdose. Feces was the main route of excretion. Less than 10% of the dose was found in urine.

Time (hr)	Cumulative % of Radioactive Dose					
	50 µg/kg IV		50 µg/kg PO		50 µg/kg SC	
	Urine	Feces	Urine	Feces	Urine	Feces
8	1.2±0.5	0.0±0	3.1±2.1	0.1±0.2	3±0.8	ND
24	3.6±0.8	39.1±9.6	6.4±1.8	58.8±10	5.2±0.8	46.3±4.1
48	4.6±0.8	61.8±3.1	7.7±1.7	72±3.6	6.3±0.8	80.7±2.6
72	5.1±0.9	64.6±2.6	8.1±1.7	74.2±4.2	6.7±0.7	90.9±0.6
96	5.6±0.9	66.1±3.5	8.2±1.7	74.8±4.4	6.8±0.7	93.8±1.2
120	5.7±0.9	67±4.2	8.4±1.8	75.6±4.4	6.9±0.7	94.6±1.3

Pharmacoinetics of Segesterone Acetate –Studies on Animals; Rats, Guinea Pigs, Rabbits (Study 17247-16-220485)	In rabbit, the urinary route of excretion was slightly more important than the biliary route, accounting for approximately 50% of the dose as compared to 30% in the feces.

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
<table>
<tr><th rowspan="3">Time (hr)</th><th colspan="4">Cumulative % of Radioactive Dose</th></tr>
<tr><th colspan="2">50 µg/kg IV</th><th colspan="2">50 µg/kg PO</th></tr>
<tr><th>Urine</th><th>Feces</th><th>Urine</th><th>Feces</th></tr>
<tr><td>8</td><td>5.1±6</td><td>1.8±2.1</td><td>4.7±4.2</td><td>3.9±1.8</td></tr>
<tr><td>24</td><td>34.3±2.8</td><td>13±1</td><td>30.6±3.2</td><td>18.9±2</td></tr>
<tr><td>48</td><td>41.4±2.3</td><td>20.4±2.5</td><td>39.7±1.3</td><td>26.4±1.2</td></tr>
<tr><td>72</td><td>42.9±2.7</td><td>23.8±2.9</td><td>41.7±1.9</td><td>28.4±1.8</td></tr>
<tr><td>96</td><td>44±2.6</td><td>24.5±3.1</td><td>42.8±2.4</td><td>29.3±2.2</td></tr>
<tr><td>120</td><td>44.4±2.6</td><td>25.5±3</td><td>43.2±2.4</td><td>30.3±2.1</td></tr>
</table>
</td></tr>
<tr><td>Pharmacoinetics of Segesterone Acetate –Studies on Animals; Beagles and Rhesus Money (Study 17247-17-220485)</td><td>In Rhesus monkeys, an approximately equal percentage of the dose was excreted in urine and feces following a single oral or IV administration of segesterone.
<table>
<tr><th rowspan="3">Time (hr)</th><th colspan="4">Cumulative % of Radioactive Dose</th></tr>
<tr><th colspan="2">50 µg/kg IV</th><th colspan="2">50 µg/kg PO</th></tr>
<tr><th>Urine</th><th>Feces</th><th>Urine</th><th>Feces</th></tr>
<tr><td>8</td><td>15-26</td><td>0-10</td><td>1-11</td><td>0-0.2</td></tr>
<tr><td>24</td><td>23-31</td><td>6-14</td><td>14-24</td><td>1-4</td></tr>
<tr><td>48</td><td>27-35</td><td>22-31</td><td>17-29</td><td>16-22</td></tr>
<tr><td>72</td><td>31-36</td><td>25-38</td><td>20-31</td><td>23-29</td></tr>
<tr><td>96</td><td>31-37</td><td>25-41</td><td>21-32</td><td>24-31</td></tr>
</table>
</td></tr>
<tr><td>Heikinehimo O, Rana S, Moo-Young A, Lahteenmaki P, Gordon K. Parenteral administration of progestin Nestorone® to lactating cynomolgus monkeys: an ideal hormonal contraceptive at lactation? Human Reproduction.1999, 14 (8): 1993-1997.</td><td><u>Monkey</u> (Females, Cynomolgus)
Dose: SC implants releasing 40 µg/day
Maternal Serum Concentration: 125 ± 33 pg/mL
Maternal Milk Concentration: 217 ± 112 pg/mL
Milk/Serum Ratio: 1.68 ± 0.12
Infant Serum Concentration: Below LLQ (<5 pg/mL)</td></tr>
<tr><td colspan="2">TK data from Safety Pharmacology and Toxicology Studies</td></tr>
<tr><td>Pulmonary Evaluation of Subcutaneously Administered Segesterone Acetate at a Dose of 10 mg/g in F emale Sprague Dawley Rats (Study 1571-013, GLP)</td><td><u>Rat</u> (Females, Sprague Dawley)
T_{max} (SC): 1 h
$T_{½}$: 1.1 h
C_{max}(SC): 745 ng/mL
AUC_{inf}(SC): 1952 ng•h/mL</td></tr>
<tr><td>4-Wee Intr avaginal Toxicity Study of Segesterone Acetate Gel in Female Mice (Study 1571-001)</td><td>
<table>
<tr><th rowspan="2"></th><th colspan="6">Dose (µg/day)</th></tr>
<tr><th colspan="2">200 (1%)</th><th colspan="2">600 (3%)</th><th colspan="2">1800 (9%)</th></tr>
<tr><th>Day</th><th>1</th><th>28</th><th>1</th><th>28</th><th>1</th><th>28</th></tr>
<tr><td>T_{max} (hr)</td><td>1</td><td>1</td><td>1</td><td>2</td><td>4</td><td>2</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>14</td><td>26</td><td>91</td><td>35</td><td>99</td><td>718</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td>AUC₀₋₂₄ (ng•h/L)</td><td>39</td><td>106</td><td>155</td><td>101</td><td>519</td><td>1991</td></tr>
</table>
</td></tr>
<tr><td>3-month Subdermal Implant Toxicity Study of Segesterone Acetate in Rats (Study 01-ST-TOX-0682)</td><td><u>Rat</u> (Both sexes, Sprague Dawley)
Dose: 86 µg/day
C_{max}(Males): 2.5 ng/mL
C_{max}(Females): 3.3 ng/mL</td></tr>
<tr><td>3-month Subdermal Implant Toxicity Study of Segesterone Acetate in Female Rabbits (Study PC-ST-05-KS/89)</td><td>
<table>
<tr><th></th><th colspan="3">Dose (µg/day)</th></tr>
<tr><th></th><th>24.6</th><th>128.9</th><th>551.4</th></tr>
<tr><td>C_{serum} (ng/mL) 4w</td><td>0.1</td><td>0.7</td><td>2.6</td></tr>
<tr><td>C_{serum} (ng/mL) 8w</td><td>0.1</td><td>0.7</td><td>2.4</td></tr>
<tr><td>C_{serum} (ng/mL) 12w</td><td>0.1</td><td>0.7</td><td>3.1</td></tr>
</table>
4w 4 weeks, 8w 8 weeks, 12w 12 weeks
</td></tr>
<tr><td>12-month Subdermal Implant Toxicity Study of Segesterone Acetate in Female Rats (Study PC-ST-03-KS/89)</td><td>
<table>
<tr><th></th><th colspan="3">Dose (µg/day)</th></tr>
<tr><th></th><th>11.4</th><th>15.1</th><th>47.8</th></tr>
<tr><td>C_{serum} (ng/mL) 1y</td><td>1.0</td><td>2.5</td><td>13.6</td></tr>
</table>
1y 1 year
</td></tr>
<tr><td>12-month Subdermal Implant Toxicity Study of Segesterone Acetate in Female Cynomolgus Money s (Study PC-ST-06-KS/90)</td><td>
<table>
<tr><th></th><th colspan="3">Dose (µg/day)</th></tr>
<tr><th></th><th>30</th><th>87</th><th>395</th></tr>
<tr><td>C_{serum} (ng/mL) 1m</td><td>0.19</td><td>0.82</td><td>4.22</td></tr>
<tr><td>C_{serum} (ng/mL) 7m</td><td>0.30</td><td>1.33</td><td>6.08</td></tr>
<tr><td>C_{serum} (ng/mL) 12m</td><td>0.26</td><td>0.85</td><td>3.45</td></tr>
</table>
1m 1 month, 2m 2 months, 3m 3 months
</td></tr>
<tr><td>A Toxicoinetic Evaluatio n of Segesterone Acetate in Pregnant Rabbits (Study 1571-020, GLP)</td><td><u>Rabbit</u> (Females, New Zealand White)
Dose: 60 µg/kg/day, SC
C_{max}(GD6): 2.69 ng/mL
AUC_{24h} (GD6): 21.7 ng•h/mL
C_{max}(GD18): 3.26 ng/mL
AUC_{24h} (GD18): 28.8 ng•h/mL

<u>Rabbit</u> (Females, New Zealand White)
Dose: 250 µg/kg/day, SC
C_{max}(GD6): 17.4 ng/mL
AUC_{24h} (GD6): 92.2 ng•h/mL
C_{max}(GD18): 24.4 ng/mL
AUC_{24h} (GD18): 111 ng•h/mL</td></tr>
<tr><td>2-Year Subdermal Implant Carcinogenicity Study of Segesterone Acetate in Rats (Study 6884-103)</td><td>
<table>
<tr><th rowspan="3">Weeks</th><th colspan="6">Serum Concentrations (ng/mL)</th></tr>
<tr><th colspan="2">40 µg/day</th><th colspan="2">100 µg/day</th><th colspan="2">200 µg/day</th></tr>
<tr><th>Males</th><th>Females</th><th>Males</th><th>Females</th><th>Males</th><th>Females</th></tr>
<tr><td>4</td><td>2.67</td><td>3.85</td><td>6.08</td><td>10.08</td><td>16.08</td><td>20.04</td></tr>
<tr><td>26</td><td>1.78</td><td>2.63</td><td>4.26</td><td>6.63</td><td>10.71</td><td>13.67</td></tr>
<tr><td>79</td><td>1.67</td><td>2.41</td><td>3.04</td><td>5.41</td><td>6.08</td><td>12.93</td></tr>
<tr><td>104</td><td>0.78</td><td>1.52</td><td>2.22</td><td>3.93</td><td>3.41</td><td>6.74</td></tr>
</table>
</td></tr>
</table>

Type of Study	Major Findings
4-Wee Local T oxicity Study of Segesterone Acetate Contraceptive Vaginal Rings in Cynomolgus Mone ys (Study 6884-102)	**Monkey (*Female, Cynomolgus*)** **Dose**: 80-100 µg/day **C_{serum} (Day 4)**: 666 ± 69 pg/mL **C_{serum} (Day 15)**: 805 ± 75 pg/mL **C_{serum} (Day 29)**: 799 ± 21 pg/mL

5.4.2. Pharmacokinetics of Ethinyl Estradiol

The bioavailability of EE from the 150/15 CVS was compared to an approved oral contraceptive product delivering doses of levonorgestrel (150 µg/day) and EE (30 µg/day) in each of the active tablets (Nordette 21; Wyeth Laboratories) for 21 days. The serum concentration of EE peaked shortly after insertion of the ring on Day 1. After 21 days, the EE plasma exposure of patients was less with the vaginal ring than with the approved oral contraceptive product. Overall, the bioavailability of EE was very similar by the oral or vaginal routes of administration.

Type of Study	Major Findings
Phase 1 Cross-over Study to Evaluate the Kinetics of Ethinyl Estradiol and Segesterone Acetate Delivered Vaginally from a Silicone Rubber Ring as Compared with Oral Administration of Ethinyl Estradiol and Levonorgestrel in an Oral Contraceptive Pill (Nordette 21®). Study 330	(b) (4)

5.5. Toxicology

5.5.1. General Toxicology of Segesterone Acetate

The toxicology of SA (segesterone) was investigated in mice, rats, rabbits and monkeys. None of the endocrinological effects were observed following oral administration, highlighting the rapid and extensive first pass metabolism of SA across nonclinical species. For this reason, oral studies provided very limited information regarding the toxicological properties of the parent molecule, and their usefulness was limited to the evaluation of the toxicity of segesterone's metabolites. The relevant toxicology studies for SA are therefore limited to parenteral routes of administration.

Single-Dose Subcutaneous Toxicity Study in Female Rats and Mice (Study PC-ST-01-KS/89 and PC-ST-02-KS/89, GLP)

Single subcutaneous injections of segesterone at 10 mg/kg in rats and 8.85 mg/kg in mice were well tolerated. All animals survived the 14-day observation period and exhibited no change in behavior, respiration or gross appearance. No changes were seen at necropsy and the organ weights were not different from the vehicle controls.

4-Week Intravaginal Toxicity Study in Female Mice (Study 1571-001, GLP)

A 4 week GLP intravaginal study was conducted in CD1® female mice, with SA administered intravaginally each day in 0.02 mL of propylparaben gel containing 1, 3 and 9% segesterone (10, 30, and 90 mg/kg/day) for 28 days.

Plasma concentrations of SA appeared to be similar on Days 1 and 28. AUC_{0-24} and C_{max} increased with the percentage of segesterone in the administered gel in a less than proportional ratio.

All animals survived to their scheduled terminal necropsy. No effect of treatment was seen in clinical findings, food consumption, hematology, clinical chemistry, macroscopic pathology examinations or organ weights. A slight test article related increase in mean body weight gain was observed in females treated with 3% and 9% SA but was not considered to be adverse. A segesterone-related alteration of the reproductive cycle in female mice was observed during microscopic examination. All animals treated with 3% and 9% gels had vaginal morphology consistent with diestrus. These changes are typical of those seen in female mice treated with progestins, are related to the pharmacology of segesterone, and not considered adverse. The NOAEL was determined to be 90 mg/kg/day in this study.

3-month Subdermal Implant Toxicity Study in Rats (Study 01-ST-TOX-0682, non-GLP)

In a non-GLP 3-month subdermal implant toxicity study, Sprague-Dawley rats were administered SA in Silastic capsules at the average daily dose of 86 µg/day (175 µg/kg/day for males and 286 µg/kg/day for females, on a live weight basis, respectively).
Serum concentrations of segesterone treated males and females on Day 90 were 2.50 ng/mL and 3.32 ng/mL, respectively.

No unscheduled death occurred in the study. The administration of SA disrupted the normal estrus cycles in females, inhibiting ovulation and stimulating mammary growth and milk secretion. Segesterone treatment produced a significant increase in female body weights (21%) as compared to controls but had no effect on the body weights of the males.

Minor changes in eosinophils and neutrophils counts, BUN/creatinine ratio, triglyceride values, calcium and albumin levels, and total bilirubin were also observed. None of these changes were deemed physiologically significant or adverse.

Mean serum testosterone in male was 4.29 ng/mL for controls, and 1.85 ng/mL for treated animals. Luteinizing hormone levels were 46.0 ng/mL for controls and 29.4 ng/mL for treated male rats.

In the male, segesterone treatment resulted in decreases in heart, kidney, liver, testes, epididymis, prostate and seminal vesicle weights, and an increase in adrenal weights. Although the smaller testes, epididymis, prostate and seminal vesicles were likely secondary to reductions in serum levels of testosterone and LH, these changes were not associated with microscopic observations. In the female, segesterone treatment resulted in an increase in heart and liver weights and a significant decrease in pituitary, ovarian and uterine weights. Histological evaluation of tissues from segesterone treated rats only revealed a segesterone-dependent effect on the primary and secondary sex organs of female rats, with no evidence of any other organ toxicity. The ovaries were anovulatory and without corpora lutea. The endometrial and vaginal mucosae were in diestrus and the mammary glands had mild to moderate acinar development with some evidences of secretory activity.
These changes in male and female reproductive tissues are typical of those seen in rats treated with progestins, and are consequences of the pharmacology of SA. The changes in liver weight (19% decrease in males and 18% increase in females) or heart weight (9% decrease in males and 13% increase in females) were not associated with histologic evidences of cellular injury or hypertrophy and were not considered adverse. The NOAEL in this study was 175 µg/kg/day for males and 286 µg/kg/day for females.

3-month Subdermal Implant Toxicity Study in Rabbits (Study PC-ST-05-KS/89, GLP)
In a 3-month subdermal implant toxicity study, female New Zealand White rabbits were administered silastic implants releasing doses of 0, 24.6, 128.9 or 551.4 µg/day, corresponding approximately to doses of 0, 15, 70 and 300 µg/kg/day).

There were no drug-related deaths in the study. Compared to controls, MCHC, MCV and the percentages of neutrophils, eosinophils and basophils were elevated in segesterone-treated groups. The serum levels of glucose, total proteins, albumin, globulin, cholesterol and triglycerides were also elevated in response to segesterone treatment, but all hematology and clinical chemistry parameters remained within the range of normality.

Segesterone treatment produced a decrease in uterine weight and an increase in liver weight at all doses, and a decrease in adrenal and thyroid weights in the high dose group. These effects were associated with adrenocortical atrophy in the mid- and high-dose groups. Hepatocytes in the high-dose group were enlarged with a swollen cytoplasm and excess glycogen content. The mammary glands of all treated animals and the uterine glands of high-dose animals were mildly dilated. Segesterone acetate displayed both a progestin activity on the reproductive organs and a glucocorticoid-type activity on the liver and the adrenal glands. The NOAEL in this study was 70 µg/kg/day.

12-month Subdermal Implant Toxicity Study in Rats (Study PC-ST-03-KS/89, GLP)

In a GLP 12-month subdermal toxicity study, female CD® rats were administered SA using subdermal silastic implants. The release rates were 0, 11.4, 15.1 and 47.8 µg/day, corresponding approximately to doses of 0, 75, 100 and 320 µg/kg/day.

A dose related increase in mean SA serum concentration was observed between the treatment groups, with the average serum concentration for the high dose (48 µg/day) reaching 36809 pmol/L at study termination.
Seven unscheduled deaths were reported in the study, one in the control group and three each in the low and high dose groups, occuring all between study day 292 and study day 359. All unscheduled deaths presented with a combination of enlarged mammary and pituitary glands. In addition, several rats across all dose groups were found at study termination with either mammary or pituitary masses. However, the incidence of mammary or pituitary lesions in the segesterone treatment groups was not significantly different from control. Uterine weights were significantly lower in segesterone treated rats as compared to vehicle controls. Histologically, segesterone effects were evident in the uterus, ovaries, vagina and mammary glands. Corpora lutea were absent from the ovaries of high dose animals suggesting a complete inhibition of ovulation. The uterus and vagina from high dose rats were characteristic of diestrus while those of the untreated and vehicle controls were primarily in proestrus. The mammary gland of high dose rats was unstimulated with little ductal or lobuloalveolar development whereas those from vehicle controls displayed varying degrees of secretory activity. Segesterone treatment also caused an increase in body weight gain and serum glucose as compared to vehicle, and a decrease in cholesterol, total proteins and globulin serum levels. These changes remained within the range of normality for untreated rats.

Segesterone is a progestin and its inhibition of gonadotropins secretion from the pituitary gland suppresses ovarian functions. All the observed effects in this study can therefore be related to excessive pharmacology of the drug. Due to the unscheduled deaths in the low dose group, no NOAEL could be established in this study.

12-month Subdermal Implant Toxicity Study in Cynomolgus Monkeys (Study PC-ST-06-KS/90, GLP)

In a GLP 12-month toxicity study, female cynomolgus monkeys were administered segesterone via subdermal silastic implants. The release rates of segesterone were 0, 30, 87 and 395 µg/day, corresponding approximately to doses of 0, 10, 30 and 130 µg/kg/day.

There were no drug-related clinical observations or unscheduled deaths in the study. The menstrual cycle of all treated animals essentially stopped within 10 days of test article implantation and a dose-related enlargement of the uterus was reported during physical examination. At necropsy, the only treatment related change was an enlarged uterus in many of the treated animals, which correlated histologically with myometrial hypertrophy, endometrial deciduation and inhibition of endometrial gland growth.

Hormonally induced changes were also seen at all treatment levels in the ovaries, cervix and vagina. Segesterone inhibited ovulation and the development of corpora lutea but allowed follicular growth up to the intermediate follicle stage. The cervical gland of all treated animals was markedly branched and contained copious amounts of thick mucous secretions. The vaginal mucosa of all treated animals was lined by very thin, non-cornified epithelium indicating minimal to non-existent endogenous estrogen stimulation.

All the effects reported in this study were consequences of the pharmacology of segesterone, and the no-observable adverse-effect-level for a year of dosing was 130 µg/kg/day. Because of the sustained-release of SA, the classical parameters of pharmacokinetics (C_{max} and AUC) could not be determined, but a dose of 395 µg/day maintained plasma concentrations between 9.3±3.2 and 18.3±4 nM over the course of 12 months.

5.5.2. Genetic Toxicology of Segesterone Acetate

Bacterial Reverse Mutation Assay (Study PC-ST-14-KS/99, GLP)

The mutagenic potential of segesterone was evaluated in the bacterial reverse mutation assay using *Salmonella Typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2 uvrA, in the presence and absence of Aroclor-induced rat liver S9 fraction. The study was considered valid and SA was not mutagenic when tested up to a dose level of 5000 µg/plate, with or without a metabolic activation.

Chromosome Aberrations in Human Peripheral Blood Lymphocytes (Study PC-ST-11-KS/94 and PC-ST-15-KS/99, GLP)

Segesterone acetate was tested in human peripheral blood lymphocytes for the ability to induce chromosomal aberrations in the absence or presence of Arochlor-induced S9 fraction. In two separate valid assays, SA did not cause chromosome aberrations in human lymphocytes at concentrations up to 100 µg/mL, with or without metabolic activation.

Micronucleus Cytogenic Assay in Mice (Study PC-ST-10-KS/94 and PC-ST-16-KS/99, GLP)

The ability of SA to increase the incidence of micronucleated polychromatic erythrocytes in the bone marrow was investigated in male and female mice. In the first assay, the animals received intraperitoneal injections of 2.5–10 mg/kg SA on two consecutive days with the two administrations separated by about 24 hours. In the second assay, mice were given single intraperitoneal injections of 500–2000 mg/kg SA. Segesterone acetate did not significantly increase the incidence of micronucleated polychromatic erythrocytes in bone marrow slides at any dose, and is not considered clastogenic in mice at doses up to 2000 mg/kg.

5.5.3. Carcinogenicity of Segesterone Acetate

2-Year Intravaginal Carcinogenicity Study in Mice (Study 1571-002, GLP)

In a 2-year carcinogenicity study in female CD1 mice, segesterone was administered intravaginally each day in gels of 0, 0.3%, 1% and 3% segesterone, providing doses of 0, 3, 10 or 30 mg/kg/day.

There was no test-article related difference in mortality between control, sham and segesterone-treated animals. Segesterone at 10 and 30 mg/kg/day produced modest but statistically significant increases in food consumption and mean body weights. No treatment-related changes in hematology, clinical chemistry or urinalysis were observed at any dose. The highest dose of segesterone (30 mg/kg/day) was found to produce an increased incidence of adenocarcinoma and lobular hyperplasia in the breast. In addition, the incidence of vaginal subchronic or chronic inflammation was increased in all segesterone gel dose groups when compared to vehicle and sham controls.

Based on the results of this 2-year carcinogenicity study, 30 mg/kg/day is considered carcinogenic in female mice. Segesterone, at all concentrations, was an irritant when administered intravaginally in a gel, producing inflammation of the proximal, mid- and distal vaginal mucosa. Exposure was not measured in the mouse carcinogenicity study, but relevant systemic exposure values were obtained in the 4-week intravaginal dose-selection study in mice (Study 1571-001). In that study, the AUC0-24h on day 1 following administration of 1% gel was 39.1 ng·h/mL and 155 ng·h/mL following the administration of 3% gel. Assuming similar exposures, the carcinogenic dose of 30 mg/kg/day is 10-fold greater than the AUC of SA in cycle one of clinical study 300PK, and the non-carcinogenic dose of 10 mg/kg/day is approximately 3-fold greater than the AUC of SA in cycle one of clinical study 300PK.

2-Year Subdermal Implant Carcinogenicity Study in Rats (Study 6884-103, GLP)

In a 2-year carcinogenicity study, segesterone was administered to 5 groups of in Sprague Dawley rats by subdermal Silastic implants. The release rates of segesterone were 0, 40, 100 or 200 µg per day (267, 667, 1333 µg/kg/day) and a sham control was included in the design. Serum samples on weeks 4, 13, 36, 53, 79, 93 and 104 showed continuous segesterone exposure throughout the study but with a decrease in circulating concentrations over time. Exposures increased with increasing dose in both sexes but the plasma levels of segesterone were higher in females than in males.

There were no treatment-related effects on survival or clinical signs in either males or females. Although all animals were provided a controlled quantity of diet daily, segesterone administration produced significant body weight increases at all doses in the females. This effect was not observed in the males. No treatment-related changes in hematology, clinical chemistry or urinalysis were observed at any dose in both sexes.

Unlike the mice, the high dose of 200 µg/day decreased the incidence of pituitary and mammary neoplasms in the rats. Non-neoplastic treatment-related findings consisted of a decreased incidence of tubular hyperplasia normally observed in aged rat ovaries, an increased incidence of endometrial glands dilation/secretion in the uterus and an increased incidence of activated/secreting mammary gland tissues. These effects have been shown in previous rat studies and are a consequence of the pharmacology of segesterone.

The results of this 2-year carcinogenicity study in rats did not provide evidence of tumorigenic effect associated with the presence of SA implants at doses up to 1333 µg/kg/day.

5.5.4. Reproductive and Developmental Toxicology of Segesterone Acetate

Fertility and Early Embryonic Development

Return to Fertility after 3-Month Subdermal Implant Administration in Rats (Study PC-ST-03-KS/89, GLP)

Satellite groups within the 12-month toxicity study of subdermal implants in female CD® rats were used to assess the return to fertility after exposure to a SA dose of 59 µg/day for 90 days (393 µg/kg/day).

Following three months of treatment, the implants were removed and the animals allowed to recover for seven weeks. Daily vaginal lavages established the return to estrus cyclicity. Cycling females were housed with adult male rats for 5 consecutive days and the presence of sperm in the vagina and copulatory plug(s) was checked daily. The females were euthanized 10 to 14 days after confirmation of mating and the number of implantation sites and corpora lutea were recorded from each female.

Segesterone acetate administration for 90 days did not impair the return to fertility in female CD® rats. More females became pregnant after segesterone treatment than in the vehicle control group, and segesterone had no effect on the number of corpora lutea or the number of implantations recorded in the animals.

Embryo-Fetal Development

Embryo-Fetal Toxicity and Teratogenic Potential Study of segesterone Administered Subcutaneously to Presumed Pregnant Female Rats (Study PC-ST-07-KS/91, GLP)

Four groups of Crl:CD® BR VAF/plus® pregnant female rats received daily subcutaneous injections of segesterone in solution between gestational day 6 and 15. Dose levels were 0, 10, 50 and 250 µg/kg/day respectively. On day 20 of presumed gestation, all rats were sacrificed and all uteri were examined to record the number of implantations, early and late resorptions, live and dead fetuses and the presence of corpora lutea. Fetus weight and sex were determined and all live fetuses were prepared for histology.

There were no treatment-related effects on survival or clinical signs in the dams. The litter averages for corpora lutea, implantations, litter size, live fetuses, early and late resorptions, fetal sex ratios and number of dams with resorptions or live fetuses were comparable in all four groups.

The fetal alterations observed during gross external, soft tissue or skeletal examination occurred in the groups treated with segesterone at frequencies that were either not

significantly different from the controls or significantly reduced rather than increased. No segesterone-treated group exhibited any unique type of fetal malformation.

The subcutaneous administration of SGT to pregnant rats at doses up to 250 µg/kg/day during gestation days 6-15 did not cause maternal toxicity, embryotoxicity or teratogenicity.

Embryo-Fetal Toxicity and Teratogenic Potential Study of segesterone Administered Subcutaneously to Presumed Pregnant Female New Zealand White Rabbits (Study PC-ST-08-KS/91, GLP)

Four groups of artificially inseminated female New Zealand White rabbits received subcutaneous injections of segesterone from gestational day 6 through gestational day 18. The animals were administered a daily dose of 0, 10, 50 and 250 µg/kg in an aqueous solution of Molecusol™ (hydroxypropyl-β-cyclodextrin). On day 29 of presumed gestation, all surviving rabbits were sacrificed and necropsied. The number and distribution of implantations, early and late resorptions, live and dead fetuses and the number of corpora lutea in each ovary were recorded. Each fetus was weighed and examined for external alterations, visceral alterations and sex and stained for skeletal deformities.

The pharmacokinetic parameters of segesterone administered by subcutaneous injection to pregnant female New Zealand White rabbits were investigated in a supporting separate study (Study 1571-020). The systemic exposure (AUC_{24h}) increased in a generally proportional manner and the C_{max} values increased in a greater than dose proportional manner. No accumulation of segesterone was observed following repeated administration from G6 to G18.

There were no treatment-related effects on survival, food consumption or body weight gain of the does. One animal in the 10 µg/kg/day dose group aborted on day 20 and one 250 µg/kg/day dosage group rabbit showed signs of genital bleeding on days 22 and 24 of gestation, followed by resorption of the entire litter. The high dose of 250 µg/kg/day increased embryo death and the litter average number of resorptions, the fraction of resorbed conceptuses and the number of does with any resorptions.

All other indicators of fetal health, i.e. litter averages for corpora lutea, implantations, fetal body weights and sex ratios were comparable among control and segesterone groups. The incidence of interrelated malformations of the vertebrae and/or ribs was increased in the high dose group. These included cervical hemivertebrae, unilateral, fused or misaligned vertebrae or ribs and thoracic vertebrae with small arches. Several soft tissue malformations were also recorded but considered unrelated to treatment since these were single events and their incidences remained within the historical control ranges.

The maternal no-observable-adverse-effect-level (NOAEL) for segesterone was 250 µg/kg/day corresponding on day 18 to an AUC_{24h} of 111 ng*hr/mL. The developmental NOAEL for segesterone was 50 µg/kg/day, corresponding approximately on day 18 to an AUC_{24h} of 28 ng*hr/mL.

Prenatal and Postnatal Development

Perinatal and Postnatal Reproduction Toxicity Study of segesterone Administered Subcutaneously to Presumed Pregnant Female Rats (Study PC-ST-09-KS/92, GLP)

Four groups of Crl:Cd®Br Vaf/Plus® presumed pregnant female rats received daily subcutaneous injections of segesterone in solution from gestational day 15 through either gestational day 25, or through day 21 of lactation. Dose levels were 0, 10, 50 and 250 µg/kg/day respectively in Phase I of the study, and 0 and 2 µg/kg/day in Phase 2.

The observations of individual births were discontinued prior to completion of all births during Phase I of the study because of prolonged gestation and parturition in all groups. Rats that did not deliver or complete delivery of a litter by day 25 of (presumed) gestation were sacrificed, and examined for gross lesions. The uteri of apparently nonpregnant rats were excised and examined. Fetuses found in rats that had partially delivered were all dead. Delivered pups were either found dead or stillborn.

Two, one and five rats in the 0 (Vehicle), 50 and 250 µg/kg/day dosage group respectively, were found dead or sacrificed for humane reasons. All segesterone-related unscheduled death were the consequence of prolonged gestation and delivery complications. Body weight gains, feed consumption and body weights were comparable among the dosage groups during gestation. The 50 µg/kg/day dosage group had significantly reduced body weight on day 1 of lactation, possibly related to the stress of prolonged gestation and parturition.

The high dose (250 µg/kg/day) of segesterone significantly increased the numbers of rats with apparent vaginal bleeding and observations related to dystocia and morbidity (red, black or brown perivaginal substance, pale appearance, coldness to touch and labored breathing). Increases in the duration of gestation were noted in the 2 µg/kg/day and higher dosages of segesterone. The duration of parturition was increased in the 10, 50 and 250 µg/kg/day dosage groups, and the cause of the increased perinatal pup deaths. Only two out of 25 high dosage group rats delivered liveborn pups. In groups given 50 and 250 µg/kg/day, a significant maternal mortality during parturition was also recorded.

Feminization of male pups, as marked by an increase of the anogenital distances was evident in the 10 and 50 µg/kg/day dosage groups on day 1 postpartum. This effect had disappeared on day 21 postpartum. No clinical or pathological observations in the pups were attributable to segesterone.

The maternal and reproductive no-observable-effect-level (NOEL) for segesterone is less than 2 µg/kg/day, as demonstrated by the weight loss on days 1 to 4 of lactation and slight increase in the duration of gestation recorded at that dose. The NOEL for viability and growth in the offspring is also less than 2 µg/kg/day since dosages of 2 µg/kg/day and higher caused perinatal mortality.

5.5.5. Other Toxicology Studies of Segesterone Acetate

4-Week Local Toxicity Study of Segesterone Contraceptive Vaginal Rings in Cynomolgus Monkeys (Study 6884-102, GLP)

Segesterone-containing vaginal rings were inserted in the vagina of five female cynomolgus monkeys and remained *in situ* for 4 weeks. The ring system released SA at a rate of approximately 80 to 100 µg/day. A control group of five animals received a placebo ring containing no SA.

The serum levels of SA in treated monkeys increased to 2.244 ± 0.219 nM by Day 8 and remained in this range through the remainder of the treatment period (Day 29).
All monkeys survived until the scheduled sacrifice. There were no treatment-related clinical observations, body weight changes, or macroscopic findings.

Monkeys treated with SA had an increased mean uterus weight and uterus-to-body weight ratio which corresponded microscopically to a secretory (progravid) endometrium and a thickened myometrium. By contrast, the endometrium from all control monkeys was in a follicular (proliferative) phase of growth. Morphologic differences were also noted in the mucosal epithelium of the vagina and cervix between the control and SA-treated monkeys; these changes were attributed to the pharmacologic effects of SA on the reproductive tract. There were no local toxic effects of SA when delivered to monkeys via vaginal rings for 4 weeks. The NOAEL in this study was 40 µg/kg/day, corresponding to a SA serum concentration 4.4-fold greater than the Cycle 1 average concentration in clinical studies.

5.5.6. Summary of Toxicity for Ethinyl Estradiol

The safety of EE is supported by a significant amount of information available in the literature, public databases and within the FDA at the proposed dose and route of administration. The information in this review was summarized from NIH Publications 10-5888 and 10-5889, the National Toxicology Program (NTP) technical report on the toxicology and carcinogenesis of EE, the EE monograph from the International Agency for Research on Cancer (IARC), the EE review conducted by the International Program on Chemical Safety (IPCS, monograph 221) and the review by Maier *et al.* in Regulatory Toxicology and Pharmacology, 2001, 34; 56-61.
In brief, the acute toxic dose for EE in rodents ranges from 0.5 to 5 g/kg, with the death of the animals attributed to liver and kidney injuries. Repeat dose toxicity studies have highlighted the exaggerated pharmacology effects of EE on the reproductive organs such as hypertrophy of the uterus, vaginal keratinization, the development of mammary glands and testicular atrophy in males. At supra-physiological doses, the toxicity of EE is mainly observed in the liver and the hematopoietic tissues. In rodents, EE at doses above 1 mg/kg/day inhibits bile production and excretion, leading to cholestasis and subsequent hepatic injury. The NOEL for cholestasis in rats is approximately 0.25 mg/kg, with some strain variations. Dogs appear less sensitive to the cholestatic effects and doses above 1 mg/kg/day EE lead instead to progressive thrombocytopenia and depressed hematopoiesis.

Ethinyl estradiol is not mutagenic in bacterial genotoxicity assays, but can induce chromosomal aberrations in some mammalian cell systems. In mice given a single IP injection of 1 or 10 mg/kg, the incidence of bone marrow micronuclei was increased. EE can act as a tumor promoter following initiation by a DNA-reactive compound. In rats, EE at doses of 0.3 to 4 mg/kg/day for two years did not increase the overall incidence of tumors or the probability of tumor development, but altered the incidence of tumor types, favoring hepatocellular adenomas, uterine polyps, pituitary adenomas and mammary gland tumors. In dogs, the chronic administration of estrogen/progestin combination elicited alopecia, pyometra and hematotoxicity. However, in five-year toxicity studies, EE in combination with Norethindrone Acetate (NA) (1:50 ratio) at doses up to 25 mg/kg/day failed to produce an increase in mammary tumors in beagle dogs. Similarly, female rhesus monkeys treated for 10 years with Norlestrin (EE/NA 1:50) up to 2.55 mg/kg/day showed no systemic toxicity or increased incidence of tumors.

Ethinyl estradiol, through its pharmacological action, can alone or in combination with progestins, prevent reproduction. The mechanism of this contraceptive effect is complex and involves impairment of the fertilized egg transport in the fallopian tubes and an alteration of the uterus lining that prevents implantation. In reproductive toxicity studies, EE was embryo lethal but not teratogenic in mice, rats or rabbits. Pregnant rhesus monkeys given doses of 5 to 25 mg/kg Norlestrin (EE/NA 1:50) during early or late gestation as well as throughout the organogenesis period had an increased incidence of fetal mortality, but the surviving offspring were devoid of teratogenic or histologic findings and did not exhibit abnormalities in neurological functions during the first year of life.

6. Clinical Pharmacology

6.1. Executive Summary

Segesterone Acetate/Ethinyl Estradiol (SA/EE) contraceptive vaginal system (CVS) is a progestin/estrogen combination hormonal contraceptive (CHC). Segesterone is a synthetic progestin and is considered as a new molecular entity (NME) in the US. SA/EE CVS contains 103 mg SA and 17.4 mg EE, which releases on average 150 µg/day of SA and 13 µg/day of EE. The applicant conducted 2 Phase III studies to support safety and efficacy of SA/EE CVS.

6.1.1. Recommendations

The Office of Clinical Pharmacology, Divisions of Clinical Pharmacology-3 and Pharmacometrics have reviewed the information contained in NDA 209627 and recommend approval of this NDA. The key review issues with specific recommendations/comments are summarized in the table below:

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	• Two pivotal Phase III studies (Study 300A and 300 B) demonstrated the safety and efficacy of SA/EE CVS for the proposed indication of prevention of pregnancy. • Dose-dependent suppression of ovulation provides supportive evidence of efficacy.
General dosing instructions	• One SA/EE CVS is inserted in the vagina. The ring should remain in place continuously for three weeks, followed by a one-week ring-free interval. SA/EE CVS is designed to be used for up to 13 cycles (1 year).
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Do not use SA/EE CVS in women with liver disease such as acute viral hepatitis or severe (decompensated) cirrhosis of the liver. • Do not use SA/EE CVS in women with renal impairment. • Use a back-up or alternative method of contraception when enzyme inducers are used with SA/EE CVS • Do not use oil-based vaginal products with SA/EE CVS
Labeling	Refer to Section 14 for the review team's recommendations.
Bridge between the to-be-marketed (TBM) and clinical trial formulations	There were minor (b) (4) manufacturing process changes between clinical trial and TBM products, which were bridged by in vitro dissolution studies (see Biopharmaceutics review).
Other (specify)	None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics Mechanism of action and pharmacodynamics (PD)

SA/EE CVS is a fixed-dose CHC, which prevents pregnancy primarily by suppressing ovulation.

Pharmacokinetics (PK) of SA and EE from SA/EE CVS

Absorption

Median T_{max} of SA and EE following vaginal administration of SA/EE CVS was around 2 hours in Cycle 1, Cycle 3, and Cycle 13. Concentrations of both components declined after T_{max} and became more constant after 96 hours post-dose. The (b) (4) release of SA and EE as indicated by C_{max} values was most significant upon initial use of the vaginal ring and became less prominent in subsequent cycles (Figure 2).

In vivo Release Rate:

Based on residual amounts of SA and EE in SA/EE CVS after 13 cycles of use, average daily release rates were 150 µg/day for SA and 13 µg/day for EE. (See Biopharmaceutics Review).

Note: Although the determined actual in vivo release rates of SA and EE from Annovera™ are 150 µg/day and 13 µg/day, respectively, the remaining review denotes Annovera™ as SA/EE 150/15 CVS*. This is to be consistent with other SA/EE dose combinations (i.e., SA/EE 200/15 CVS and SA/EE 150/20 CVS) studied under this NDA.*

Distribution

The volume of distribution of SA was 19.6 L/kg (Study POP-648). SA is approximately 95% bound to human serum proteins and has negligible binding affinity for sex hormone-binding globulin (SHBG). EE is highly (98.5%) but not specifically bound to serum albumin.

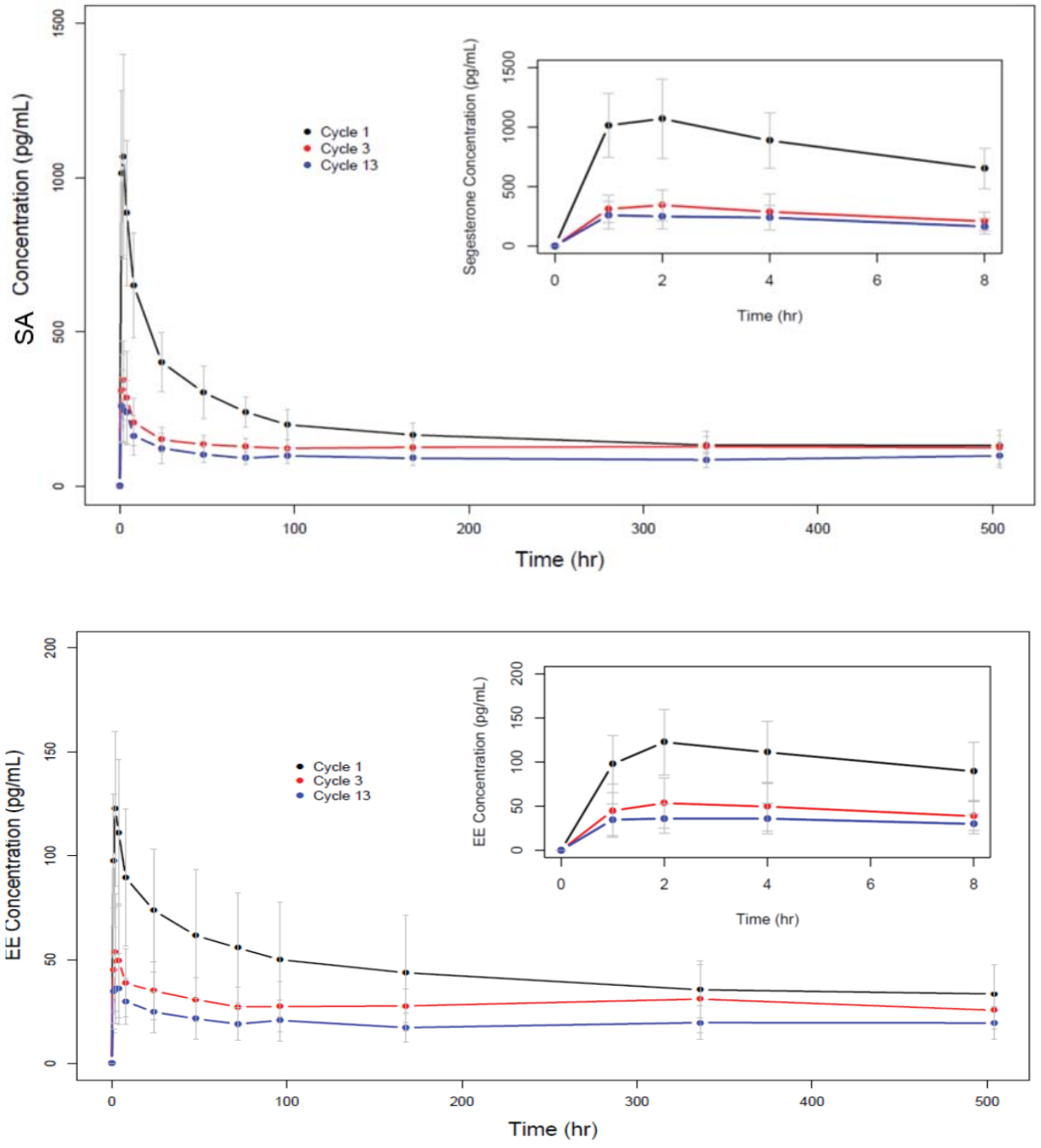
Metabolism

In vitro data shows that both SA and EE are metabolized by cytochrome P450 (CYP) 3A4. In human serum, two oxidative metabolites (5α-dihydro- and 17α-hydroxy-5α-dihydro metabolites) constitute 50% of exposure relative to SA. Both metabolites are not considered as active metabolites with 10-fold higher EC_{50} to progesterone receptor than that of SA. EE is primarily metabolized by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as sulfate and glucuronide conjugates. The hydroxylated EE metabolites have weak estrogenic activity.

Excretion

Mass balance study of SA was not conducted. The median apparent terminal elimination half-life ($T_{1/2}$) of SA is approximately 3.7 hours. EE is known to be excreted in the urine and feces as glucuronide and sulfate conjugates, and it undergoes enterohepatic recirculation. The median half-life ($T_{1/2}$) for EE from SA/EE CVS is 16.5 hours.

Figure 2 Mean SA and EE Serum Concentrations-Time Profiles Delivered by SA/EE CVS (Study 300-PK)



6.2.2. General Dosing and Therapeutic Individualization

General Dosing

One SA/EE CVS is inserted in the vagina. The ring must remain in place continuously for three weeks, followed by a one-week ring-free interval. SA/EE CVS is designed to be used for up to 13 cycles (1 year).

Therapeutic Individualization

Hepatic Impairment

The effect of hepatic impairment on the PK of SA/EE CVS has not been studied. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal and CHC causation has been excluded.

Renal Impairment

The effect of renal impairment on the PK of SA/EE CVS has not been studied. Given the lack of mass balance study and renal impairment study, it is not known whether renal excretion plays a significant role in the clearance of SA and/or metabolites. Therefore, SA/EE CVS is not recommended in patients with renal impairment.

Drug-Drug Interaction (DDI)

- DDI with other vaginal products: Clinical DDI Study (Study 571) showed that a single-dose vaginal administration of an oil-based 1200 mg miconazole suppository increased the systemic exposure of EE and SA by 67% and 19%, respectively. Following multiple-doses of 200 mg miconazole vaginal suppository, the systemic exposure of EE and SA increased by 42% and 27%, respectively. Water-based vaginal miconazole cream had no effect on SA/EE CVS. Therefore, concurrent use of oil-based vaginal products should not occur with SA/EE CVS use due to acute and potential long-term effect on the ring. If there is a need to treat a vaginal condition, water-based vaginal cream or oral therapy may be used concurrently with the ring.

- CYP-mediated DDI: No clinical DDI studies have been conducted to assess the effects of strong CYP3A induction and inhibition on the PK of SA and EE from SA/EE CVS. Considering similar metabolic pathway of progestins (i.e., via CYP3A4) and EE as a commonly used estrogen component in CHCs, CHC class labeling is applied to describe the general trend of PK changes of SA/EE CVS in the presence of CYP3A modulating drugs and support the management strategy for CYP-based DDI with SA/EE CVS. Particularly, decreased exposure of the estrogen and/or progestin component of CHCs may potentially diminish the effectiveness of CHCs and may lead to contraceptive failure or an increase in breakthrough bleeding. An alternative method of contraception or a backup method should be used when enzyme inducers are used with CHCs.

Obesity

SA and EE concentrations decreased with increased body weight. There was limited information on the safety and efficacy of SA/EE CVS in females of reproductive potential with BMI >29.0 kg/m^2 due to insufficient number of obese subjects in the Phase III studies.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	CHC lowers the risk of becoming pregnant primarily by suppressing ovulation.
Active Moieties	SA and EE
QT Prolongation	No QT interval prolongation of clinical concern was observed at a single i.v. bolus dose of 200 µg SA.
General Information	
Bioanalysis	SA and EE concentrations in serum were measured using validated GC-MS/MS methods. A summary of the method validation reports is included in Section 22.1.1.
Healthy vs. Patients	The target population of SA/EE CVS are healthy pre-menopausal women
Drug exposure at steady state (Mean ± SD)	SA/EE CVS is to be used under a 21/7-day in/out regimen in each cycle with a total of 13 cycles. SA $AUC_{0\text{-}504h}$ for Cycles 1 and 13 were 96243 ± 16881 and 47162 ± 10148 pg•h/mL, respectively. EE $AUC_{0\text{-}504h}$ for Cycles 1 and 13 were 22158 ± 9795 and 9568 ± 4059 pg•h/mL, respectively.
Minimal effective dose or exposure	Phase III studies assessed the efficacy (Pearl Index) of SA/EE CVS at one dose level, i.e., 150 µg/day SA combined with 15 µg/day EE[1]. See Pharmacodynamics section below
Maximally tolerated dose or exposure	Maximally tolerated dose has not been established. SA/EE 200 µg/15µg CVS and SA/EE 150 µg/20 µg CVS were studied in healthy women for 1 year.
Pharmacodynamics	Data showed when SA/EE CVS was used as directed, luteal activity, as measured by progesterone and E2 levels, remained adequately suppressed
Dose Proportionality	Slightly less than dose proportional in the dose range of 50-150 µg/day SA
Accumulation	SA and EE concentrations decrease to zero during 7-day ring-free period. No residual concentrations are accumulated to the subsequent cycle.

Variability	SA CV% for C_{max}: 27~39% and $AUC_{0\text{-}21days}$: 17~22% EE CV% for C_{max} : 30~53 % and $AUC_{0\text{-}21days}$: 32~42%
Absorption	
Bioavailability	The absolute bioavailability in humans has not been established.
T_{max} (Median)	SA: 2.0 hours; EE: 2.0 hours
Food effect	N/A
Distribution	
Volume of Distribution	SA: 19.6 L/kg
Plasma Protein Binding	Fraction unbound of SA in human plasma is 5%. SA has negligible binding affinity for SHBG.
Elimination	
Terminal Elimination half-life (Mean ± SD)	SA: 4.5±3.4 hours; EE: 15.1 ± 7.5 hours from SA/EE CVS
Metabolism	
Primary metabolic pathway(s)	In vitro data shows that SA is primarily metabolized by CYP 3A4. In human serum, two oxidative metabolites (5α-dihydro- and 17α-hydroxy-5α-dihydro metabolites) constitute 50% of exposure relative to SA. Both metabolites are not considered as active metabolites with EC_{50} to progesterone receptor 10- fold higher than that of SA. EE is primarily metabolized by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as sulfate and glucuronide conjugates. The hydroxylated EE metabolites have weak estrogenic activity[2].
Excretion	
Primary excretion pathways (% dose) ±SD	Unknown due to lack of mass balance study
In vitro interaction liability (Drug as perpetrator)	
Inhibition/Induction of metabolism	SA is unlikely to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 or induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 at clinically relevant dose.

Notes:
[1] Although the determined actual in vivo release rates of SA and EE from Annovera™ are 150 µg/day and 13 µg/day, respectively, the remaining review denotes AnnoveraTM as SA/EE 150/15 CVS.
[2] Information on metabolism of EE comes from approved EE- containing product label.

6.3.1. Clinical Pharmacology Questions

To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

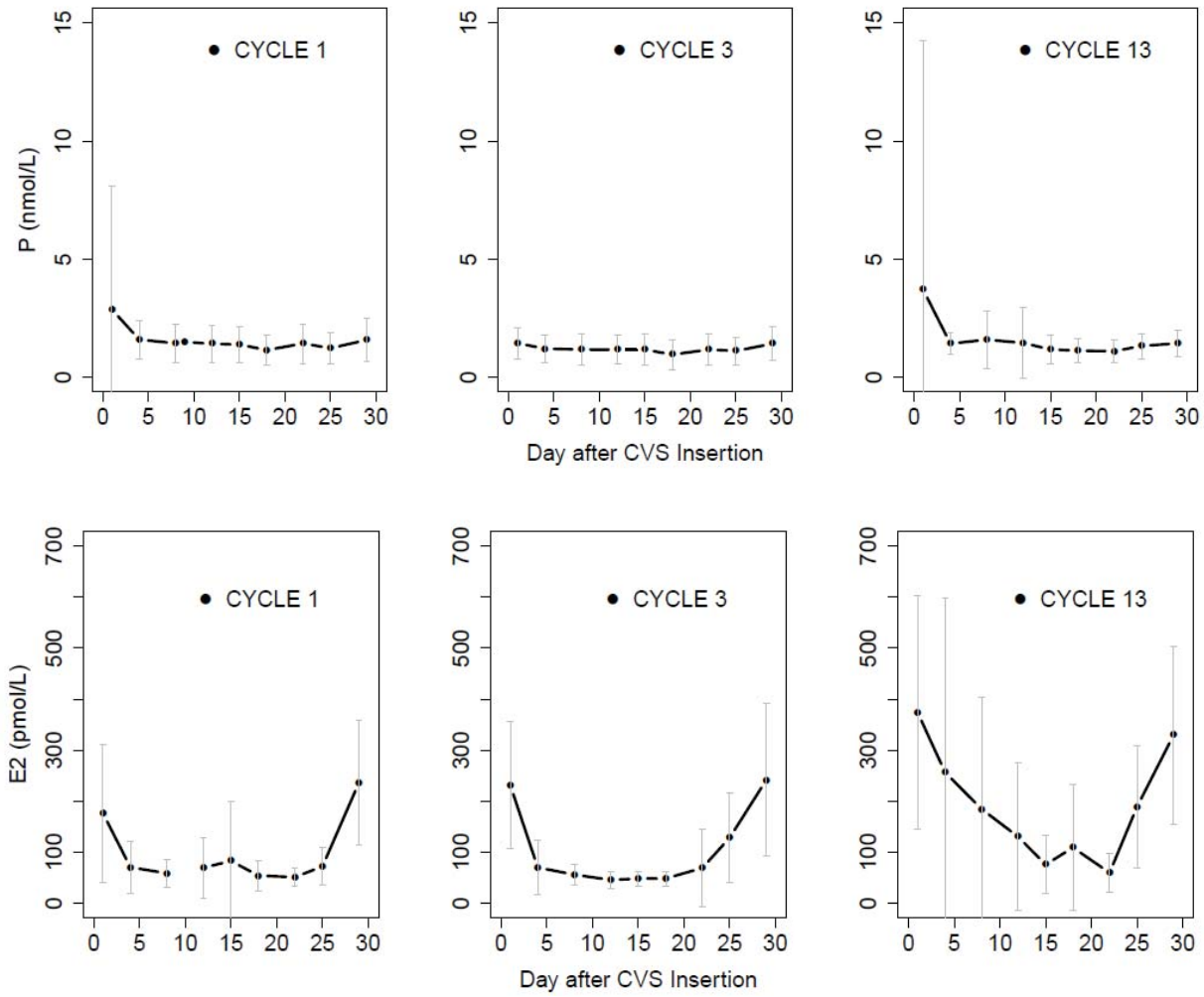
Two open labelled Phase III studies (Studies 300A and 300B) provided the pivotal evidence to support efficacy for SA/EE 150/15 CVS. In the pooled database, the pregnancy rate (Pearl Index) in the subgroup of women ≤35 years of age using pregnancies from evaluable cycles within 14 days from CVS removal (the Primary Subgroup; n= 2111) was 3.36 (95% CI [2.45, 4.49]) per 100

woman-years of CVS use (See clinical review). The clinical pharmacology information which provides supportive evidence of effectiveness is presented below.

As a CHC, SA/EE CVS lowers the risk of pregnancy primarily by suppressing ovulation. PD data in Study 300PK suggested that when SA/EE CVS was used as directed, luteal activity remained adequately suppressed.

Study 300PK assessed the effect of SA/EE CVS on ovulation suppression in 39 subjects by measuring serum estradiol (E2) and progesterone (P) levels twice a week during Cycles 1, 3 and 13 of SA/EE CVS use. No study subjects had luteal activity, defined as two consecutive P measurements of more than 10 nmol/L. One subjects had 1 serum P concentration > 10 nmol/L in Cycles 13. Serum E2 concentrations were also suppressed during the 21-day period of the cycle when the CVS was in place (Figure 3).

Figure 3. P Serum Concentrations for Cycle 1 (N=39), Cycle 3 (N=35), and Cycle 13 (N=27)[8]



Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The following can be considered regarding the selection of the (b) (4) dosing regimen of 21-day continuous use followed by 7-day ring-free interval.

- Earlier clinical studies (Study 124, Study 174 and some literature reports) evaluated the effects of continuous use of SA alone on luteal activity. The data showed an exposure-response in ovulation suppression and a SA serum concentration ≥ 100 pmol/L (37 pg/mL) was demonstrated to inhibit ovulation in most cycles.

[8] In Cycle 13, three study subjects were excluded from analysis due to compliance issue as evidenced by undetectable segesterone concentrations.

- (b) (4)

- Study 181 compared the efficacy of SA/EE CVS in preventing ovulation between two different dosing regimens: 21 days in/7 days out versus 26 days in/4 days out. This 6-month study showed comparable luteal suppression, bleeding control and safety profiles between the two regimens. Therefore, the 21/7-day regimen, was selected based on lower SA and EE exposure.

SA Concentrations Associated with Ovulation Inhibition

(b) (4) cut-off value should not be applied to SA/EE 150/15 CVS due to the following concerns:

- (b) (4) the product in the current submission is a fixed-dose combination of SA and EE administered under a 21/7-day in/out regimen. (b) (4)
- Different bioanalytical techniques (i.e., RIA vs. GC-MS/MS) were used to determine SA serum concentrations and the values from one assay may not be interchangeable with another assay.

VTE Risks Associated with EE Exposure

It is known that higher EE exposure associates with increased VTE risks. The applicant compared EE systemic exposure from SA/EE 150/15 CVS to an approved oral contraceptive (OC) containing 30 µg EE to support the safety of SA/EE CVS on VTE risk (Study 330). However, the result of study is not considered valuable, as the CVS formulation used in this study is different from the TBM formulation and no adequate bridge has been made between the two formulations. A post-marketing safety requirement to assess the VTE risks of SA/EE CVS is recommended by the review team.

QTc Assessment

The effect of SA on QT interval prolongation was evaluated in healthy premenopausal women and no significant QTc prolongation effect was detected following a single i.v. bolus dose of 200

µg SA. The supra-therapeutic SA dose (200 µg) produced a mean SA C_{max} value (5150.2 ± 3333.2 pg/mL) of ~4.5-fold the mean C_{max} (1147.1 ± 315.3 pg/mL) at the therapeutic dose of SA/EE CVS.

Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes. Comments for each specific population are provided below.

Renal Impairment

The effect of renal impairment on the PK of SA/EE CVS has not been studied. Given the lack of mass balance study and renal impairment study, it is not known whether renal excretion plays a significant role in the clearance of SA and/or metabolites. Therefore, the review team agrees with the applicant and recommends SA/EE CVS not to be used in patients with renal impairment.

Hepatic Impairment

The effect of hepatic impairment on the PK of SA/EE CVS has not been studied. Steroid hormones such as SA and EE may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of SA/EE CVS use until markers of liver function return to normal.

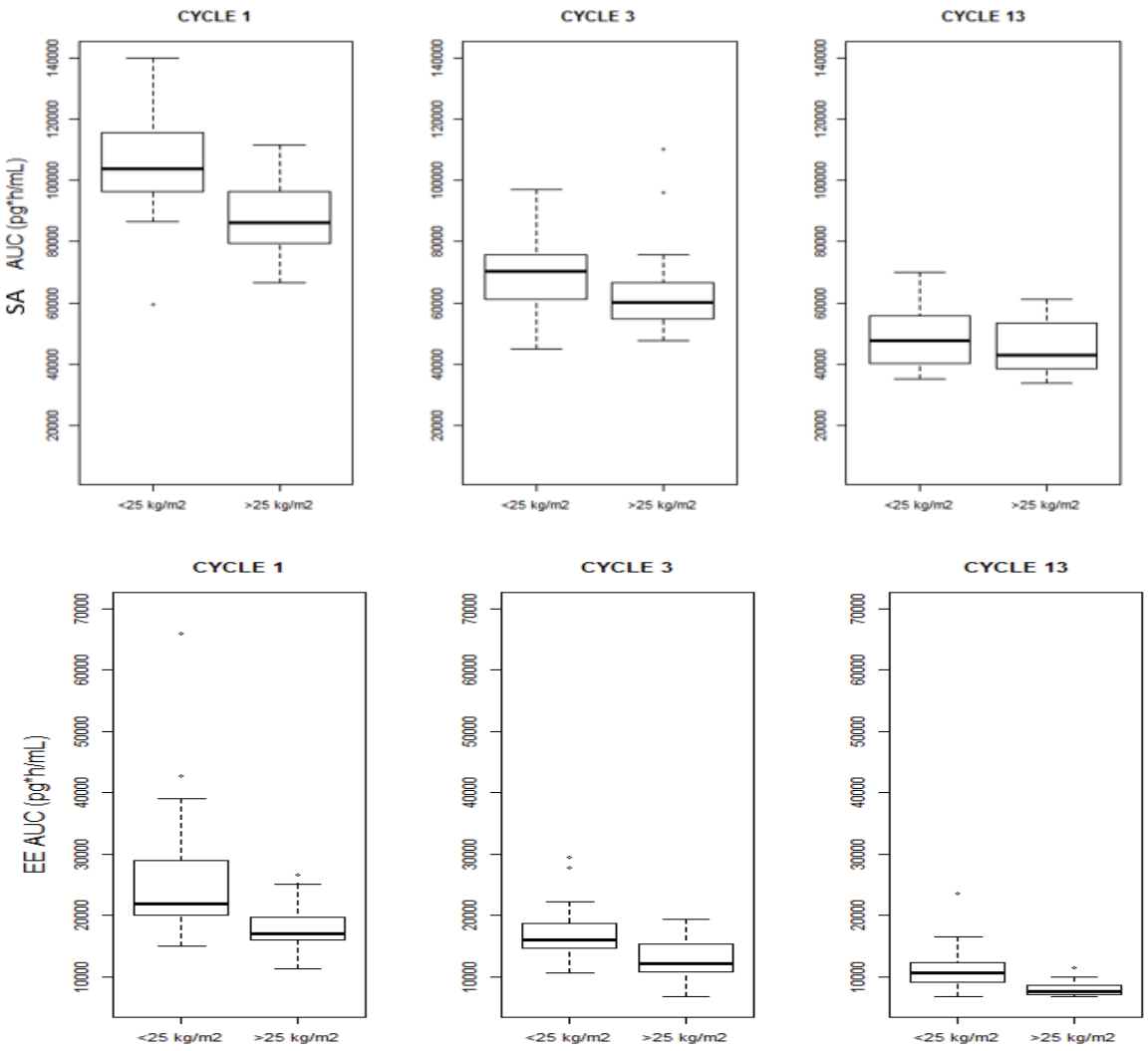
Age

SA/EE CVS is only indicated for use in females of reproductive potential. No PK study has been done in post-pubertal adolescents under the age of 18. Nonetheless, PK of SA/EE CVS is expected to be the same for post-pubertal adolescents under the age of 18 as for users 18 years and older. Use of SA/EE CVS before menarche is not indicated. SA/EE CVS has not been studied in women who have reached menopause and is not indicated in this population.

Body Weight and Body Mass Index (BMI)

The applicant did not conduct population PK analysis to assess the effect of body weight on the PK of SA and EE. Based on the PK data from individual PK studies, decreased systemic exposures of SA and EE were observed with increased body weight of the study subjects. Study 300PK evaluated PK of SA and EE in Cycle 1, Cycle 3 and Cycle 13 of SA/EE CVS use. Of 39 subjects who completed the study, 18 women had BMI < 25 (range: 16.89 - 24.34) kg/m^2 and 21 women had BMI > 25 (range: 25.15 - 37.46) kg/m^2. As shown in Figure 4, SA $AUC_{0\text{-}504h}$ was 7% -16% lower in subjects with BMI > 25 kg/m^2 compared to subjects with BMI < 25 kg/m^2 in the tested cycles. $AUC_{0\text{-}504h}$ of EE was 26% - 33% lower in subjects with BMI > 25 kg/m^2 compared to subjects with BMI < 25 kg/m^2. There was limited information on the safety and efficacy of SA/EE CVS in females of reproductive potential with BMI >29.0 kg/m^2 due to insufficient number of obese subjects in the Phase III studies. The clinical relevance of the observed lower SA and EE exposure in subjects with higher BMI is not known.

Figure 4. Box-plot Comparison of SA and EE Systemic Exposure Grouped by BMI (Study 300PK)



Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Yes, the applicant conducted one clinical DDI study, one physiologically-based PK (PBPK) model and several in vitro studies to assess the DDI potential of SA/EE CVS.

<u>Effect of other drugs or vaginal products on the PK of SA/EE CVS</u>

- CYP-based DDI

In vitro data showed that CYP3A contributes at least 30% of hepatic clearance of SA (Study XT174098). The applicant used physiology-based PK (PBPK) model to predict the impact of CYP3A inhibition and induction on the systemic exposure of SA following parenteral administration. (b) (4)

Upon detailed review, the review team concluded that the PBPK model

performance was not adequately qualified, and thus the model is not adequate to support waiver of clinical DDI studies between SA/EE CVS and CYP3A modulating drugs (See Appendix 17.4).

This issue will be addressed through a postmarketing requirement. Particularly, the review team recommends the applicant conduct a clinical DDI study to assess the effects of strong CYP3A induction and inhibition on the PK of SA and EE from SA/EE CVS (See Section 16). Given similar metabolic pathway of SA compared to other progestins and EE as commonly used estrogen component in CHCs, CHC class labeling is used to describe the general trend of PK changes of SA/EE CVS in the presence of CYP3A modulating drugs and support the general management strategy for CYP-based DDI with SA/EE CVS.

- DDI with other vaginal products

The applicant conducted a randomized, cross-over DDI study (Study 571) to evaluate the effects of vaginal antimycotic medication (miconazole nitrate) on the PK of SA and EE in 29 women using SA/EE CVS. The results showed that 1) vaginal administration of a single-dose of 1200 mg miconazole suppository on Day 8 of CVS use increased the systemic exposure of EE ($AUC_{Day8-21}$) by approximately 67%. Similar trend was observed with SA with AUC_{Day8-9}, $AUC_{Day8-10}$ and $AUC_{Day8-21}$ increasing by approximately 30%, 32% and 19%, respectively (Figure 5 and Table 4); 2) When 200 mg miconazole vaginal suppository were administered on Day 8, Day 9 and Day 10 of CVS use, EE $AUC_{Day8-11}$ and $AUC_{Day8-21}$ were increased by 9% and 42%, respectively. SA $AUC_{Day8-11}$and $AUC_{Day8-21}$ were increased by 28% and 27%, respectively (Figure 6 and Table 4); 3) EE and SA exposure (AUC_{Day10}, $AUC_{Day\ 8-11}$ and $AUC_{Day8-21}$) was bioequivalent with or without 3-Day (Day 8 - Day 10) treatment of vaginal miconazole cream, indicating no PK interaction between SA/EE vaginal ring and miconazole vaginal cream (Figure 7 and Table 4).

These findings suggest that the active ingredient, miconazole, does not affect the PK of SA and EE from the CVS; but the lipophilic nature of suppository formulation may enhance release and/or absorption of the lipophilic steroids contained in the CVS. The increase in exposure to EE extended beyond the duration of concomitant administration with the suppositories suggesting a potential alteration in the release characteristic of the CVS. Given
the potential long-term effect on the ring's performance, the review team recommends the following in the label: concurrent use of oil-based vaginal suppositories should not occur with SA/EE CVS use. If there is a need to treat a vaginal condition, water-based vaginal cream or oral therapy may be used concurrently with the ring. No further evaluation or studies are necessary based on this data.

Figure 5 Arithmetic Mean SA and EE Serum Concentration-Time Profiles Following Administration of CVS Alone (Treatment A) or CVS with a Single-Dose of Miconazole Nitrate Suppository (Treatment B1) in Healthy Female Subjects in Study 571

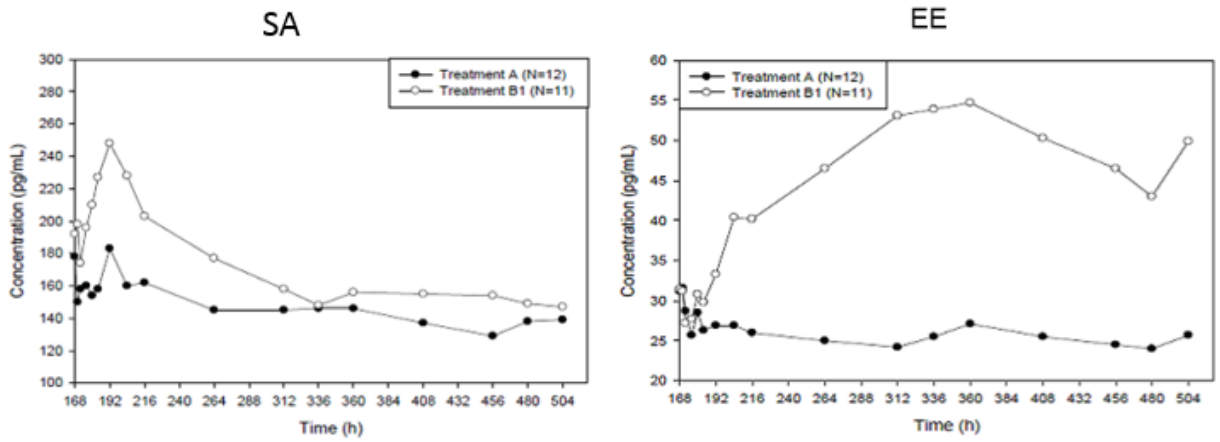


Figure 6 Arithmetic Mean SA and EE Serum Concentration-Time Profiles Following Administration of CVS Alone (Treatment A) or CVS with Three-Day Regimen of Miconazole Nitrate Suppository (Treatment B2) in Healthy Female Subjects in Study 571

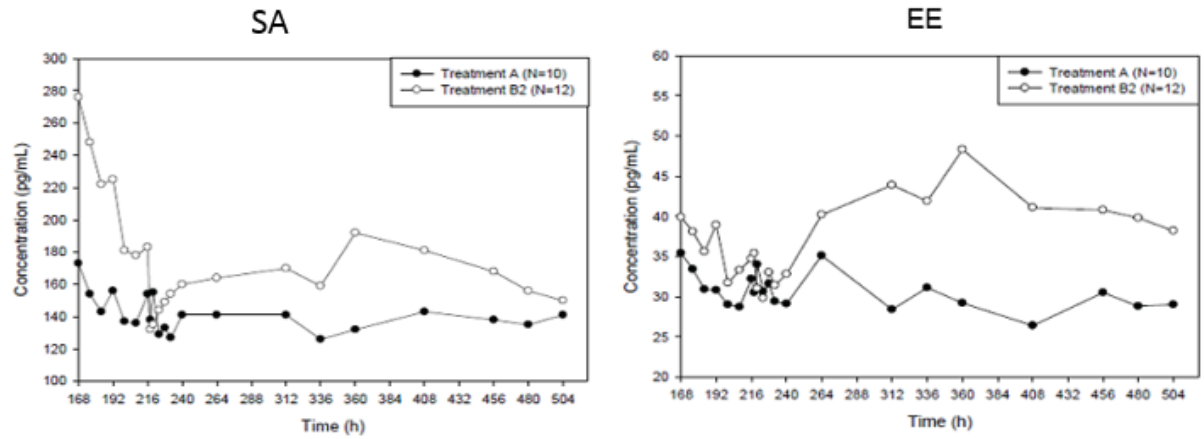


Figure 7 Arithmetic Mean SA and EE Serum Concentration-Time Profiles Following Administration of CVS Alone (Treatment A) or CVS with Three-Day Regimen of Miconazole Nitrate Cream (Treatment B3) in Healthy Female Subjects in Study 571

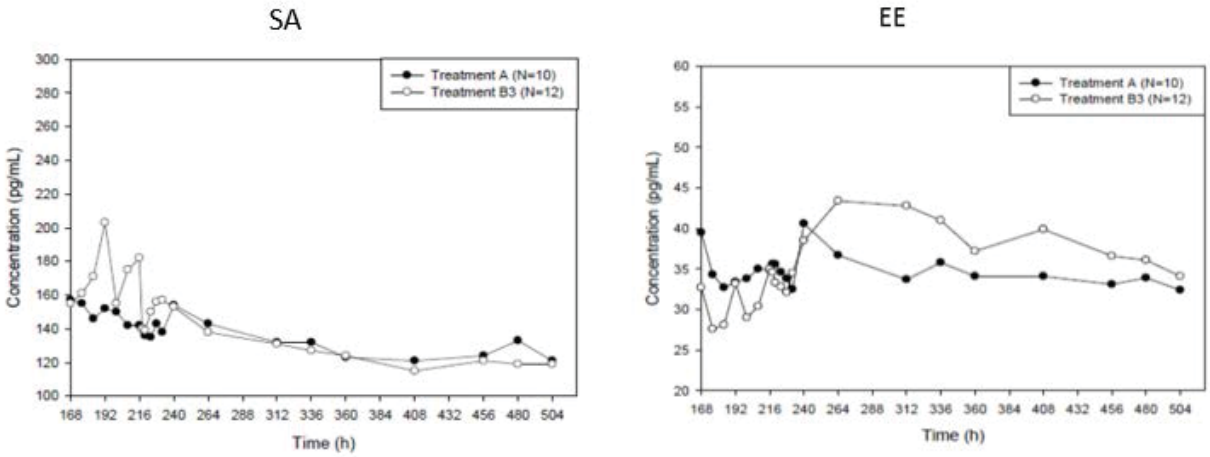


Table 4.Comparisons of SA and EE PK Parameters after administration of SA/EE CVS Alone or with Miconazole Vaginal Suppository or Cream

Geometric mean (90% CI) of Test to Reference Ratio			
Treatments	PK Parameters	SA	EE
Concomitant use of a single dose of miconazole vaginal suppository with CVS (test) vs CVS alone (Reference)	AUC_{Day8-9}	1.30 (1.19, 1.41)	1.04 (0.91, 1.19)
	$AUC_{Day\ 8-10}$	1.32 (1.19, 1.47)	1.18 (1.04, 1.35)
	$AUC_{Day\ 8-21}$	1.19 (1.04, 1.36)	1.67 (1.51, 1.86)
3-Day concomitant use of miconazole vaginal suppository with CVS (test) vs CVS alone (Reference)	$AUC_{Day8-11}$	1.28 (1.03, 1.58)	1.09 (0.84, 1.40)
	$AUC_{Day\ 8-15}$	1.26 (1.10, 1.43)	1.28 (1.08, 1.53)
	$AUC_{Day\ 8-21}$	1.27 (1.15, 1.40)	1.42 (1.21, 1.66)
3-Day concomitant use of miconazole vaginal cream with CVS (test) vs CVS alone (Reference)	$AUC_{Day8-11}$	1.19 (1.15, 1.22)	0.98 (0.81, 1.11)
	$AUC_{Day\ 8-15}$	1.11 (1.09, 1.14)	1.12 (1.01, 1.25)
	$AUC_{Day\ 8-21}$	1.09 (1.04, 1.14)	1.14 (1.07, 1.21)

The applicant also assessed the effects of various water- and oil-based lubricants on SA/EE CVS. The results showed the oil silicone based lubricants significantly increased the size of the ring and led to much higher in vitro release rates of SA and EE from the ring. The applicant proposed to avoid the concurrent use of SA/EE CVS with vaginal lubricants containing silicone (See CDRH review for details).

Effect of SA/EE CVS on Other Drugs

In vitro data showed that SA did not inhibit or induce the liver enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP2E at concentrations up to 1 µM. At concentrations of 1 µM and above, SA may have the potential to cause metabolism-dependent inhibition of CYP3A4. As the observed mean SA C_{max} of 1147 ng/mL (3 nM) following the vaginal administration of SA/EE CVS is about 333-fold lower than SA concentrations with DDI potential,

the in vitro studies suggest that SA/EE CVS is unlikely to inhibit or induce CYP enzymes at the therapeutic dose.

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

No, compared to the Phase III clinical trial formulation, which was also used in the pivotal PK study 300PK, the to-be-marketed (TBM) formulation had some minor changes in (b) (4) manufacturing process. Nonetheless, these changes are considered as minor and were bridged by *in vitro* dissolution studies (see Biopharmaceutics review). There were 2 prior formulations that are not adequately bridged to the TBM formulation. A brief summary of formulations is provided below.

During the drug development program, three formulations have been used for SA/EE CVS, i.e., Phase 1 Formulation and Phase 2 Formulation manufactured by Population Council, and Phase 3 Formulation manufactured by QPharma.

- Phase 1 Formulation by Population Council: used in Clinical Study 64 and 97.
- Phase 2 Formulation by Population Council: used in several clinical studies including Study 180, Study 181 and Study 330. The applicant attempted to use (b) (4) in vitro/in vivo correlation (IVIVC) to demonstrate the similarity of the QPharma-manufactured Phase 3 batch to an earlier Phase 2 batch manufactured by the Population Council. However, this IVIVC method is not considered as reliable per Biopharmacetics reviewer. Therefore, there is no adequate bridge between Phase 2 Formulation and Phase 3 Formulation.
- Phase 3 Formulation by QPharma: used in two pivotal Phase III studies (Study 300A and 300B) and a PK study (Study 300PK)
- TBM Formulation: used in a clinical DDI study (Study 571)

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The following are the studies conducted to support the efficacy and safety of SA/EE CVS.

Table 5. Table of Clinical Trials

Study **Phase** **Dates** **Duration** **NCT number**	**Trial Design** **Country** **Number of sites**	**Study Population** **Dose regimen**	**Endpoints**	**Number of subjects analyzed**
300A Phase 3 Dec 2006- Oct 2009 up to13 cycles NCT00455156	Open-label, single arm, prospective US 15 sites	Healthy, sexually active women with regular menses 18-40.0 yo* 150 µg SA/15 µg EE CVS Vaginal, 21/7 days in/out for up to 13 cycles	Pearl Index Life Table analysis Cycle control Safety	1129
Endometrial	sub-study	same as 300A	Histology of endometrium	159
Hepatic	sub-study		Hepatic proteins	129
Microbiology	sub-study		Presence of vaginal microbes	120
300B Phase 3 Nov 2006 – July 2009 up to 13 cycles NCT00263342	Open-label, single arm, prospective 8 countries 12 sites 5 US 3 Latin America 3 Europe 1 Australia	Healthy, sexually active women with regular menses 18-40.8 yo* 150 µg SA/15 µg EE CVS Vaginal, 21/7 days in/out for up to 13 cycles	Pearl Index Life Table analysis Cycle control Safety	1135
300PK Phase 1 Dec 2005- Jun 2007 up to 13 cycles	Open-label, non-randomized PK/PD study 3 countries/sites Chile Dominican Republic US	Healthy, sexually active women 18-38 yo 150 µg SA/15 µg EE CVS Vaginal, 21/7 days in/out for up to 13 cycles	Estradiol and Progesterone levels Luteal activity (based on consecutive progesterone levels)	39

			SA and EE serum concentrations: Cmax, AUC, steady-state	
180 Phase 2 May 1996- Jul 1998 up to 13 cycles	Randomized, parallel-group, dose finding study 4 countries 5 sites Dominican Republic Finland Chile US – 2 sites	Healthy, sexually active women with regular menses, 18-38 yo 150 µg SA/15 µg EE 150 µg SA/20 µg EE 200µg SA/15 µg EE CVS, Vaginal, 21/7 days in/out for up to 13 cycles	SA and EE serum levels Luteal activity (based on progesterone levels) Vaginal effects Adverse effects Bleeding patterns	150
181 Phase 2 Feb 1997- Dec 1998 6 cycles	Randomized parallel-group open-label 4 countries/sites Dominican Republic Finland Australia US	Healthy, sexually active women with regular cycles, 18-35 y/o 150 µg SA/15 µg EE CVS, vaginal, 21/7 OR 26/4 days in/out for 6 cycles	SA and EE serum levels Luteal activity including ultrasound Bleeding patterns	101
204OL Phase 2 Dec 1999- Aug 2001 6 cycles	Single group, open-label 5 countries/sites Dominican Republic Australia Chile US Finland	Healthy, sexually active women with regular menses, 18-38 y/o ≤80 kg 150 µg SA/15 µg EE CVS, vaginal, remove with bleeding for 4 days followed by insertion into vagina for at least 2 weeks	Ovulation inhibition (based on progesterone levels) Menstrual patterns SA and EE serum levels	76

Source: NDA 209627, Module 2.5, Clinical Overview, Table 1 p 11/68
*weight exclusion >29 kg/m^2 after September 25 and October 4, 2007

7.2. Review Strategy

Studies 300A and 300B provide the efficacy data and most of the safety data. Details for these two studies are provided in section 8 of this review. Pooled data from Studies 300A and 300B were used to evaluate the primary efficacy endpoint. We used this review strategy because neither trial provided the 10,000 evaluable menstrual cycles that the Agency generally requires for contraceptive trials; because the trials were of similar design, pooling was possible to derive the required number of evaluable cycles to establish efficacy of the product. The evaluation and

conclusions in Section 8 represents the combined evaluation of the clinical and statistical teams.

Additional safety data are derived from two phase 1 trials (Studies 300 PK and 330—not listed in the table above) and four phase 2 trials (Studies 180, 181, 2040L and 323—not listed in the table above). Because SA is an NME, the Division requested safety data for other formulations of the SA CVS, which included an SA/EE CVS with lower doses (204R) and CVS with only SA (174, 175). See 10.2 Review of the Safety Database for more detailed information on the safety analysis sets.

8. Statistical and Clinical Evaluation of Efficacy

Financial Disclosure

The applicant provided financial disclosure (FD) for all clinical investigators involved in all studies in one Form 3454 and one Form 3455. The FD information is provided here rather than presenting the information twice under each of the pivotal studies.

There were no funds furnished to clinical investigators or other individuals or groups working on the sponsored studies. Funds provided were to be used for the sponsored studies. Population Council is a non-profit organization and there are no stocks or possibility of full or partial ownership. Population Council did not believe FD requirements (21CFR Part 54), effective February 2, 1999, applied to their organization due to its non-profit status. In April 2011, an outside auditor inquired about the FD requirements for Population Council. FDA advised retrospective compliance with FD regulations with post-hoc collection of FD forms being acceptable for inclusion in the NDA. For investigators who could not be located, the reviewer concluded that the Applicant made appropriate due diligence efforts to document all financial information.

Table 6. Investigators with Financial Disclosure

Protocol	Investigator	Compensation	Amount	Minimized Bias
331	(b) (6)	ICCR* membership annual stipend	$17,500 @ year 1999-2014	Endpoints are results of laboratory studies, therefore, unlikely to be subject to bias. PK/PD study involving safety measures of EE on vaginal vs oral administration.
		attendance 3 day meeting	$6,000 @ year	
300B, 300PK (b) (6)	(b) (6)	ICCR membership annual stipend	$10,000 @ year 1999-2004 $17,500 @ year 2005-2014	Site PI higher, therefore, unlikely investigator biased tests to have higher PI

		attendance 3 day meeting	$6,000 @ year	
300B, 300PK (b) (6)	(b) (6)	ICCR membership annual stipend	$17,500 @ year 1992-2008	Site PI was lower than FD site PI but not statistically significant, therefore bias did not occur
300B (b) (6)	(b) (6)	ICCR membership annual stipend	$17,500 @ year 1992-2014	Site PI higher, therefore, unlikely investigator biased tests to have higher PI
300B (b) (6)	(b) (6)	ICCR membership annual stipend	$17,500 @ year 2007-2014	Site PI higher, therefore, unlikely investigator biased tests to have higher PI
		3 day meeting	$6,000	
300A (b) (6)	(b) (6)	ICCR membership	$17,500 @ year 2009-2015	Site had no pregnancies and unable to perform statistical analysis
300B, 300PK (b) (6)	(b) (6)	ICCR membership	17,500 @ year 1999-2014	Site PI higher, therefore, unlikely investigator biased tests to have higher PI
300B (b) (6)	(b) (6)	Spouse receives salary from Population Council		Investigator never involved in subject selection, subject assessments, or recording of any data. Bias unlikely given the lack of participation in critical study procedures

* Population Council's International Committee for Contraception Research (ICCR)

Source: NDA 209627, Module 1.3.4 Financial Certificate and Disclosure Form 3455

Despite due diligence there were eight clinical investigators from whom FD information could not be obtained: (b) (6) None of these investigators was a principal investigator and each site had four or more investigators. Together, the sites where these eight investigators participated contributed a total of 402 (17.4%) subjects to both 300A and 300B (2308 subjects).

The applicant has disclosed key financial interests/arrangements with the clinical investigators and disclosures from all major investigative sites. No concerns were raised by the clinical review team regarding the overall integrity of the data.

The Financial Disclosure table is provided in 17.1 Appendices.

8.1. Study 300A : A Multicenter, 0pen-label study on the efficacy, cycle control and safety of a contraceptive vaginal ring delivering a daily dose of 150 mcg of Nesterone®* and 15 mcg of ethinyl estradiol (*Nesterone = segesterone acetate)

8.1.1. Study Design

Overview and Objective

The primary objective of Study 300A was to evaluate the contraceptive efficacy and safety of the CVS as a new drug delivery system for contraception. The secondary objectives were to evaluate cycle control and side effects of the 21-day continuous use regimen, followed by one week off per 28-day cycle. There were three sub-studies nested in Study 300A, with each evaluating a separate aspect of CVS use. The three sub-studies' objectives were to evaluate the CVS effect on hepatic factors, endometrial safety, and vaginal microbiology, and these results are discussed in Section 10.8 10.8 Specific Safety Studies/Clinical Trials.

Trial Design

Study 300A was designed as a phase 3, multicenter, open-label, uncontrolled clinical trial in US sites. The drug regimen was 21 days of CVS use followed by seven days without CVS use (during which the vaginal ring was removed). One CVS was used for up to thirteen 28-day cycles (i.e. up to a full year).

The study consisted of a screening period of up to 90 days, a treatment period of up to 12 months (thirteen 28-day cycles), and an optional recovery (post-treatment) period of up to six months to assess return to fertility. Enrollment began in November 2006 and continued through June 2008. All subjects had to finish active treatment by December 31, 2008 when the CVS expired; therefore, not all subjects were eligible to complete all 13 cycles. The study ended when the last subject completed the recovery period.

The study plan called for enrollment of 1200 healthy heterosexually active women aged 18 to <40 years at risk of becoming pregnant. The pregnancy rate was assessed by the PI and life table methods. All pregnancies with an estimated date of conception within 7 days after the last study treatment were to be counted as "on treatment" pregnancies.

Removal of subjects was allowed due to an AE, violation of inclusion or exclusion criteria, non-compliance, withdrawal of consent by the subject, pregnancy, and safety and administrative reasons.

Key inclusion criteria:

1. Sexually active females at risk for pregnancy
2. Age 18 to <40 years at time of enrollment
3. Able to complete study procedures including required diaries and visits
4. Must have a history of regular menstrual cycles (21-35 days in length)

5. Be willing to discontinue current contraceptive method

Key exclusion criteria:

1. Conditions (history or presence of) which are contraindications to use of CHC, including thromboembolic disorders, cerebrovascular or coronary artery disease or myocardial infarction; diabetes mellitus; migraine headaches with focal, neurological symptoms; chronic renal disease; diastolic blood pressure (BP) > 85 mmHg and or systolic BP > 135 mmHg; cholestatic jaundice; estrogen-dependent neoplasia; undiagnosed abnormal genital bleeding; impaired liver function; hepatic adenomas or carcinomas; retinal vascular lesions; family history of thromboembolic disorders
2. History of infertility or sterilization in either partner
3. History of toxic shock syndrome or history of PID since last pregnancy
4. Vaginal discharge, lesions or abnormalities
5. Papanicolaou (pap) smear with high-grade precancerous lesions
6. Cystoceles or rectoceles or anatomical abnormality that would preclude use of CVS
7. Known hypersensitivity to estrogens, progestins, or silicone rubber
8. Smoking in women >35 years and women <35 years who smoke 15 cigarettes or more need evaluation by PI for inclusion based on risk factors
9. Known or suspected pregnancy, breast feeding
10. Severe depression
11. Severe constipation
12. Known or suspected alcoholism or drug abuse
13. Use of injectable or implanted hormonal contraceptives
14. Known HIV or women at high risk of contracting HIV
15. Use of liver enzyme inducers on a regular basis
16. Body mass index (BMI) > 29 (Amendment 1.1)
17. Exclusionary concomitant medication taken chronically included isotretinoin, any sex steroid hormonal treatments, anticonvulsant therapies (except valproic acid), rifampicin, Griseofulvin, retinoic acid, ketoconazole, St. John's Wort. Use of vaginal lubricant containing mineral oil or any other oil-based vaginal products.

Study visits and procedure schedule are shown in Table 7.

Table 7. Study Flow Chart 300A

Cycle #	Pre-Study Screening	Baseline	1	3	4	6	7	9	10	11	13[a] Final	14	Follow Up
Visit (V) No. or Telephone Call (T)	V0	V1	T1	V2	T2	V3	T3[b]	V4[b]	T4[b]	T5[b]	V5 or Early Term	V6 or Final Visit +1[c]	V7.1-7.3

Treatment Cycle Day		1	22-29	1-7d	22-29	1-7d	22-29	1-7d	22-29	22-29	21-27	+1-2 wks	+ mos. 1-6
Informed consent signed	X												
Complete medical & gynecologic history	X												
Complete physical & gynecologic examination	X					X					X		
Sitting blood pressure & pulse	X	X		X		X		X			X	X	
Weight/BMI	X	X		X		X		X			X	X	
Height	X												
Pap smears	X										X		
Hematology	X										X		
Chlamydia and gonorrhea	X										X		
Clinical chemistry	X										X		
Urinalysis	X												
Pregnancy test (urine)	X	X		X		X		X			X	X	
Pregnancy determination			X		X		X		X	X			Xe
Telephone contact			Xf		Xf		Xf		Xf	Xf			Xe
AE recording			X	X	X	X	X	X	X	X	X	X	X
SAE reporting			X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
CVSs													
Dispensed		X											
Returned											X		
Diary card													
Dispensed		X		X		X		X			X		
Reviewed/Returned				X		X		X			X	X	
Sub-studiesh													
Hepatic Factors Sub-study	X					X					X		
Endometrial Safety Sub-study	X					X					X		
Microbiology Sub-study	X					X					X		
Visit (V) No. or Telephone Call (T)	V0	V1	T1	V2	T2	V3	T3b	V4b	T4b	T5b	V5 or Early Term	V6 or Final Visit +1c	V7.1-7.3
Treatment Cycle Day		1	22-29	1-7d	22-29	1-7d	22-29	1-7d	22-29	22-29	21-27	+1-2 wks	+ mos. 1-6

aFor subjects scheduled to complete < 13 cycles, the Visit 5 assessments were performed at their last scheduled cycle visit (Final Cycle Visit).

If the last scheduled cycle was a cycle for which a telephone visit would have been scheduled (Cycles 4, 7, 10, or 11), the subjects returned to the site for Visit 5
assessments instead. All subjects were to complete Visit 6 assessment as their Final Cycle +1 visit.

[b]Completed as needed, based on subject's contraceptive vaginal ring (CVS) start date.

[c]Subjects returned to the clinic within 1 to 2 weeks of CVS removal for pregnancy determination via urine human chorionic gonadotropin (hCG) and diary review.

[d]Scheduled within 1 week following CVS insertion.

[e]Follow-up phone calls occurred for applicable subjects once every 2 months for a maximum of 6 months. If a subject could not be reached by telephone then office visits were scheduled every 2 months. If a subject suspected pregnancy a visit was scheduled to confirm status.

[f]Subjects were contacted during the last week of the cycle.

[h]Details of procedures for the sub-studies are provided in individual sub-study reports included in the appendices.

Source: NDA 209627, Module 5.3.5.2 Study Report 300A, Table 1 p 44/1147

All women in the active treatment phase of the study had up to seven clinic visits. Prior to subject enrollment (V1), the investigator reviewed the results of laboratory tests obtained from the pre-study visit (V0). The V1 visit occurred on day 2 to 5 of the woman's menstrual cycle, when use of the CVS started. Clinic visits occurred at 3, 6, and 9 months during days 1-7 of each menstrual cycle. The exit visit (V5) occurred at the end of cycle 13 and the CVS was collected at the study site. One to two weeks after the exit visit a final visit occurred (V6). If early discontinuation of the study occurred, the exit and final visit were completed together. Subjects who enrolled in the return to fertility phase of the study had an additional visit between one to 6 months post-treatment. Telephone contact between clinic visits to enhance compliance occurred during cycles 1, 4, 7, 10, and 11.

Complete physical and gynecologic examinations were performed at Visit 0, 3, and 5 (or at early termination). Urine pregnancy tests (UPT) were done at each clinic visit. Blood samples for complete blood count (CBC) and chemistry (glucose, SGOT, SGPT, creatinine, total bilirubin, GGT, potassium, sodium, BUN, cholesterol, HDL, LDL, triglycerides, albumin, calcium) were obtained at Visit 0 and 5 (or early discontinuation). Pap smears and tests for chlamydia and gonorrhea were performed at the site in accordance with local standards. Safety assessments were done at each clinic visit and all AEs and concomitant medications were recorded on CRFs.

All subjects were to complete a paper diary and record days the CVS was in and out of the vagina, the number of hours the CVS was out if > 2 hours, days when bleeding or spotting occurred, whether vaginal intercourse occurred during each 2-week interval, dates of condom or other contraception use, any complete or partial expulsions, any CVS problems or medical problems, and any concomitant medication. Bleeding and spotting were defined per Mishell[9]. Subjects were to choose between no bleeding, spotting, normal bleeding, or heavy bleeding in their diary. Diary entries were used to determine treatment compliance.

Post-treatment follow-up for women no longer using hormonal contraception documented the timing of the first spontaneous menstrual cycle; for women wishing to become pregnant, follow

[9] Mishell, DR, Jr. et al. Recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials. Contraception 2007; 75(1):11-5.

up continued until pregnancy or six months had elapsed, whichever occurred first.

Study Endpoints

The primary efficacy analysis was based on the PI in women 18-35 years of age at time of entry into study. Included cycles were those in which the subjects used the CVS for at least 1 day as the only method of contraception. Cycles excluded from the PI were those in which a subject became pregnant, cycles in which adjunctive (back-up) contraception was used, and cycles beyond one year from the date of first CVS insertion.

The endpoint was "on treatment" pregnancy defined as the estimated date of conception within seven (7) days of last CVS use. The estimated date of conception was derived from the gestational age and the date gestational age was determined, the estimated date of delivery, and the date of last menses. The estimated date of conception was compared with the last CVS use to determine if pregnancy conception occurred within seven days of CVS use.

> ***Comment:*** *The endpoint of pregnancy conception within seven days of CVS use was requested by the Division, and is consistent with the NuvaRing efficacy endpoint. In COC trials, "on treatment" pregnancy has been defined as any pregnancy occurring within 14 days after the last dose of the study drug, which may include placebo pills. Therefore, the number of days without hormones in defining "on treatment" pregnancy varies depending on the combined hormonal contraceptive being evaluated. In this submission, the above endpoint allows for exclusion of pregnancies that would have been included in other contraceptive studies (i.e. pregnancies that occur between day 8-14). The Division requested the applicant to calculate PI for pregnancies through day 14 as a sensitivity analysis.*
>
> *The Division also requested removal of cycles when heterosexual intercourse did not occur from the "at-ris " cycles when calculating the PI, as this information was collected on the subject diary cards. However, at the Late Cycle Meeting the applicant noted that data on occurrence of intercourse was not reliable, i.e. this data was not confirmed at clinic visits. Further, the applicant stated that two pregnancies occurred during cycles where the diary noted no intercourse had occurred. In addition, the SAP for this Phase 3 study specified that only cycles during which backup contraception was used would be excluded from the primary efficacy analysis. Exclusion of cycles during which no intercourse occurred was not prespecified for calculation of the primary efficacy endpoint. Therefore, the Division determined that the primary efficacy endpoint presented in labeling would be the PI, calculated by excluding only cycles during which backup contraception was used, consistent with the prespecified SAP and considering the unreliable intercourse diary data.*

Supportive efficacy variables were life table analyses using all cycles for all women and for subjects 35 years or younger, and PIs (with 95% CI) of all users with and without adjunctive contraception.

Secondary endpoints were cycle control characteristics and vaginal bleeding patterns. For data to be included in these analyses, 15 days of bleeding entries during weeks 1-3 and at least three days of bleeding entries during week 4 were required.

Cycle control summarized the number of unscheduled and scheduled bleeding or spotting days and number of all bleeding and spotting days. Week 4 was classified as scheduled bleeding even if the subject used the CVS during that week. Scheduled bleeding was bleeding during ring free intervals and the first 4 days of CVS use each cycle.

Vaginal bleeding information was derived from subject diary entries describing bleeding as none, spotting, normal or heavy bleeding. Spotting did not require protection and bleeding required a tampon or pad. The normal and heavy bleeding categories were combined for the bleeding variable.

Safety analysis included assessment of SAEs, AEs, use of concomitant medications, clinical laboratory and urinalysis evaluations, physical and gynecological examinations, and vital signs.

Statistical Analysis Plan

The primary endpoint was the Pearl Index for women ≤ 35 years of age (at enrollment) derived from all cycles from which no back-up contraception was used. The statistical methodologies and rationale for this endpoint were described above in the Study Endpoints section.

The applicant followed the Agency's recommendations for a phase 3 trial of a new contraceptive containing a new molecular entity, which stipulate that participants be exposed to the drug for approximately 20,000 cycles, with at least 400 women completing one year of use.

Considering the premature drop-outs during the study, about 1200 subjects were planned for enrollment in Study 300A. Another 1200 subjects were planned for enrollment in Study 300B.

The following subject populations were used for analysis of the study:

- Enrolled: all subjects who were enrolled into the study.
- Evaluable for Safety: all enrolled subjects that inserted the ring.
- Evaluable for Efficacy: all subjects Evaluable for Safety who used study drug for at least one day, provided diary card data, and were not pregnant at the start of Cycle 1. If no diary data was available, then the enrolled subject needed to have the date of last ring use recorded in their CRFs, along with the other criteria to be included this population.

Eight subjects were enrolled who were not included in the Evaluable for Efficacy population, because they fell into the following categories:

- Enrollment with overlapping dates at 2 study sites (five subjects)
- Second enrollment in the same study with non-overlapping dates (three subjects)

For the first category, the applicant excluded all data from these five subjects from the Evaluable for Efficacy population, with the possible exception of any pregnancies that may have occurred. For the second category, the applicant excluded all data from these three subjects' second study enrollment from the Evaluable for Efficacy population, while data from these three subjects' first study enrollment were included.

Protocol Amendments

The applicant submitted Amendment 1.1 on October 4, 2007, with the following protocol changes:

- Exclusion criteria:
  - Change in exclusion of subjects with weight >95 kg or >209 pounds to exclusion of subjects with BMI >29 kg/m^2, based on the study's DSMB recommendations after review of VTEs. See Section 10.5.1 (Analysis of VTEs) for detailed discussion.
  - Diastolic BP >85 mmHg and/or systolic BP >135 mmHg after 5-10 minute rest
- Analysis of Efficacy: the applicant added the Safety and Efficacy Review committee (SERC) to meet quarterly to review efficacy data
- Bleeding Pattern: further defined that menstrual diaries will be examined to determine the number of days of scheduled bleeding (bleeding/spotting when the ring is out according to the prescribed ring schedule) and unscheduled bleeding (any other bleeding)

The applicant submitted Amendment 2 on December 3, 2007, with the following protocol changes:

- Amended the 1-year duration of CVS use to less than 1 year if subject enrolled in the study after January 2008
- Specified that all subjects must be discontinued from the trial by December 31, 2008 because the batches of rings were expiring, and modified visits depending on subject date of study entry
- Changed exclusion criterion for abnormal Pap smear as follows: subjects with CIN 1 lesions that did not require treatment were allowed to participate in the study
- Further defined primary objective for CVS "when used for up to 13 consecutive cycles", and secondary objective to define cycle control/bleeding patterns of a 21-day continuous use regimen followed by 1 week off per cycle

8.1.2. Study Results

Compliance with Good Clinical Practices

The study report states that Study 300A was conducted according to the guidelines of Good Clinical Practices (GCP) and the International Conference on Harmonization (ICH) in compliance with the regulations of the Declaration of Helsinki regarding the ethical use of human subjects in clinical trials. Institutional Review Boards (IRB) for each study site reviewed and approved the study protocol and subsequent amendments. In addition, an autonomous DSMB was

established and conducted regular reviews of pregnancies and safety data. Population Council SERC convened quarterly to review data in relation to study objectives.

Data Quality and Integrity
Each site underwent a study initiation visit to review study conduct and procedures. During the study, regular monitoring visits were made to each site to assess compliance. Data management review was conducted on Case Report Form (CRF) data and queries were sent to the sites to address any discrepancies or missing data.

During review of this study, issues that were of concern for data quality and integrity included:

- Subject exclusion
    - 5 subjects were excluded from the efficacy analysis because of concomitant enrollment at two sites. The applicant stated that by excluding these subjects no pregnancies were excluded. However, at the time of adjudication of pregnancies, one of the subjects did have an on-treatment pregnancy.
    - 3 additional subjects enrolled at two sites sequentially, and only the data from the first site was included in the safety analysis. The data from the second site was excluded.
    - All eight of the above subjects were enrolled at the same two sites.

- Inconsistent data
    - There were instances in which subject-entered diary data did not agree with clinic-entered data on the CRF. Examples of these inconsistencies included information regarding last menstrual period (LMP) and date of last CVS use. In these instances, the applicant provided additional information (i.e. phone call records) to corroborate the clinic-entered data.

    Comment: *After review of the data, it was determined that the clinic-entered data, as opposed to the diary data, was of sufficient quality for review, and the noted inconsistencies did not affect the adequacy of the overall dataset to complete the clinical review.*

Patient Disposition
There were 1,806 subjects screened of which 1,135 were randomized (62.8%). The Efficacy and Safety populations included 1,129 unique subjects. Six (6) subjects were excluded from both analyses: five of these were concurrently enrolled at two sites and one subject never inserted the CVS. Subject disposition information is shown in Table 8.

Table 8. Disposition of Study 300A Subjects

	Study 300A

Disposition	(N=1129) n (%)
Completed the Study	582 (51.6)
Discontinued Study	547 (48.4)
Reason for Discontinuation	
Lost to follow-up	138 (12.2)
Adverse Event	130 (11.5)
Withdrew consent	129 (11.4)
Eligibility BMI>29 kg/m2	88 (7.8)
Compliance	26 (2.3)
Pregnancy	24 (2.1)
Expulsions	9 (0.8)
Eligibility other	2 (0.2)
Other	1 (0.1)

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, p 67/1147

Two hundred and twelve subjects (212) or 18.8% of the population enrolled in the 6-month follow-up for return to fertility data.

The overall subject discontinuation rate was 48% which is comparable with discontinuation rates in other Phase 3 trials for similar products (i.e. 41% and 40% discontinuation rates in the NuvaRing and Quartette trials, respectively). In this US study, approximately 12% of subjects were lost to follow up. Discontinuations due to AEs and withdrawal of consent occurred in approximately 11% of subjects each. Withdrawal of consent included subjects who were no longer sexually active, reported personal problems, relocated, were planning pregnancy, as well as four subjects with reasons suggestive of AEs: two with medical problems, one with mood change, and one with pelvic problems. These proportions are comparable to other contraceptive trials in North America where AEs accounted for 11-13% of discontinuations, withdrawal of consent accounted for 6-9%, and loss-to-follow up accounted for 13-14%. Overall, the disposition of subjects in 300A is within the expected range for contraceptive trials.

Protocol Violations/Deviations

There were 56 eligibility criteria violations. Of these, 33 violations encompassed abnormal serum chemistry values, 10 violations were due to subjects' not having a history of regular menses, and 9 violations were due to abnormal Pap smears suggestive of HGSIL.

There were 3,004 other deviations: 1,203 related to visits outside of the protocol time window, 358 where CVS was not returned, 354 due to noncompliance with CVS, and 264 where visits were not completed.

In addition, there were 86 exclusion criteria violations noted by study monitors, involving deviation in laboratory tests or blood pressure, errors in signatures and dates on screening visit

test results. All subjects signed an informed consent form (ICF) but there were 72 cases where subjects were not re-consented to protocol amendments and 29 violations where subjects did not initial all pages of ICF.

A total of 1,143 CVS were distributed to the 15 sites. Eighty percent (80%) or 908 of the CVSs were returned.

> ***Comments:*** *The majority of protocol violatons/deviations involved visits outside the protocol time window with only a small number of visits not completed. Thus, the protocol violations and deviations are unlie ly to have significantly altered our overall conclusion regarding the product's efficacy.*

Demographic Characteristics

The Safety and Efficacy populations are the same. The applicant's table of summary demographics and baseline characteristics is shown below.

Table 9. Demographics 300A

Characteristic	Study 300A (N=1129) n (%)
Race (Multiple Races Allowed per Subject)	
Asian	67 (5.9)
Black or African American	261 (23.1)
American Indian or Native Alaskan	12 (1.1)
Native Hawaiian or Pacific Islander	10 (0.9)
White	748 (66.3)
Other/Unknown	76 (6.7)
Ethnicity	
Hispanic or Latina	148 (13.1)
Not Hispanic or Latina	981 (86.9)
Marital Status	
Never married	808 (71.6)
Married	232 (20.5)
Divorced	62 (5.5)
Separated	26 (2.3)
Widowed	1 (0.1)
Age (y)	
18 – 19	56 (5.0)
20 – 24	436 (38.6)
25 – 29	376 (33.3)
30 – 35	186 (16.5)

Characteristic	Study 300A (N=1129) n (%)
36 +	75 (6.6)
Education: Highest Level Attained	
College degree or higher	537 (47.6)
Some college	452 (40.0)
High school diploma/equivalent	115 (10.2)
Less than high school	25 (2.2)
Subject Desires to Have Children After the Study	
Yes	596 (52.8)
No	302 (26.7)
Unsure	231 (20.5)
Body Mass Index (kg/m2)	
value < 20	131 (11.6)
20 ≤ value < 25	588 (52.1)
25 ≤ value < 27	162 (14.3)
27 ≤ value ≤ 29	128 (11.3)
29 > value	120 (10.6)
Smoking	
Never smoked	764 (67.7)
Former smoker	209 (18.5)
Current smoker	155 (13.7)
Unknown	1 (0.1)
Alcohol Use History	
Never drank	190 (16.8)
Former drinker	87 (7.7)
Current drinker	852 (75.5)

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, Table 5 p 72/1147

The mean age was 26.6 ± 5.0 years and the mean BMI was 24.1 ± 3.9 kg/m^2.

Menstrual characteristics showed 67.6% of subjects had moderate menstrual flow and 98.3% of subjects had menstrual flow ≤ 7 days. Over 50% of subjects reported mood changes, cramps, and bloating associated with menstruation.

The majority of subjects used condoms or hormonal contraception in the 6 months prior to enrollment into the study. The breakdown of contraceptive use is shown in the table below.

Table 10. Contraceptive Use Within 6 Months of Enrollment (Study 300A)

Type of contraceptive	Study 300A (N=1129) n (%)
Condoms	520 (46.1)
Withdrawal	117 (10.4)
Hormonal contraceptives	515 (45.6)
Vaginal rings	265 (23.3)
COC	225 (19.9)
Transdermal patch	22 (1.9)

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, p 380/1147

Twenty-three percent (23%) of subjects used hormonal contraception within 30 days prior to CVS: 210 (18.5%) of subjects used the vaginal ring and 61 (5.4%) used other CHCs.

> ***Comment:*** *Almost a quarter of the subjects could be considered continuous contraceptive users (within 4 weeks of enrollment) and over 45% were prior users. Overall, 64.6% of enrolled subjects had used non-hormonal contraceptives within 6 months of enrollment which is expected in U.S. populations recruited for contraceptive trials.*

Table 11 lists selected active medical history in the study population by preferred term.

Table 11. Selected Active Medical History of Subjects (Study 300A)

Preferred Term	Study 300A (N=1129) n (%)
Headache	311 (27.5)
Drug Hypersensitivity	154 (13.6)
Acne	152 (13.5)
Dysmenorrhea	145 (12.8)
Premenstrual Syndrome	101 (8.9)
Depression	72 (6.4)
Migraine	61 (5.4)
UTI	43 (3.8)

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, Table 14.1.7 p360/1147

Concomitant Medications and Treatment Compliance

1,035 (91.7%) of subjects used concomitant medication. A table of the most common concomitant medication (excluding cough, cold, and nasal preparations and vitamin/mineral supplementation) is shown below.

Table 12. Concomitant Medication Use in Subjects (Study 300A)

Level 2 Therapeutic Class	Study 300A (N=1129) n (%)
Anti-inflammatory (including NSAIDs*)	723 (64.0)
Analgesics (majority acetaminophen)	679 (60.1)
Antihistamines for systemic use	389 (34.5)
Antibacterial for system use	337 (29.8)
Psychoanaleptics (including SSRIs**)	138 (12.2)
Antidiarrheal	134 (11.9)
Antimycotic for systemic use***	105 (9.3)

*nonsteroidal anti-inflammatory drugs
**selective serotonin reuptake inhibitor
*** includes 104 fluconazole users but does not include gynecological anti-infective and antiseptics (miconazole, terconazole, clotrimazole = 68 subjects).
Source: NDA 209627, Module 5.3.5.2, 300A Study Report, Table 14.1.9.3 p 389/1147

> ***Comment:*** *A reasonable assumption is that fluconazole was used for vaginal candidiasis in this study population (as opposed to oropharyngeal/esophageal candidiasis and cryptococcal meningitis). Therefore, vaginal antimycotic use can be estimated by use of fluconazole and gynecological antimycotics, i.e. 172 subjects or 15.2% of the study population. Vaginal candidiasis is common in females of reproductive age, and although it is uncomfortable, it is rarely a serious adverse event. The applicant's microbiology substudy also did not raise concern for elevated ris of vaginal infections with this product. Vaginal infections, including candidiasis, will be labeled among adverse events observed in the CVS clinical trials.*

Compliance was determined by the subjects' diary cards. Only subjects who provided diary cards that confirmed insertion of CVS on day 1 for the given cycle were included in the compliance data. A subject was considered in compliance if the CVS was inserted on day 1 and had continuous use for the first 21 days of the cycle, with no more than 2 hours' interruption per day, followed by 7 days of nonuse. Using this definition, perfect compliance for subjects was >81%.

Efficacy Results – Primary Endpoint

Efficacy was based on the PI using "on-treatment" pregnancies. On-treatment pregnancies were defined as those pregnancies for which conception occurred on or after the date of the first insertion of CVS and extended through seven days following removal of CVS. The PI was derived from women ages 18-35 years at time of entry. All 28-day cycles where additional back-up methods of birth control occurred were excluded.

The applicant identified 17 on-treatment pregnancies. Upon detailed review, two additional pregnancies were adjudicated as on-treatment for a total of 19 on-treatment pregnancies for Study 300A. The details of the two additional on-treatment pregnancies are as follows:

Subject [redacted] enrolled in April 2008 at age 22 years. At her [redacted] clinic visit a UPT was performed due to late withdrawal bleed. The UPT was negative but due to the subject's symptoms, a βhCG was obtained and reported as 70 mIU/mL. On [redacted] the subject removed the CVS and a repeat βhCG was reported as 20 mIU/mL. An ultrasound on [redacted] showed no evidence of pregnancy. The narrative states the subject subsequently had return to menses but the date is not given. The applicant justified excluding this pregnancy from the efficacy population stating it was a non-pregnancy and due to heterophilic antibodies, i.e. a false βhCG test result.

> ***Comment:*** *The narrative is most consistent with an early missed abortion/blighted ovum; thus, should be counted as an on-treatment pregnancy, despite the outcome of early pregnancy failure.*

Subject [redacted] enrolled on [redacted] at age 20 years. She removed her CVS for 13 days, from [redacted] through [redacted], and then reinserted the CVS. On [redacted], her βhCG level was 388 mIU/mL. An ultrasound preformed on [redacted] determined the gestational age (GA) of the pregnancy to be 5 weeks and 5 days, with an estimated date of conception of [redacted]. The applicant dated this pregnancy as occurring 8-14 days after CVS use because the subject did not use the CVS correctly.

> ***Comment:*** *We include compliant and non-compliant patients in the PI calculation as this more accurately reflects real-world use of contraceptives. Because the subject reinserted her CVS, this pregnancy is considered on-treatment.*

In addition, there were two subjects ([redacted] and [redacted]) that were considered to have on-treatment pregnancies based on diary entries, and one subject ([redacted]) considered to have an on-treatment pregnancy based on a dating ultrasound. In response to an information request (IR) sent on December 19, 2017 , the applicant forwarded clinical notes stating that the two subjects ([redacted] and [redacted]) had incorrectly entered dates of CVS use in their diaries, and the dating ultrasound report confirming date of conception occurred 8-14 days after last CVS use in subject [redacted].

One additional subject, [redacted], was excluded from the efficacy analysis. This 29-year-old subject's last clinic visit was in [redacted]. She did not complete any diary cards. In [redacted], she contacted the site via telephone to report she was pregnant but did not return for confirmation. She was lost to follow up after that call. In [redacted], the CVS and some diary cards were delivered to the clinic. Because the diary entries were never reviewed with the subject and the pregnancy was unconfirmed, this subject was not included in the efficacy analysis.

Comment: *We agree with excluding this subject from the efficacy analysis since her pregnancy was never confirmed.*

Table 13. Adjudicated Pregnancies (300A)

Subject	Start drug	Last CVS use	LMP	Pregnancy confirm	Estimated date of Conception	Applicant	Medical Officer Determination
(b) (6)		per crf (b) (6) per diary (b) (6)	(b) (6)	narrative: neg UPT (b) (6) ßhCG 70 (b) (6) ßHCG 20.	(b) (6)	false serum hcg and excluded	On Chemical pregnancies count in contraceptive trials
		(b) (6)		date of GA confirmation (b) (6) (b) (6) (NOT) with US dating 23 wks.		8-14 days after CVS use	8-14 days after CVS use
		(b) (6) . per diary: (b) (6)		(b) (6) ßhCG 3917. US (b) (6) GA 6w6d		8-14 days after CVS use	8-14 days after CVS use (discount diary)
		(b) (6) . per diary: (b) (6)		(b) (6) ßhCG 579 US (b) (6) 4w6d		15+ days after CVS use	15+ days after CVS use (discount diary)

		per diary: (b) (6)	per crf: (b) (6) per diary: spotting (b) (6)	(b) (6) ßhCG 388 US (b) (6) 5w5d	(b) (6)	8-14 days after CVS use	On Incorrect use doesn't exclude pregnancy

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, p 205/1147, Response to IR Submitted 1/16/2018

For the analysis of PI in studies 300A, 300B and the integrated analysis of effectiveness, the FDA clinical team and the statistical team agreed to follow the statistical methodology specified in the statistical analysis plan of both studies 300A and 300B. The Pearl Index was based on the evaluable for efficacy population and cycles in which no adjunctive contraceptives were used. If a subject had more than 13 cycles during the study, her first 13 cycles were counted towards the evaluable cycles. The applicant submitted data file EFF.XPT, under sequence # 007, on December 5, 2017 was the source data for the FDA statistical reviewer's analyses.

Table 14. Study 300 A: Pearl Index for subjects ≤ 35 years old using pregnancies from evaluable cycles within 7 days from CVS removal

		Efficacy Population		
Study	**N**	**Number of Pregnancies**	**Number of evaluable cycles**	**PI using evaluable cycles (95% CI)**
300A	1055	19	7970	3.10 (1.87, 4.84)

Source: Reviewer's analysis. Data: \NDA209627\0007\m5\datasets\ise\analysis\legacy\datasets\eff.xpt.
Note: 1. Include pregnancy from subject 11086. 2. Cycles beyond cycles 13 were not included in the calculation.
3. 95% CI was based on the Poisson distribution.

Comments: *The PI and 95% CI for the CVS in this study are consistent with those of two recently approved CHCs: Quartette [approved in 2013 with PI 3.19 (2.49, 4.03)] and Lo Loestrin Fe [approved in 2010 with PI 2.92 (1.94, 4.21)]. All the studies calculated the PI similarly, with a 7-day on treatment pregnancy window and removing cycles where bac up contraception was used.*

The Division also requested analyses of the PI and 95% CI for pregnancies that occurred within 14 days after last CVS use. The applicant initially assigned four pregnancies conceived 8-14 days after CVS use. One of these (Subject (b) (6)) was recategorized to on-treatment. The Division agreed that the other three pregnancies occurred 8-14 days post CVS use.

Table 15. Study 300 A: Pearl Index for subjects ≤ 35 years old using pregnancies from evaluable cycles within 14 days from CVS removal

		Efficacy Population		
Study	**N**	**Number of Pregnancies**	**Number of evaluable cycles**	**PI using evaluable cycles (95% CI)**
300A	1055	22	7970	3.59 (2.25, 5.43)

Source: Reviewer's analysis. Data: \NDA209627\0007\m5\datasets\ise\analysis\legacy\datasets\eff.xpt.
Note: 1. Include pregnancy from subject (b) (6) 2. Cycles beyond cycles 13 were not included in the calculation.
3. 95% CI was based on the Poisson distribution.

Comment: *The PI increases further when on-treatment pregnancy is defined as up to 14 days after CVS use. This demonstrates the need for prompt reinsertion of the CVS seven days after removal.*

Efficacy Results – Supportive endpoints

Life table analyses of cumulative pregnancy rates were a supportive endpoint to CVS efficacy. The applicant's cumulative pregnancy rates for subjects ≤ 35 years old with pregnancies within seven days of last CVS use utilizing all cycles[10] are very similar to the cumulative pregnancy rate calculated by the FDA, as shown in Table 16 below.

Table 16. Study 300A: Kaplan-Meier Analysis of Pregnancy Among Subjects ≤ 35 Years Old Using All Cycles

Cycle	**Subjects at Risk**	**Number of Pregnancies (with 7 days)**	**Cumulative Probability of Pregnancy (95% CI)**
0	1055	2	0
1	1055	2	0.0019 (0.0005, 0.0076)
2	977	4	0.0060 (0.0027, 0.0133)
3	927	3	0.0092 (0.0048, 0.0176)
4	864	2	0.0115 (0.0064, 0.0207)
5	824	0	0.0115 (0.0064, 0.0207)
6	775	2	0.0140 (0.0082, 0.0241)
7	705	0	0.0140 (0.0082, 0.0241)
8	664	2	0.0170 (0.0102, 0.0282)
9	596	1	0.0187 (0.0114, 0.0305)
10	532	1	0.0205 (0.0127, 0.0331)
11	476	0	0.0205 (0.0127, 0.0331)
12	428	2	0.0251 (0.0157, 0.0399)
13	398	0	0.0251 (0.0157, 0.0399)

Source: Reviewer's analysis. Data: \NDA209627\0007\m5\datasets\ise\analysis\legacy\datasets\eff.xpt.
Note: 1. Include pregnancy from subject (b) (6) 2. Cycles beyond cycles 13 were not included in the calculation.

[10] NDA 209627, Module 5.3.5.2, 300A Study Report, Table 14.2.2.1, p 425/1147

Comment: *The cumulative pregnancy rate of 2.5% (95% CI: 1.57, 3.99%) at one year is comparable to the PI of 3.10 (95% CI: 1.87, 4.84).*

Efficacy Results - Secondary endpoints

Cycle control:

Overall, greater than 95% of subjects had some bleeding or spotting each cycle. The mean number of days was 5.0 and did not decrease with subsequent cycles. Between 2.5 and 4.4% of subjects had amenorrhea for any given cycle with an overall amenorrhea rate of 0.7%. Scheduled and unscheduled bleeding and spotting is presented in the table below.

Table 17. Scheduled and Unscheduled Bleeding and Spotting (Study 300A)

Cycle	N	none	% with no bleeding/spotting	Mean	SD	Min	Median	Max
1	988	43	4.4	6.2	3.62	0	5.0	24
2	901	29	3.2	5.3	2.85	0	5.0	24
3	783	23	2.9	5.3	2.61	0	5.0	28
4	752	21	2.8	5.2	2.77	0	5.0	31
5	755	23	3.0	5.2	2.42	0	5.0	28
6	649	16	2.5	5.2	2.45	0	5.0	27
7	633	20	3.2	5.4	2.78	0	5.0	25
8	620	23	3.7	5.3	2.64	0	5.0	25
9	529	16	3.0	5.4	2.67	0	5.0	25
10	476	13	2.7	5.5	2.71	0	5.0	23
11	439	13	3.0	5.6	2.92	0	5.0	24
12	397	11	2.8	5.7	3.24	0	5.0	26
13	340	13	3.8	5.3	2.87	0	5.0	19
Overall	1010	7	0.7	5.5	2.01	0	5.2	21

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, Table 14.2.3.1 page 431/1147

The number of women with scheduled bleeding and/or spotting (withdrawal bleed at appropriate time) was greater than 91% for each cycle with the average of five days of bleeding and/or spotting. The longest withdrawal bleeding and/or spotting was 11 days and this did not decrease with subsequent cycles.

Table 18. Scheduled Bleeding and Spotting (Study 300A)

Cycle	N	n none	% no scheduled bleeding/ spotting	Mean	SD	Min	Median	Max
1	991	61	6.2	4.9	1.96	0	5.0	11
2	907	69	7.6	4.5	1.92	0	5.0	11

3	788	54	6.9	4.6	1.90	0	5.0	11
4	761	55	7.2	4.6	1.98	0	5.0	11
5	756	63	8.3	4.4	1.97	0	5.0	11
6	653	46	7.0	4.5	1.88	0	5.0	11
7	637	54	8.5	4.5	1.94	0	5.0	11
8	621	55	8.9	4.4	1.96	0	5.0	11
9	530	42	7.9	4.5	1.95	0	5.0	11
10	477	37	7.8	4.5	2.00	0	5.0	9
11	440	36	8.2	4.5	1.94	0	5.0	10
12	398	31	7.8	4.5	1.94	0	5.0	11
13	341	27	7.9	4.3	1.88	0	4.0	11
Overall	1101	22	2.2	4.5	1.46	0	4.6	8

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, Table 14.2.3.1 p 429/1147

Approximately 25% of subjects had unscheduled bleeding and/or spotting (day 1-21) for each cycle. The length of unscheduled bleeding and/or spotting averaged 0.8 to 1.3 days each cycle. The unscheduled bleeding and/or spotting did not decrease with subsequent cycles.

Table 19. Unscheduled Bleeding and Spotting (300A)

Cycle	N	n none	% no unscheduled bleeding/ spotting	Mean	SD	Min	Median	Max
1	995	747	75.1	1.3	2.91	0	0.0	14
2	905	735	81.2	0.8	2.29	0	0.0	17
3	791	640	80.9	0.7	1.94	0	0.0	19
4	761	644	84.6	0.7	2.16	0	0.0	20
5	760	623	82.0	0.7	1.97	0	0.0	17
6	659	521	79.1	0.7	1.91	0	0.0	16
7	638	505	79.2	1.0	2.38	0	0.0	16
8	625	482	77.1	0.9	2.13	0	0.0	17
9	533	415	77.9	0.9	2.20	0	0.0	18
10	481	366	76.1	1.0	2.37	0	0.0	16
11	442	343	77.6	1.1	2.57	0	0.0	17
12	399	302	75.7	1.2	2.76	0	0.0	21
13	366	272	74.3	1.1	2.46	0	0.3	15
Overall	1016	364	35.8	1.0	1.66	0	0.3	14

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, Table 14.2.3.1 p 430/1147

Most subjects provided data for cycle control with CVS use. Over 91% of subjects had an appropriately timed withdrawal bleed with the average duration of five days. Eighty-seven (87%) to 93% of subjects had no unscheduled bleeding any given cycle. Seventy-four (74%) to

85% of subjects had no unscheduled bleeding and/or spotting any given cycle; conversely 15% to 26% of subjects had unscheduled bleeding and/or spotting in any given cycle. When unscheduled bleeding and/or spotting occurred, the average length was one day. The maximum length of time for all bleeding and/or spotting (scheduled and unscheduled) ranged from 19-31 days/cycle. The number of days of bleeding or spotting did not decrease with subsequent cycles. The unscheduled bleeding incidence for this CVS (15-26%) is higher than the incidence of unscheduled bleeding and/or spotting for other products (i.e. 7-12% for NuvaRing and 6-18% for Ortho Evra). Compared to COCs, this CVS's unscheduled bleeding and/or spotting incidence is somewhat higher than that of a low dose COC (e.g. 6-12% for Yasmin), but not as high as that of Lo Loestrin FE (36-86%), which contains 10 µg of EE.

This CVS has a similar amenorrhea incidence as other non-oral CHCs (0.3-3.8%). Approximately 3% of subjects experienced amenorrhea for any given cycle with an overall amenorrhea rate of 0.7%.

Comment: *The bleeding profile from subject diaries will be noted in the label.*

8.2. Study 300B: A Multicenter, open-label study on the efficacy, cycle control and safety of a contraceptive vaginal ring delivering a daily dose of 150 mcg of Nesterone®* and 15 mcg of ethinyl estradiol (*segesterone acetate)

8.2.1. Study Design

Study 300B was conducted in eight countries including the US. The objectives, study design, and study endpoints of Study 300B were the same as Study 300A, except there were no routine laboratory tests at 6 months.

There was one additional procedure in 300B that was not included in 300A—an acceptability questionnaire. This questionnaire assessed the following CVS features:

- Ease of use
- Effects on sexual activity, including subjects' partners' perceptions of its impact on their sexual activity
- Satisfaction with the CVS, aspects of the CVS that subjects like or did not like, comparison with other contraceptive methods, and perception regarding using CVS for delivery of other therapies.

The acceptability questionnaire information was obtained by an interview administered by study site personnel or via audio computer assisted self-interviewing method (ACASI) during Cycle 3 (V2) and Cycle 13 or early termination (V5). Responses to the questionnaire were summarized using descriptive statistics.

There were no sub-studies in 300B. There was an extension study to 300B, called 300EX which allowed subjects to continue using the CVS after one year (a new CVS was dispensed) but this study was discontinued after 12 subjects had enrolled because the additional exposure after one year could not be used to meet the 20,000 cycles of exposure required for approval.

Statistical Analysis Plan
The primary endpoint was the Pearl Index for women ≤ 35 years of age (at enrollment) derived from all cycles in which no back-up contraception was used. Detailed statistical methodologies for this endpoint are described in the Study Endpoints section.

The applicant followed FDA recommendations for a phase 3 trial of a new contraceptive containing a new chemical entity, stipulating that participants be exposed to the drug for approximately 20,000 cycles with at least 400 women completing one year of use. Considering the premature drop-outs during the study, about 1000 subjects were planned for study 300 B.

The following subject populations were used in the study:

- Enrolled: all subjects who were enrolled into the study.
- Evaluable for Safety: all enrolled subjects who inserted the ring.
- Evaluable for Efficacy: all subjects Evaluable for Safety who used the study drug for at least one day, provided diary card data, and were not pregnant at the start of Cycle 1. If no diary data was available, then the enrolled subject needed to have the date of last ring use recorded in their CRFs along with the other criteria to be included this population.

Protocol Amendments:
The applicant submitted Amendment 7 on July 29, 2007 with the following protocol changes:

- Exclusion criteria for weight changed from >95 kg to BMI ≥ 35 kg/m^2, with exclusion of subjects with BMI >29 kg/m^2 who were <35 years old and had a risk factor for VTE.
- Two US study sites were added
- Changed requirement for two subsequent menses postpartum to one for post-abortal subjects and none for postpartum subjects.
- Changed upper limit of BP to >135/>85 from ≥135/≥85.
- Added randomization scheme to assign subjects to different methods of completing the acceptability interview.

The applicant submitted Amendment 8 on September 25, 2007, with the following protocol changes:

- Exclusion criteria weight changed to BMI >29 kg/m^2 per the study DSMB recommendation due to review of VTEs. See section 10.5.1, Analysis of VTE, for detailed discussion.

- Postpartum women must have history of regular menses and have resumed at least 1 cycle postpartum with cycle length consistent with past cycles

The applicant submitted Amendment 9 on November 28, 2007, with the following protocol changes:

- Amended 1 year duration use to less than 1 year if enrolled after January 2008. Specified all subjects must discontinue from trial December 31, 2008 because batches of CVS were expiring and modified ICF for shorted treatment period.
- Physical and gynecological exams at visit 3 removed for subjects who started CVS in 2007 only.

The applicant submitted Amendment 9EX on November 28, 2007, with the following protocol changes:

- Added extension phase to Study 300B allowing subjects to enroll for up to 1 year of additional CVS use.

The applicant advised the Division of discontinuation of enrollment into EX study on February 7, 2008:

- Extension study terminated because the applicant could not use cycle exposure data for FDA efficacy data.

8.2.2. Study Results

Compliance with Good Clinical Practices

The study report states that Study 300B was conducted according to guidelines of Good Clinical Practices (GCP) and the International Conference on Harmonization (ICH) in compliance with the regulations of the Declaration of Helsinki regarding the ethical use of human subjects in clinical trials. Institutional Review Boards (IRB) for each study site reviewed and approved the study protocol and subsequent amendments. In addition, an autonomous DSMB was established and conducted regular reviews of pregnancies and safety data. Population Council's SERC convened quarterly to review data in relation to study objectives.

Data Quality and Integrity

Each site underwent a study initiation visit to review study conduct and procedures. During the study, regular monitoring visits were made to each site to assess compliance. Data management review was conducted on CRF data and queries were sent to the sites to address any discrepancies or missing data.

During review of this study, the major concern regarding data quality and integrity was inconsistency in data between the patient diaries and CRFs. This included:

- Reconciliation of the inconsistencies occurred years after data were originally entered; therefore, any clarification of inconsistencies was not possible at this later date
- Many of the inconsistencies occurred at one site (Site 3, Santo Domingo, DR). Because this site had a large number of pregnancies, an analysis of PI with exclusion of the site was performed. By excluding site 3, the overall PI for study 300B was lower. Therefore, the site was not excluded for any of the PI calculations in this review. In addition, OSI selected this clinical site for inspection, and after their review classified the site as no deviation from regulation (NAI).

During review of study forms, there were instances of inconsistent documentation of subject information in the appropriate documents. An example of this was subject (b) (6), whose pregnancy was documented as a spontaneous abortion in the narratives for pregnancies occurring >7 days post CVS use AND as an ectopic pregnancy during CVS use in the narratives for SAEs.

Comments: *The lack of cross referencing data in real time and obtaining clarifying documentation decreased the quality of some information available in this study report. In addition, the inability to obtain information during the review process because the studies were conducted 10 years ago decreased the ability to evaluate data quality. However, the OSI inspection provided support that overall, the data quality and integrity for this study were sufficiently acceptable to support the indication. We then worked with the applicant to clarify issues that arose when the subject diaries and records were discordant.*

Patient Disposition

There were 1,537 subjects screened of which 1,135 were randomized (73.8%). The efficacy and safety populations included 1,135 subjects.

Table 20. Disposition of Study 300B Subjects

Disposition	Study 300B (N=1135) n (%)
Completed the Study	721 (63.5)
Discontinued Study	414 (36.5)
Reason for Discontinuation	
Lost to follow-up	76 (6.7)
Adverse Event	146 (12.9)
Withdrew consent	64 (5.6)
Eligibility BMI>29 kg/m2	50 (4.4)
Compliance	19 (1.7)

Pregnancy	29 (2.6)
Expulsions	24 (2.1)
Eligibility other	6 (0.5)
Other	0

Source: NDA 209627, Module 5.3.5.2, 300B Study Report, Figure 1 p 62/626

One hundred and fifty-eight subjects (158) or 13.9% enrolled in the 6-month follow up for return to fertility data.

The overall discontinuation rate for this global trial was 37%, which is lower than the US-only population trial (48%). This finding has been noted in other contraceptive trials such as NuvaRing with a 41% discontinuation rate in the US trial compared with a 30% discontinuation rate in the European trials. AEs accounted for 13% of discontinuations, with loss-to-follow up and withdrew consent accounting for 7% and 5% of the subjects. The majority of withdrew consent was due to other personal problems (24 subjects) and relocation (21 subjects). This is comparable to the Ortho Evra US/European trial with discontinuations occurring in 13%, 7%, and 5% of subjects for AEs, withdraw consent, and lost to follow up respectively.

Protocol Violations/Deviations

There were 40 eligibility criteria violations. Of these, 32 involved exclusions criteria violations: 12 abnormal serum chemistry, 8 abnormal blood pressure, 5 abnormal Pap smear, 4 smoking and ≥ 35 years old. There were six inclusion criteria deviations for healthy women aged 18 to 40 years of age at enrollment who wished to use CHC.

There were 548 deviations during the study recorded in a separate database by study monitors. The applicant does not provide totals for categories of deviations, i.e. visits out of time window, CVS not returned, deviations in laboratory tests, blood pressure, etc. Instead the largest number of deviations (20) noted by the applicant occurred for incorrectly measured height at site 9.

There were 1,135 CVSs distributed to 12 sites. Eighty-eight percent (88.5%) or 1,004 CVSs were returned.

> ***Comment:*** *The number of eligibility criteria violations is surprising since all results were to be reviewed prior to enrollment of subjects and all the eligibility criteria were clearly delineated in the inclusion criteria. The finding that there were incorrect height measurements by study staff leads to concerns for possible inaccurate BMI data. Overall, based on detailed review, we conclude that the protocol violations and deviations did not affect the efficacy outcome of the study to any significant degree and actually may have allowed a more representative population of patients to be enrolled.*

Demographic Characteristics

The safety and efficacy populations are the same. The applicant's table of summary demographics and baseline characteristics is shown in Table 21.

Table 21. Demographics 300B

Characteristic	Study 300B (N=1135) n (%)
Race (Multiple Races Allowed per Subject)	
Asian	35 (3.1)
Black or African American	150 (13.2)
American Indian or Native Alaskan	13 (1.1)
Native Hawaiian or Pacific Islander	3 (0.3)
White	985 (86.8)
Other/Unknown	42 (3.7)
Ethnicity	
Hispanic or Latina	502 (44.2)
Not Hispanic or Latina	633 (55.8)
Marital Status	
Never married	776 (68.4)
Married	303 (26.7)
Divorced	33 (2.9)
Separated	22 (1.9)
Widowed	1 (0.1)
Age (years)	
18 – 19	84 (7.4)
20 – 24	405 (35.7)
25 – 29	368 (32.4)
30 – 35	199 (17.5)
36 +	79 (7.0)
Education: Highest Level Attained	
College degree or higher	411 (36.2)
Some college	298 (26.3)
High school diploma/equivalent	304 (26.8)
Less than high school	122 (10.7)
Subject Desires to Have Children After the Study	
Yes	611 (53.8)
No	316 (27.8)
Unsure	208 (18.3)
Body Mass Index (kg/m2)	

Characteristic	Study 300B (N=1135) n (%)
value < 20	117 (10.3)
20 ≤ value < 25	642 (56.6)
25 ≤ value < 27	168 (14.8)
27 ≤ value ≤ 29	128 (11.3)
29 > value	80 (7.0)
Smoking	
Never smoked	825 (72.7)
Former smoker	122 (10.7)
Current smoker	188 (16.6)
Unknown	0
Alcohol Use History	
Never drank	394 (34.7)
Former drinker	19 (1.7)
Current drinker	722 (63.6)

Source: NDA 209627, Module 5.3.5.2, Study Report 300B, p 67/626

The mean age was 26.7 ±5.2 years and the mean BMI was 23.8 ±3.5 kg/m^2. Most subjects were White, never married, educated, nonsmokers, with desire for future fertility. Five hundred and seventy-five (575) or 50.7% of subjects were nulliparous.

> ***Comment:*** *Overall, the subjects in this study have characteristics that are generalizable to the US population that use hormonal contraceptive products.*

Menstrual characteristics showed 70.0% of subjects had moderate menstrual flow and 97.1% of subjects had menstrual flow ≤ 7 days. Typical symptoms associated with menstruation in this study population were 64% with cramps, 40% with mood changes, and 31.7% with bloating.

The majority of subjects used condoms or hormonal contraception in the 6 months prior to enrollment into the study. Some subjects used more than one type of contraceptive during this 6 month time period. The breakdown of contraception used is shown in the table below.

Table 22. Contraceptive Use Within 6 Month of Enrollment (Study 300B)

Type of contraceptive	Study 300B (N=1135) n (%)
Condoms	384 (33.8)
non-hormonal IUD	26 (2.3)
Withdrawal	36 (3.2)

hormonal contraceptives	638 (56.2)
vaginal rings	198 (17.4)
COC	410 (36.1)
transdermal patch	11 (1.0)

Source: NDA 209627, Module 5.3.5.2, Study Report 300B, p 265/626

Twenty-three percent (23.6%) of subjects used hormonal contraception for systemic use within 30 days prior to CVS use: 148 (13.0%) of subjects used a vaginal ring and 193 (17.0%) used other CHCs. Almost a quarter of subjects could be considered continuous users of contraception and over 56% were prior users.

The table below lists selected active medical history by preferred term.

Table 23. Selected Active Medical History of Subjects (Study 300B)

Preferred Term	**Study 300B (N=1135) n (%)**
Headache	216 (19.0)
Dysmenorrhea	106 (9.3)
Drug Hypersensitivity	99 (8.7)
UTI	61 (5.4)
Acne	30 (2.6)
Depression	29 (2.5)

Source: NDA 209627, Module 5.3.5.2, Study Report 300B, p 258/626

Concomitant Medications and Treatment Compliance

946 (83.3%) subjects used at least one concomitant medication. A table of concomitant medication used in >10% of subjects (not including vitamins) is shown below.

Table 24. Concomitant Medication Use in Subjects (Study 300B)

Level 2 Therapeutic Class	**Study 300B (N=1135) n (%)**
Anti-inflammatory (including NSAIDs*)	512 (45.1)
Analgesics (majority acetaminophen)	498 (43.9)
Antibacterial for system use	303 (26.7)
Antihistamines for systemic use	202 (17.8)
Antimycotic for systemic use***	134 (11.8)

*does not include gynecological anti-infective and antiseptics (clotrimazole, miconazole, clindamycin, nystatin and combinations = 77 subjects).

Source: NDA 209627, Module 5.3.5.2, Study Report 300B, Table 14.1.9.3 p 272/626

Compliance was determined by the subjects' diary cards. Only subjects who provided diary cards that confirmed insertion of CVS on day 1 for the given cycle were included in the compliance data. A subject was considered in compliance if the CVS was inserted on day 1 and had continuous use for the first 21 days of the cycles with no more than 2 hours interruption per day followed by 7 days of nonuse. The perfect compliance is >83.8% as defined above.

Efficacy Results – Primary Endpoint

Efficacy was based on the PI using all "on-treatment" pregnancies. On-treatment pregnancies were defined as those pregnancies for which conception occurred on or after the date of the first insertion of CVS and extended through seven days following removal of the CVS. The PI was derived from the population of women ages 18-35 years at the time of entry with exclusion of cycles where back-up contraception was used.

The applicant identified 22 on-treatment pregnancies. One pregnancy was in a 38 year old; therefore, there were 21 on-treatment pregnancies contributing to the PI for Study 300B. After detailed review and interaction with the applicant via Information Requests and responses, there was agreement between the Division and the applicant regarding these 21 on-treatment pregnancies (see detailed discussion below).

An IR, sent December 19, 2017, inquired about five additional pregnancies, four of which occurred in subjects whose diary data was crossed out and replaced with different dates added for last CVS use. The applicant provided source data obtained by the clinic staff which supports the assertion that these subjects filled out their diaries in advance of the actual dates of CVS usage. The fifth pregnancy occurred in Subject (b) (6), who had a βhCG level of 20 mIU/ml, and per laboratory report was categorized as inconclusive for pregnancy, with a follow up negative UPT.

Table 25. Adjudicated Pregnancies (Study 300B)

Subject	Start Drug	Last CVS Use	LMP	Pregnancy Confirm	Estimated date of Conception	Applicant	Medical Officer Determination
(b) (6)	(b) (6)	(b) (6) per crf (b) (6) (crossed out) per diary ring out (b) (6) Ring back in (b) (6) (all crossed out)	(b) (6) per crf (b) (6) (crossed out)	positive UPT (b) (6) US (b) (6) 5w3d pregnancy notification	(b) (6)	15+	off (discount diary)

				dates crossed out and changed.			
(b) (6)	(b) (6)	(b) (6) per narrative subject "admitted" she d/c ring use (b) (6) but completed diary per schedule. diary shows use through (b) (6) (crossed out)	(b) (6) per crf (b) (6) (crossed out)	positive UPT (b) (6) US (b) (6) 9wk3d negative UPT (b) (6)	(b) (6)	15+	off (discount diary)
(b) (6)	(b) (6)	(b) (6) per narrative subject "admitted: to d/c ring (b) (6) but completed her diary per schedule. per crf last use (b) (6) (crossed out and (b) (6) placed) per diary CVS out (b) (6) and in (b) (6) and out (b) (6) and in (b) (6) and out (b) (6) (Most of (b) (6) crossed out and written over)	(b) (6) per diary bleeding (b) (6) and bleeding (b) (6)	ßhCG 3,729 mIU/ml on (b) (6) per CRF, spontaneous abortion in progress US no evidence of IUP	(b) (6) based on lmp	off	off (discount diary)

(b) (6)	(b) (6)	(b) (6) after questioning by study staff "admitted" to filling out diary according to what should have been her schedule per crf (b) (6) (crossed out and (b) (6) placed) per diary CVS out (b) (6) with nothing checked until (b) (6) when CVS back in until (b) (6), out (b) (6) and in (b) (6) (most crossed out)	(b) (6)	Positive UPT (b) (6) US (b) (6) 6 wk GA	(b) (6)	8-14 day	8-14 day (discount diary)
(b) (6)	(b) (6)	"unsure" per narrative per crf (b) (6) per diary (b) (6)	(b) (6) per preg notification diary	ßhCG 20 mIU/ml and negative UPT on (b) (6) negative UPT (b) (6)		excluded from analyses "only documentation preg test is equivocal. We are unclear if she was ever pregnant" Applicate states possible "chemical pregnancy" and has excluded subject from efficacy	ßhCG inconclusive per lab test therefore agree with excluding this subject from efficacy analysis

						analyses p 191 narrative.	

Source: NDA 209627, Module 5.3.5.2, 300B Study Report, Response to IR Submitted 1/16/2018

Comment: *Three of the four subjects with diary data crossed out were enrolled at the same study site—Site 3. A sensitivity analysis was done for PIs, calculating PIs with and without subjects from Clinic 3 which showed a lower PI if Site 3 was excluded. In addition, this site was selected for inspection by OSI, and classified as NAI.*

There was one additional pregnancy in Subject (b) (6) which was identified as an ectopic pregnancy in a patient whose last date of CVS use was after she had a laparoscopic salpingectomy. The applicant provided chart documentation showing the date of conception occurred 15+ days after last use of the CVS. The subject subsequently restarted the CVS after her laparoscopic surgery. This same pregnancy was also reported as an off-treatment pregnancy ending in spontaneous abortion. The narrative describing this pregnancy as a spontaneous abortion was based on evidence of sequential decreasing βhCG levels and was classified as such prior to the diagnosis of the ectopic pregnancy.

The FDA statistical reviewer's analysis of the PI (primary endpoint) is shown in the table below.

Table 26. Study 300 B: Pearl Index for subjects ≤ 35 years old using pregnancies from evaluable cycles within 7 days from CVS removal

		Efficacy Population		
Study	**N**	**Number of Pregnancies**	**Number of evaluable cycles**	**PI using evaluable cycles (95% CI)**
300B	1056	21	9457	2.89 (1.79, 4.41)

Source: Reviewer's analysis. Data: \NDA209627\0007\m5\datasets\ise\analysis\legacy\datasets\eff.xpt.
Note: 1. Cycles beyond cycles 13 were not included in the calculation. 2. 95% CI was based on the Poisson distribution.

Comment: *The PI and 95% CI for the CVS in this one study are consistent with two recently approved CHCs: Quartette in 2013 with PI 3.19 (2.49, 4.03) and Lo Loestrin FE in 2010 with PI 2.92 (1.94, 4.21). All of the studies calculated the PI similarly, with a 7-day on treatment pregnancy window and removing cycles where bac up contraception was used. The findings in Study 300B are similar to the findings in Study 300A.*

The Division also requested analysis of the PI for pregnancies that occurred within 14 days after last CVS use. The applicant and Division agreed on two additional pregnancies conceived 8-14 days after CVS, providing a total of 23 pregnancies. The PI for pregnancies occurring within 14 days after last CVS use in women ≤ 35 years with back up cycles removed was calculated by the applicant to be 2.99 (2.16, 4.00)[11]. The FDA statistical reviewer's analysis is presented in the table below.

Table 27. Study 300B: Pearl Index for subjects ≤ 35 years old using pregnancies from evaluable cycles within 14 days from CVS removal

		Efficacy Population		
Study	**N**	**Number of Pregnancies**	**Number of evaluable cycles**	**PI using evaluable cycles (95% CI)**
300B	1056	23	9457	3.16 (2.00, 4.74)

Source: Reviewer's analysis. Data: \NDA209627\0007\m5\datasets\ise\analysis\legacy\datasets\eff.xpt.
Note: 1. Cycles beyond cycles 13 were not included in the calculation. 2. 95% CI was based on the Poisson distribution.

Comment: *The PI increases further when on-treatment pregnancy is defined as up to 14 days after CVS use. This demonstrates the need for prompt use of the CVS after seven days with no use.*

Efficacy Results – Supportive endpoints

Life table methods of cumulative pregnancy rates were a supportive endpoint for CVS efficacy. The applicant's cumulative pregnancy rates for subjects ≤ 35 years old with pregnancies occurring within seven days of last CVS use utilizing all cycles[12] are very similar to the cumulative pregnancy rate calculated by the FDA shown in the table below.

Table 28. Study 300B: Kaplan-Meier Analysis of Pregnancy Among Subjects ≤ 35 Years Old Using All Cycles

Cycle	Subjects at Risk	Number of Pregnancies (with 7 days)	Cumulative Probability of Pregnancy (95% CI)
1	1056	0	0
2	1002	3	0.0030 (0.0010, 0.0093)
3	957	2	0.0051 (0.0021, 0.0122)
4	902	0	0.0051 (0.0021, 0.0122)
5	869	4	0.0097 (0.0050, 0.0185)
6	848	0	0.0097 (0.0050, 0.0185)
7	805	0	0.0097 (0.0050, 0.0185)
8	772	2	0.0122 (0.0068, 0.0220)
9	708	2	0.0150 (0.0087, 0.0258)
10	648	3	0.0196 (0.0120, 0.0319)

[11] \\cdsesub1\evsprod\nda209627\0007\m5\53-clin-stud-rep\535-rep-effic-safety-stud\contraception\5353-rep-analys-data-more-one-stud\ise\day-74-requests.pdf
[12] NDA 209627, Module 5.3.5.2, 300B Study Report, Table 14.2.2.1 p 343/626

Cycle	Subjects at Risk	Number of Pregnancies (with 7 days)	Cumulative Probability of Pregnancy (95% CI)
11	585	3	0.0246 (0.0156, 0.0386)
12	533	1	0.0264 (0.0170, 0.0410)
13	499	1	0.0284 (0.0184, 0.0436)

Source: Table 14.2.2.1 in Study 300B CSR and reviewer's analysis. Data: \NDA209627\0007\m5\datasets\ise\analysis\legacy\datasets\eff.xpt.

Comment: *The cumulative pregnancy rate of 2.84% at one year is comparable to the PI of 2.89 with a 95% Cl between 1.79 and 4.41.*

Efficacy Results – Secondary endpoints

Cycle Control

Based on subject diary data, greater than 93% of subjects had some bleeding and/or spotting each cycle. The mean number of days of bleeding and/or spotting was between 4.8-5.8 days each cycle. The number of days of bleeding and/or spotting did not decrease with subsequent cycles. Between 2.5 and 6.2% of subjects had amenorrhea for any given cycle with an overall amenorrhea rate of 1.1%.

Table 29. Scheduled and Unscheduled Bleeding and Spotting (Study 300B)

		no bleeding or spotting		bleeding or spotting number of days				
Cycle	N	n	%	Mean	SD	Min	Median	Max
1	1020	26	2.5	5.8	3.26	0	5	25
2	831	34	4.1	4.9	2.38	0	5	28
3	716	21	2.9	5	2.12	0	5	19
4	693	22	3.2	5	2.31	0	5	26
5	649	23	3.5	5	2.34	0	5	22
6	603	28	4.6	5	2.41	0	5	22
7	573	15	2.6	5.1	2.52	0	5	27
8	550	26	4.7	5	2.57	0	5	20
9	490	23	4.7	5.2	2.58	0	5	17
10	455	19	4.2	5.2	2.62	0	5	21
11	410	11	2.7	5.4	2.62	0	5	19
12	381	9	2.4	5.2	2.47	0	5	18
13	307	19	6.2	4.8	2.6	0	5	20
Overall	1042	11	1.1	5.2	2.04	0	5	25

Source: NDA 209627, Module 5.3.5.2, 300B Study Report, Table 14.2.3.1 p 349/626

The number of women with scheduled bleeding and/or spotting (withdrawal bleed at appropriate time) was greater than 92% for each cycle with the average of 5 days of bleeding and/or spotting. The longest withdrawal bleeding and/or spotting was 11 days and this did not decrease with subsequent cycles.

Table 30. Scheduled Bleeding and/or Spotting (Study 300B)

Cycle	N	none	% with no bleeding/spotting	Mean	SD	Min	Median	Max
1	1029	51	5.0	4.8	1.83	0	5.0	11
2	837	50	6.0	4.5	1.82	0	5.0	11
3	721	32	4.4	4.7	1.71	0	5.0	11
4	695	29	4.2	4.7	1.67	0	5.0	9
5	650	31	4.8	4.6	1.74	0	5.0	11
6	606	36	5.9	4.6	1.83	0	5.0	11
7	577	22	3.8	4.6	1.71	0	5.0	11
8	553	34	6.1	4.5	1.82	0	5.0	10
9	492	33	6.7	4.6	1.90	0	5.0	11
10	455	23	5.1	4.6	1.88	0	5.0	10
11	410	16	3.9	4.7	1.80	0	5.0	11
12	382	13	3.4	4.7	1.78	0	5.0	10
13	308	25	8.1	4.2	1.98	0	4.0	9
Overall	1044	22	2.1	4.5	1.44	0	4.6	11

Source: NDA 209627, Module 5.3.5.2, 300B Study Report, Table 14.2.3.1 p 347/626

Approximately 10-18% of subjects had unscheduled bleeding and/or spotting (day 1-21) for each cycle. The length of unscheduled bleeding and/or spotting averaged less than one day and did not decrease with subsequent cycles.

Table 31. Unscheduled Bleeding and/or Spotting (Study 300B)

Cycle	N	none	% with no bleeding/spotting	Mean	SD	Min	Median	Max
1	1034	844	81.6	0.9	2.66	0	0.0	14
2	849	743	87.5	0.4	1.57	0	0.0	17
3	729	632	86.7	0.4	1.35	0	0.0	17
4	699	624	89.3	0.3	1.44	0	0.0	17
5	657	577	87.8	0.4	1.56	0	0.0	15
6	608	516	84.9	0.5	1.51	0	0.0	16
7	576	503	87.3	0.5	1.67	0	0.0	16
8	553	480	86.8	0.5	1.66	0	0.0	14

Cycle	N	none	% with no bleeding/spotting	Mean	SD	Min	Median	Max
9	494	419	84.8	0.6	1.82	0	0.0	12
10	458	390	85.2	0.6	1.86	0	0.0	13
11	414	341	82.4	0.7	1.98	0	0.0	17
12	384	320	83.3	0.6	1.74	0	0.0	12
13	347	286	82.4	0.7	1.92	0	0.0	13
Overall	1052	539	51.2	0.7	1.46	0	0.0	14

Source: NDA 209627, Module 5.3.5.2, 300B Study Report, Table 14.2.3.1 p 348/626

Most subjects provided data for cycle control with CVS use that was usable for analysis. Over 93% of subjects had a withdrawal bleed the four week of each cycle with the average duration of five days. Ninety-two to 97% of subjects had no unscheduled bleeding any given cycles. Eighty-two (82%) to 89% of subjects had no unscheduled bleeding and/or spotting any given cycles, with the remaining 11-18% of subjects with unscheduled bleeding and/or spotting in any given cycle. When unscheduled bleeding and/or spotting occurred, the average length was less than one day. The maximum length of time for all bleeding and/or spotting ranged from 17-28 days/cycle. The number of days of spotting or bleeding did not decrease with subsequent cycles. For comparison, in the non-US trial of NuvaRing, unscheduled bleeding and/or spotting occurred in 3-9% of the subjects during cycles 1-13 and the European trials for Ortho Evra had 14% of subjects with unscheduled bleeding and/or spotting at cycle 3 decreasing to 9% at cycle 6.

Approximately 4% of subjects experienced amenorrhea for any given cycle with an overall amenorrhea rate of 1.1%. Amenorrhea in the non-US NuvaRing trial was up to 2%.

> ***Comment:*** *Overall, the CVS has a somewhat higher incidence of unscheduled bleeding and/or spotting and a comparable incidence of amenorrhea compared with other non-oral CHCs. The label will address the above bleeding/spotting patterns so that users are aware of these issues.*

8.3. Integrated Summary of Effectiveness (ISE)

The ISE analysis for PI, life table estimates, and cycle control and how the four studies contributed to the different analysis sets is shown below (Table 35).

Table 32. Pooled ISE Analysis Sets

	Total		300A		300B		300 B-Ex		300 PK	
Analysis set	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Total	2317		1143		1135		12		39	

All cycle	2303	99.4	1129	98.8	1135	100	12	100	39	100
Life table	2264	97.7	1129	98.8	1135	100	0		0	
Pearl Index	2062	89	997	87.2	1065	93.8	0		0	
Primary subgroup*	1923	83	931	81.5	992	87.4	0		0	
All cycle control	2108	91	1016	88.9	1054	92.9	5	41.7	38	97.4
Pivotal	2070	89.3	1016	88.9	1054	92.9	0		0	

*primary ISE
Source: NDA 209627, Module 5.3.5.3, ISE Table 8-1, p42/433

The Analysis sets excluded 17 subject numbers from Study 300A involving nine subjects. One subject never used the CVS, five subjects enrolled at two concurrent sites (accounting for a total of 10 subject numbers), and three subjects enrolled at two sites sequentially. One subject (b) (6) was added when her pregnancy was determined to be on-treatment.

The ISE PI was derived from the Primary subgroup of the Pearl Index Analysis set, that is subjects ≤35 years of age at enrollment into studies 300A and 300B, and based on cycles excluding the ones where adjunctive contraception was used. The Life table analysis set included all subjects from 300A and 300B and included all cycles. The secondary efficacy endpoint (cycle control) was evaluated using the All cycle control and pivotal cycle control analysis sets which differed by the 43 subjects from 300B-Ex and 300PK.

> ***Comment:*** *During the review cycle, the Division also requested removal of cycles when heterosexual intercourse did not occur from the "at-ris " cycles when calculating the PI, as this information was collected on the diary cards. However, late in the cycle the applicant noted that data on occurrence of intercourse was not reliable, i.e. this data was not confirmed at clinic visits. Further, the applicant noted that two pregnancies occurred in cycles where the diary noted no intercourse had occurred. Because of the above information, and because the SAP did not specify removal of cycles where intercourse did not occur, the Division withdrew the request to remove these cycles for this application.*

Demographics
Selective demographic parameters of the Primary subgroup Pearl Index (used for PI), Life table (used for cumulative pregnancy), and the All cycle control analysis set (one of two analysis sets used to describe bleeding patterns) are shown in the table below.

Table 33. Selected Demographics for Three ISE Analysis Sets

Characteristic	Primary subgroup of Pearl Index N=1923	Life table N=2264	All cycle control N=2108
Mean age (SD)	25.9 (4.2)	26.7 (5.1)	26.7 (5.1)
BMI (SD)	23.9 (3.6)	24.2 (3.7)	24.0 (3.7)

Caucasian race %	78.1	76.8	77.6
Non-Hispanic ethnicity %	70.3	71.3	70.1
Never married %	72.0	70.7	68.4
College degree or higher %	42.2	41.9	42.2
Never smoked %	71.5	71.4	70.1

Source: NDA 209627, Module 5.3.5.3, ISE Table 1.3.1 p 83/433, Table 1.3.2 p90/433

The majority of subjects in the All cycle analysis set [1,531 out of 2303 (66.5%)] were from the US.

Medical and gynecologic history were similar between the ISE analysis sets.

Disposition

Subject dispositions in the ISE analysis sets were very similar. The three analysis sets differed in proportion of subjects completing the study and early termination due to loss-to-follow up. The All cycle control set and the Primary subgroup of PI compared with the Life table analysis set had a higher completion (62% vs 58%) and a lower loss-to-follow-up proportion (6.4% vs 9.5%).

Disposition of the primary ISE and comparison to the two pivotal trials is shown below in the applicant's table.

Table 34. Subject Disposition, Pooled Studies 300A and 300B

Disposition	Study 300A (N=1129) n (%)	Study 300B (N=1135) n (%)
Completed the Study	582 (51.6)	721 (63.5)
Discontinued Study	547 (48.4)	414 (36.5)
Reason for Discontinuation		
Lost to follow-up	138 (12.2)	76 (6.7)
Adverse Event	130 (11.5)	146 (12.9)
Withdrew consent	129 (11.4)	64 (5.6)
Eligibility BMI>29 kg/m2	88 (7.8)	50 (4.4)
Compliance	26 (2.3)	19 (1.7)
Pregnancy	24 (2.1)	29 (2.6)
Expulsions	9 (0.8)	24 (2.1)
Eligibility other	2 (0.2)	6 (0.5)
Other	1 (0.1)	0

Source: NDA 209627, Module 5.3.5.3, ISE, p 50/433

Comment: *Comparing subject disposition between the two pivotal studies shows the US only study had a higher overall discontinuation rate with withdrew consent and lost to follow-up being higher than the global study. For the global population, AEs were the most frequent reason for discontinuation, and this proportion was higher than the US only population. Having a BMI >29 g/ m^2 was the overwhelming reason for discontinuation due to eligibility and this was higher in the US study. The overall disposition of subjects in the two studies are similar with the differences being noted in other US and global contraceptive studies. Overall, the clinical reviewer concluded that there were sufficient numbers of cycles in women in the US to adequately assess efficacy of the product in the indicated population.*

9. Integrated Review of Effectiveness

9.1. Assessment of Efficacy Across Trials

9.1.1. Primary Endpoints

The primary endpoints are the PI derived from studies 300A and 300B separately and combined, using pregnancies occurring in women ≤35 years old at time of study entry whose date of conception was within seven days of last CVS use. Cycles in which adjunctive (or back-up) contraception was used were excluded.

The PI (95% CI) for the CVS based on the primary efficacy endpoints are shown in Table 35.

Table 35. Studies 300A and 300B: Pearl Index for subjects ≤ 35 years old using pregnancies from evaluable cycles within 7 days from CVS removal

		Efficacy Population		
Study	**N**	**Number of Pregnancies**	**Number of evaluable cycles**	**PI using evaluable cycles (95% CI)**
300A	1055	19	7970	3.10 (1.87, 4.84)
300B	1056	21	9457	2.89 (1.79, 4.41)
Pooled	2111	40	17427	2.98 (2.13, 4.06)

Source: Reviewer's analysis. Data: \NDA209627\0007\m5\datasets\ise\analysis\legacy\datasets\eff.xpt.
Notes: 1. Include pregnancy from subject (b) (6). 2. Cycles beyond cycles 13 were not included in the calculation. 3. 95% CI was based on the Poisson distribution.

Comments: *The pooled PI of 2.98 with an upper bound of the 95% CI of 4.06 is in line with two recently approved CHCs: Quartette 3.19 (upper bound of the 95% CI of 4.03) and Lo Loestrin 2.92 (upper bound of the 95% CI of 4.21). The pooled PI utilizes 17,000 cycles and provides a narrower 95% CI than either trial alone; the pooled PI and 95% CI is the primary efficacy endpoint included in the labeling of this product.*

The key supportive endpoints for efficacy of the CVS presented in this review are:

- PI for subjects ≤ 35 y/o using at cycles with no back-up contraception for pregnancies within 14 days
- Life table analysis for cumulative pregnancy rate for ≤ 35 y/o using all cycles for pregnancies within 7 days
- Life table analysis for cumulative pregnancy rate for all subjects using all cycles for pregnancies within 7 days

Extending the on-treatment pregnancy window to within 14 days after CVS use increased the PI for both studies as shown below.

Table 36. Studies 300A and 300B: Pearl Index for subjects ≤ 35 years old using pregnancies from evaluable cycles within 14 days from CVS removal

Efficacy Population

Study	N	Number of Pregnancies	Number of evaluable cycles	PI using evaluable cycles (95% CI)
300A	1055	22	7970	3.59 (2.25, 5.43)
300B	1056	23	9457	3.16 (2.00, 4.74)
Pooled	2111	45	17427	3.36 (2.45, 4.49)

Source: Reviewer's analysis. Data: \NDA209627\0007\m5\datasets\ise\analysis\legacy\datasets\eff.xpt.
Notes: 1. Include pregnancy from subject (b) (6)2. Cycles beyond cycles 13 were not included in the calculation.
3 95% CI was based on the Poisson distribution.

The Life table analysis for cumulative probably of pregnancy occurring within seven days of last CVS use provided by the applicant[13] is similar to the analysis performed by the FDA statistician in the table below.

Table 37. Kaplan-Meier Analysis of Pregnancy Among Subjects ≤ 35 Years Old Using All Cycles

Cycle	Subjects at Risk	Number of Pregnancies (with 7 days)	Cumulative Probability of Pregnancy (95% CI)
0	2111	2	0
1	2111	2	0.0009 (0.0002, 0.0038)
2	1979	7	0.0045 (0.0023, 0.0086)
3	1884	5	0.0071 (0.0042, 0.0120)
4	1766	2	0.0082 (0.0051, 0.0134)
5	1693	4	0.0106 (0.0068, 0.0164)
6	1623	2	0.0118 (0.0078, 0.0179)
7	1510	0	0.0118 (0.0078, 0.0179)
8	1436	4	0.0146 (0.0099, 0.0214)
9	1304	3	0.0168 (0.0117, 0.0242)

[13] Application 209627 - Sequence 0018 - Integrated Summary of Efficacy - Table 2.3.1 Kaplan-Meier Life Tables of Pregnancy (Revised)

Cycle	Subjects at Risk	Number of Pregnancies (with 7 days)	Cumulative Probability of Pregnancy (95% CI)
10	1180	4	0.0202 (0.0143, 0.0284)
11	1061	3	0.0229 (0.0165, 0.0319)
12	961	3	0.0260 (0.0189, 0.0358)
13	897	1	0.0271 (0.0197, 0.0371)

Source: Reviewer's analysis. Data: \NDA209627\0007\m5\datasets\ise\analysis\legacy\datasets\eff.xpt.

The Life table analysis for cumulative probably of pregnancy for all subjects in the pivotal trials, irrespective of age, occurring within seven days of last CVS use was 0.0251 (95% CI 0.0346, 0.0182)[14].

> ***Comment:*** *The cumulative probably of pregnancy in women ≤ 35 years for the CVS at one year (2.71% [95% CI:1.97, 3.71]) is comparable to the pooled primary efficacy PI of 2.98 with a 95% CI between 2.13 and 4.06. Because life-table analysis is a secondary and supportive analysis, these results will not be included in labeling.*

9.1.2. Secondary Endpoints

We consider Cycle Control to be an important secondary efficacy endpoint because it often leads to method discontinuation. Cycle control was evaluated using two analysis sets, the All-Cycle Control Analysis Set and the Pivotal Cycle Control Analysis Set. The All-Cycle Control analysis set contained data from all 4 studies (300A, 300B, 300 PK, 300 Ex) while the Pivotal Cycle Control analysis set contained data from studies 300A and 300B only. To be included, the subject had to have diary entries on bleeding for at least 15 of 21 days during ring-in period and at least 3 of 7 days during the ring-out period. The subjects recorded spotting (no sanitary protections used), normal and heavy bleeding (sanitary protection used) with normal and heavy bleeding combined into one category "bleeding." Bleeding/spotting that occurred during the ring free interval and continuing through Day 1-4 was not considered unscheduled. Bleeding/spotting during Days 1-7 of the first cycle was not considered unscheduled.

In the pivotal cycle control analysis set, scheduled bleeding and/or spotting occurred in over 92% of users each cycle with the median number of 5 days with 1 year use, shown in Table 38. The number of days of scheduled bleeding did not decrease with use. Amenorrhea occurred in 3-5% of users each cycle over 1 year use and 0.9% overall (data not shown[15]).

Table 38. Pivotal Cycle Control, Scheduled Bleeding and/or Spotting

Cycle	N	n bleeding and/or spotting	mean days of bleeding and/or spotting	SD	maximum days of bleeding

[14] NDA 209627, Module 5.3.5.3, ISE p 8/433
[15] NDA 209627, Module 5.3.5.3, ISE, Table 2.4.1 p 391/433

		(%)			and/or spotting
1	2020	1908 (94.5)	4.9	1.89	11
2	1744	1625 (93.2)	4.5	1.87	11
3	1509	1423 (94.3)	4.6	1.81	11
4	1456	1372 (94.2)	4.6	1.84	11
5	1406	1312 (93.3)	4.5	1.87	11
6	1259	1177 (93.5)	4.5	1.85	11
7	1214	1138 (93.7)	4.5	1.83	11
8	1174	1085	4.5	1.90	11
9	1022	947	4.5	1.93	11
10	932	872	4.5	1.94	10
11	850	798	4.6	1.88	11
12	780	736	4.6	1.86	11
13	649	597	4.2	1.93	11
Overall	2055	2011	4.5	1.45	11

Source NDA 209627, Module 5.3.5.3, ISE, Table 2.4.1 p 389/433

Over 78% of subjects had no unscheduled bleeding and/or spotting in any given cycle. Of the 13-21% of subjects with unscheduled bleeding and/or spotting, the mean number of days was less than one.

Table 39. Pivotal Cycle Control, Unscheduled Bleeding and/or Spotting

Cycle	N	None* n (%)	Any* n (%)	mean days	SD Days	max days
1	2029	1591 (78.4)	438 (21.6)	1.1	2.79	14
2	1754	1478 (84.3)	276 (15.7)	0.6	1.98	17
3	1520	1272 (83.7)	248 (16.3)	0.6	1.69	19
4	1460	1268 (86.8)	192 (13.2)	0.5	1.85	20
5	1417	1200 (84.7)	217 (15.3)	0.6	1.80	17
6	1267	1037 (81.8)	230 (18.2)	0.6	1.73	16
7	1214	1008 (83.0)	206 (17.0)	0.7	2.09	16
8	1178	962 (81.7)	216 (18.3)	0.7	1.93	17
9	1027	834 (81.2)	193 (18.8)	0.8	2.03	18
10	939	756 (80.5)	183 (19.5)	0.8	2.15	16
11	856	684 (79.9)	172 (20.1)	0.9	2.31	17
12	783	622 (79.4)	161 (20.6)	0.9	2.33	21
13	713	558 (78.3)	155 (21.7)	0.9	2.22	15
Overall	2068	903 (43.7)	1165 (56.3)	0.8	1.57	14

*unscheduled bleeding and/or spotting
Source NDA 209627, Module 5.3.5.3, ISE, Table 2.4.1. p 390/433

Comment: *The label will reflect that over 92% of users have withdrawal bleeding, up to 5% of subjects have amenorrhea, and 5-10% have unscheduled bleeding. The CVS bleeding profile has a higher incidence of unscheduled bleeding and/or spotting (up to 22%) compared with most other CHCs, and an amenorrheic rate similar to other non-oral CHCs. This information is important for providers and patients when considering use of this product.*

9.1.3. Subpopulations

The applicant provided subgroup analyses of the PI utilizing the All Cycle Population for the following subgroups:

- Race group (only Black, only White, Other/unknown)
- Ethnicity (Hispanic, Non-Hispanic)
- BMI (≤ 29 kg/m^2 vs. > 29 kg/m^2)
- Geographic region (US vs. non-US, Europe vs non-Europe)
- Parity (0 vs. ≥1)
- Age (≤35 vs. > 36)
- Age quartiles
- Age of ring (post-hoc analysis)

The Division requested geographic subgroups for US/non-US. Subjects from the US made up 66-67% of the All-cycle and primary ISE analysis sets. Based on FDA analysis, US subjects contributed 62.7% of the 18,745 evaluable cycles (all ages).

Table 40. US/Non-US Subjects and Cycles Used for PI

Study	Country	# subjects in the safety and efficacy populations	# all cycles based on efficacy population	# evaluable cycles based on efficacy population*	# pregnancies within 7 days of
300A	US	1130	9880	8572	19
300 B	US	389	3433	3194	7
	Non-US	746	7509	6979	15
Total	**US**	1519	13313	11766	**26**

Source: electronic communication 4/10/18 from W. Zhang, PhD, FDA Statistician
* Evaluable cycles are the cycles excluding adjunctive contraception.
* This table included all subjects 18-40 years of age in the study.

The applicant presents subgroup analyses using the All Cycle population prior to adjudication of pregnancies and defining on treatment pregnancy within 7 days of last CVS use. The PIs with 95% CI submitted by the applicant[16] are similar to the PIs using all cycles of the primary ISE as calculated by FDA's statistician shown in the table below.

[16] Application 209627 - Sequence 0001 - Integrated Summary of Efficacy, Table 10-4 p 58/433

Table 41. Pearl Index for subjects ≤ 35 years old by subgroup

Efficacy Population

Subgroup	N	Number of pregnancies	Number of evaluable cycles	Pear Index using evaluable cycles (95% CI)	Number of all cycles	Pear Index using all cycles (95% CI)
Race - White only	1511	18	13036	1.80 (1.06, 2.84)	14352	1.63 (0.97, 2.58)
- Black only	296	12	1867	8.36 (4.32, 14.60)	2279	6.85 (3.54, 11.96)
- Other races*	304	10	2524	5.15 (2.47, 9.47)	2774	4.69 (2.25, 8.62)
Ethnicity – Hispanic	618	27	5494	6.39 (4.21, 9.30)	5921	5.93 (3.91, 8.63)
- Non-Hispanic	1493	13	11933	1.42 (0.75, 2.42)	13484	1.25 (0.67, 2.14)
BMI ≤ 29	1935	38	16604	2.98 (2.11, 4.08)	18455	2.68 (1.89, 3.67)
> 29	176	2	823	3.16 (0.38, 11.41)	950	2.74 (0.33, 9.89)
Site – USA	1423	26	11015	3.07 (2.00, 4.50)	12499	2.70 (1.77, 3.96)
- Non-USA	688	14	6412	2.84 (1.55, 4.76)	6906	2.64 (1.44, 4.42)
Site – Europe	278	1	2477	0.52 (0.01, 2.92)	2692	0.48 (0.01, 2.69)
- Non-Europe	1833	39	14950	3.39 (2.41, 4.64)	16713	3.03 (2.16, 4.15)
Parity = 0	1441	14	12031	1.51 (0.83, 2.54)	13531	1.35 (0.74, 2.26)
> 0	670	26	5396	6.26 (4.09, 9.18)	5874	5.75 (3.76, 8.43)

Source: NDA209627\0017\m1\us\111-info-amend\mult-mod-info-amend.pdf and reviewer's analysis.
Data: \NDA209627\0007\m5\datasets\ise\analysis\legacy\datasets\eff.xpt.
Note: Using evaluable cycles and pregnancies with 7 days. * include Asian, American Indian / Alaska Native, Native Hawaiian / Pacific Islander, or multi-races.

There are large differences in the PIs based on race, ethnicity, European vs non-European population, and parity. The studies were not statistically powered to detect differences in any of the above subgroups. Each subgroup is skewed in numbers of subjects producing PIs with wide 95% CIs. Because of this, meaningful comparisons are not possible. Physiologically, the CVS should be effective regardless of race or ethnicity. In general, PIs in European populations are consistently lower in CHC trials as compared to those that use US populations, a finding thought to be due to factors other than the CHC being studied, such as more adherent users and/or lower body mass index in the European clinical trial populations. Women of parity have proven fertility and may indeed be a different population than nulliparous women, but definitive conclusions cannot be drawn from the small number of parous subjects. For this application, we determined that although there are significant differences across the regions under study, there was sufficient cycle information from women in the US to allowing labeling for the indicated population.

> ***Comment:*** *Interestingly, the one subgroup that might be expected to show a difference, subjects with higher BMIs, had a PI similar to that of the general study population. The applicant's reasoning for this unexpected finding is discussed in Section* 10.11 Integrated Assessment of Safety**.**

Analysis of PIs in the All Cycle analysis set based on age of CVS was performed post-hoc by the

applicant.

Table 42. Pearl Index by Age of CVS at Insertion

Analysis Set	Age of Ring	Pregnancies	N	Cycles	Pearl Index	95% CI
All Cycle	2 years or greater	13	745	5261	2.47	(1.93, 3.16)
	1.69 years thru 1.99 years	16	777	6598	2 96	(2.42, 3.61)
	Less then 1.69 years	12	781	6199	2 31	(1.82, 2.92)
	Age of Ring Tertiles (Ratio)	.	.	.	1 04	(0.88, 1.22)

Source: NDA 209627, Module 5.3.5.3, ISE Table 2.5.1 p 405/433

Comment: *Age of CVS at time of insertion does not appear to affect efficacy of the CVS; therefore, no labeling on this is necessary.*

9.1.4. Considerations on Benefit in the Postmarket Setting

9.1.5. Other Relevant Benefits

9.2. Statistical Issues

It was noted during the review that five subjects with 10 unique subject IDs who were enrolled in two centers at the same time were excluded from the efficacy and safety analyses. Three subjects with six unique subject IDs were enrolled in two centers sequentially and only clinical data from the first site was included in the efficacy and safety datasets. These issues were addressed in Study 300A's CSR and the ISE. An information request was sent on April 17, 2018 for further clarification. In the response submitted on April 26, 2018, the applicant confirmed that the five subjects were enrolled and received CVSs from two centers, attended visits at two centers, and four of them completed an end of study visit at both centers. Three of the sixteen CVSs dispensed to these eight subjects were not returned. Considering the feasibility of separating the cycles from the two sites for a subject and to be conservative to estimate the Pearl Index, we accepted the applicant's approach to exclude 7 subjects from the efficacy analysis while including one subject (Subject ID: (b) (6)) who was identified as pregnant by the clinical reviewer during the study.

We agreed that the impact of the data from these menstrual cycles on the Pearl Index calculation is minimal and did not affect the overall conclusion.

9.3. Integrated Assessment of Effectiveness

The fundamental goal of a contraceptive is to effectively prevent pregnancy. Contraceptive efficacy was based on the PI derived from the two pivotal trials (300A and 300B). Subjects ≤ 35 years at the time of entry into the trial were exposed to the risk of pregnancy using only the CVS for contraception for 17,427 28-day cycles. Over 800 subjects completed at least 13 cycles. There were 40 on-treatment pregnancies as determined by adjudication between the applicant and us. An on-treatment pregnancy was defined as a pregnancy with date of conception occurring within 7 days of CVS use.

Table 43. Primary Efficacy of CVS (Primary ISE)

	N subjects	number of on-treatment pregnancies (7 days)	number of evaluable cycles	PI using evaluable cycles (95%CI)
Pooled	2111	40	17427	2.98 (2.13, 4.06)

Source: Statistical reviewer's analysis

For CHCs, a minimum of 10,000 28-day cycles with at least 200 subjects completing 13 cycles and at least 50% of subjects from the North American population are usually required for efficacy review. For the CVS, the Division had initially requested 20,000 cycles but agreed to fewer cycles for efficacy evaluation as long as there were 20,000 cycles from pooled data for CVS safety evaluation. There were 21,590 cycles for safety; therefore, the Division deemed the >15,000 28-day cycles adequate to evaluate the CVS for efficacy. US subjects contributed 9,006 or 62.7% of the evaluable cycles—close to the 10,000 cycles requested.

The PI of 2.98 with an upper bound of the 95% CI of 4.06 from all evaluable cycles is consistent with the PIs from two recently approved CHCs, both COCs. These PIs are shown in the table below along with the PI for the other approved vaginal contraceptive ring, NuvaRing.

Table 44. PI (95% CI) for Selected CHCs

CHC	Year Approved	PI (95% CI)
Quartette	2013	3.19 (2.49, 4.03)
Lo Loestrin FE	2010	2.92 (1.94, 4.21)
NuvaRing	2001	2.02 (1.1, 3.4)

Source: FDA approved USPI labels

Comment: *The CVS pivotal trials chece d urine pregnancy tests (UPTs) every three months, which is consistent with other recent contraceptive trials. The applicant presented pregnancies as user or method failure, with 68% of the pregnancies due to*

method failure. However, in recent contraceptive trials, pregnancies that occur, even with incorrect use, are counted because this represents actual use of the contraceptive ("real world use"). Labeling for this product will therefore include all evaluable cycles for efficacy, as this would best represent how the product is lie ly to perform in the intended US population.

Overall, the CVS is effective in preventing pregnancy in females of reproductive potential. The efficacy conclusions for the CVS are:

- *The total number of 28-day cycles of exposure used to calculate the PI in the pivotal trials was adequate (17,427 cycles) for efficacy determination*
- *The PI of 2.98 with upper bound of 95% CI of 4.06 is acceptable for approval for contraceptive efficacy*
- *The cumulative probability of pregnancy of 2.71% over 13 cycles supports the efficacy of the CVS*

The bleeding profile of the CVS was studied in a secondary efficacy analysis. The findings were summarized descriptively.

The conclusions for the bleeding profile of CVS are:

- Over 92% of users had a monthly withdrawal bleed
- The average withdrawal bleed duration was 5 days
- Amenorrhea occurred in up to 5% of users any given cycle
- 5-10% of users experienced unscheduled bleeding per cycle
- The average unscheduled bleeding or spotting duration was less than one day

Comment: *The bleeding profile of the CVS will be included in labeling to alert prescribers to this important information to discuss with women when initiating use of this product, because unscheduled bleeding can lead to method discontinuation.*

10.Review of Safety

10.1. Safety Review Approach

In women using combined hormonal contraceptive products, including the proposed CVS, the predominant safety concern is the risk of thromboembolism. The development program for the SA/EE CVS involved two manufacturers: SA-only CVSs and SA/EE CVSs with different combined doses. The safety analysis sets were separated by manufacturer and dosage with the All NES*/EE CVS analysis set including all combined SA/EE CVSs. The primary ISS (All QPharma NES*/EE CVS) contains the to-be-marketed CVSs. The application uses the abbreviation NES for

nestorone, which is the Population Council's proprietary name for segesterone acetate. (*NES = SA)

The applicant provided the following table listing studies included in each safety analysis set.

Table 45. Studies Contributing Safety Data and Pooled Analysis Sets in the ISS

					Pooled Analysis Set			
Protocol No. Number of Study Centers and Location	**Number of Subjects in Pooled Analyses**	**Product**	**Dose(s) µg/d**	**Treatment Period; Duration of Study**	**All QPharma NES*/EE CVS (N=2308)**	**All NES*/EE CVS (N=2843)**	**All NES*/EE 150/15 CVS (N=2569)**	**NES*-Only CVS (N=209)**
300A 15 sites (US)	1134	QPharma NES/EE CVS	150/15	Thirteen 28 day (21/7) cycles; approximately 1 year	X	X	X	
300B 12 sites; US (5), Europe (3), Latin America (3), and Australia (1)	1135[b**]	QPharma NES/EE CVS	150/15	Thirteen 28 day (21/7) cycles; approximately 1 year	X	X	X	
300PK 3 sites; Latin America (2) and US (1)	39	QPharma NES/EE CVS	150/15	Thirteen 28 day (21/7) cycles; approximately 1 year	X	X	X	
180 5 sites; US (2), Latin America (2) and Europe (1)	150	Population Council NES/EE CVS	150/15 150/20 200/15	Thirteen 28 day (21/7) cycles; approximately 1 year		X	X	
181 4 sites; US (1), Latin America (1), Europe (1) and Australia (1)	101	Population Council NES/EE CVS	150/15	Six 28 day (21/7) or 30 day cycles (26/4); approximately 6 months		X	X	

204R/2040L 5 sites; Latin America (2), US (1), Europe (1) and Australia (1)	250	Population Council NES/EE CVS	50/10 50/20 150/15	Menstrually signaled regimen; approximately 6 months		X	X	
323 1 site (Europe)	23	Population Council NES/EE CVS	150/15	Three 28 day (21/7) cycles; approximately 6 months		X	X	
174 3 sites; US (1), Latin America (1) and Europe (1)	179	Population Council NES CVS	50 75 100	Six 28-day continuous use cycles; approximately 6 months				X
175 1 site (Australia)	30	Population Council NES CVS	100	Six 28-day continuous use cycles; approximately 6 months				X

*NES = SA
**b includes 12 subjects enrolled in Study 300BEx. These subjects are only counted once
Source: NDA 209627, Module 2.7.4 Summary of Clinical Safety, Table 1 p 12/134

This safety review includes analysis of:

- Study 300A
- Study 300B
- Primary ISS (All QPharma SA/EE CVS)
- Secondary ISS SA/EE 150/15 CVS
- Secondary ISS All SA/EE CVS
- SA only CVS analysis set
- Safety Reports from 8 INDs for SA-only formulations (implant, CVS, IUS) and SA/EE CVSs not in analysis sets listed

The primary ISS analysis will inform the clinical trial safety sections of labeling since these studies utilized the to-be-marketed CVS.

The secondary ISS SA/EE 150/15 CVS data set was also reviewed, but is not described in detail in this review because the results are very similar to the secondary ISS All SA/EE CVS. The number of cycles that are contributed by CVSs other than 150/15 in the All SA/EE CVS analysis set is 2,233 cycles or 8.7% of the total number of safety cycles. Therefore, most of the findings reflect the 150/15 CVSs. Analyses of the All SA/EE CVS ISS and the SA-only CVS data set are utilized to capture any safety signals.

Other major adverse events of interest that were evaluated in the trials included hereditary angioedema, hypersensitivity/rash, liver disease, gallbladder disease, hypertension, adverse carbohydrate and lipid metabolic effects, headache, bleeding irregularities, and depression. With vaginal systems, findings related to expulsion, vaginal irritation, vaginal discharge, and infections including toxic shock syndrome were of particular interest and there was no indication that this differed across any subgroup, such as race or age.

10.2. Review of the Safety Database

10.2.1. Overall Exposure

Table 46. ISS Subject Totals and Cycles of Therapy by Pooled Safety Analysis Set

Population / Analysis Set	Total Subjects	Total Cycles	Subjects Completing at Least 13 Cycles
All NES*/EE CVS	2843	25,532	11090
All NES*/EE 150/15 CVS	2569	23,299	10343
All QPharma NES/EE CVS	2308	21,590	999
Subgroup w/ BMI ≤29.0 kg/m^2	2099	20,366	963
Subgroup w/ BMI >29.0 kg/m^2	209	1254	36
Subgroup w/ Age <36 years	2146	20,031	924
Subgroup w/ Age ≥36 years	162	1559	75
NES*-only CVS	209	1262	NA[a]

*NES=SA

Source: NDA 209627, Module 5.3.5.3 ISS Table 1.1.6 p 53/3781

[a] NES*-only CVS studies were 6 cycles in total duration

The All QPharma CVS is the primary ISS and included 300A, 300B, 300BEX, 300 PK where usage of CVS was confirmed by subjects' diary data. Study 300 PK added 39 subjects with a maximum of 13 cycles of exposure per subject. 300BEX included 12 subjects who used a second ring after completing 13 cycles for a total additional exposure of 3,267 days.

Although the All SA/EE CVS analysis set included studies that used different doses of SA and EE in the CVS, the majority (>91%) of cycles were derived from the to-be-marketed formulation, SA/EE 150/15 CVSs.

The NES*-only analysis set contained studies which used varying doses of SA-only CVSs, all with less than 150µg SA.

Study 300A had a total of 1,129 subjects who used the CVS for at least 1 day and provided 9,874 cycles of CVS use. Of the 834 subjects who were eligible to complete 13 full cycles, 426 subjects (51.1%) completed one full year of treatment, contributing 5,538 cycles (56.1% of total exposure). An additional 295 subjects who were enrolled for less than one year contributed 2,233 cycles. Sixteen subjects used the same CVS for more than 13 cycles (against protocol) and were included in the overall number of cycle exposure.

Study 300B had 1,135 subjects who used the CVS for a total of 10,979 cycles. Of the 860 subjects eligible to complete 13 full cycles, 62.1% or 534 subjects completed one full year of treatment, contributing 5,538 cycles (50.4% total exposure). An additional 275 subjects who were not eligible for a full 13 cycles of use completed 2,273 cycles. Fifty-three subjects completed 14 cycles and 5 subjects completed 15 cycles against protocol but are included in exposure.

10.2.2. Relevant characteristics of the safety population:

300A

The study population in 300A was from the US with subjects between ages 18 and 40.0 years. Seventy-five subjects or 6.6% of the study population were between 35 and 40 years old. Sixty-six percent (66%) of subjects were White, 23% were Black, and 13% were Hispanic. Due to change in weight exclusion criteria only 2 subjects with a BMI > 29kg/m^2 completed 13 cycles of CVS. Overall, the 88 subjects with a BMI > 29 kg/m^2 contributed to 413 cycles used for the efficacy data base.

300B

The study population in 300B included subjects from US, Europe (Finland, Hungary, Sweden), South America, and Australia clinics between the ages of 18 and 40.8 years. Seventy-nine subjects or 7.0% of the study population were > 35 years old. Eighty-seven percent (87%) of subjects were White, 13% were Black, and 44% were Hispanic. Due to the change in weight exclusion criteria only seven subjects with a BMI >29 kg/m^2 completed 13 cycles of CVS. Overall, the 57 subjects with a BMI > 29 kg/m^2 contributed 345 cycles used for the efficacy data base.

ISS

In the primary ISS, the majority of subjects were White (71%), non-Hispanic (70%), nulliparous (64%) with a mean age of 26.7 years and mean BMI of 24.1 kg/m^2. The majority (67%) of the subjects were from the US.

Demographics of the primary ISS population categorized by BMI subgroup are shown in Table 47. Subjects with a BMI >29 kg/m^2 tended to be older (median age 27.9 years), parous (38% were nulliparous), from the US (81%), and Black (32% with BMI >29 kg/m^2 vs 12% with BMI ≤29 kg/m^2).

Table 47 Demographics and Baseline Characteristics of the Primary ISS with BMI Subgroups

Characteristic	**Primary ISS** (N=2308) n(%)	**Primary ISS ≤ 29.0 kg/m^2** (N=2099) n(%)	**Primary ISS > 29.0 kg/m^2** (N=209) n(%)
Age (years)			
Mean	26.7	26.6	28.3
Median	25.9	25.7	27.9
Min-Max	18.1-40.8	18.1-40.8	18.1-40.0
Race			
Asian	82 (4)	81 (4)	1 (<1)
Black or African American	328 (14)	261 (12)	67 (32)
Caucasian	1628 (71)	1526 (73)	112 (54)
Other	248 (11)	220 (10)	28 (13)
Unknown	12 (<1)	11 (<1)	1 (<1)
Ethnicity			
Hispanic or Latina	690 (30)	619 (29)	71 (34)
Non-Hispanic or Latina	1618 (70)	1480 (71)	138 (66)
USA geographic			
USA	1536 (67)	1367 (65)	169 (81)
Non-USA	772 (33)	732 (35)	40 (19)
Parity			
0	1478 (64)	1398 (67)	80 (38)
≥ 1	830 (36)	701 (33)	129 (62)

Source: NDA 209627, Module 5.3.5.3 ISS, Table 7-1 p 63,64/3781

Comment: *There was a larger number of Hispanics (30%) in the ISS than in the 2010 US census population overall (16%). In the BMI >29 kg/m^2 category Blacks were over-represented and Asians were under-represented.*

Important populations that are lie ly to use hormonal contraception that were not sufficiently represented in the pivotal trials are women >40 years old and women with BMI >29 g/m^2. The lac of data on these groups will be noted in the label.

The secondary ISS analysis sets (the All SA/EE and 150/15 CVS sets) were similar to the primary ISS while the SA-only CVS set had some differences. The 209 subjects that made up the SA-only CVS analysis set were older (average age 28.2 years; 15% ≥36 years old), parous (57%), from non-US countries (71%), and 15% had a BMI >29 kg/m^2. Race and ethnicity were not reported.

10.2.3. Adequacy of the safety database:

For contraceptive trials containing a NME, the Division requests a total of 20,000 cycles with at least 200 subjects completing one year of use. The primary ISS population had over 21,000 cycles of exposure with over 900 subjects completing one year. Most of these cycles (19,726 cycles) and subjects were from the two pivotal trials (300A and 300B).

The study populations for 300A and 300B were limited for weight, initially excluding subjects >95 kg or >209 pounds, then excluding subjects with BMI >29 kg/m^2, and for age, excluding subjects 40 years of age or older. Because of these limitations, the safety database does not adequately reflect women with a BMI >29 kg/m^2 or women over 40 years old.

10.3. Adequacy of Applicant's Clinical Safety Assessments

10.3.1. Issues Regarding Data Integrity and Submission Quality

The quality and integrity of the NDA acceptable for review. The NDA was organized with appropriately identified headings and subheadings that facilitated access to pertinent information for this clinical review.

The safety data sets included appropriate studies as requested by the Division. The grouping of the studies in the different ISSs limited our ability to analyze studies other than the pivotal trials because the secondary ISSs were composed predominantly of subjects and cycles from the pivotal trials, so the results overwhelmingly reflected the data from the primary ISS rather than the additional subjects' safety data.

Most of the studies were conducted over 10 years ago, therefore, the applicant's ability to obtain additional information was limited. Some narratives recorded the final diagnosis based on the subjects' telephone contact without further confirmation from medical records. The applicant worked with us to resolve outstanding questions so that there was sufficient information to allow analysis of individual adverse events.

AEs were reported for up to 14 days after last CVS use, and although the investigator was to note whether the AE was ongoing or resolved by the 14-day window, no further follow up was required. Therefore, in some cases, documentation of a TEAE or reason for early discontinuation of the CVS were missing. This is illustrated by Subject (b) (6) who discontinued the CVS due to vaginal discharge and irritation. At her termination visit, vaginal candidiasis and a UTI were diagnosed and treated but because the visit was >14 days after her last CVS use, neither of these diagnoses were documented as a TEAE or reason for early discontinuation of the CVS. There were also subjects with abnormal laboratories at the time of discontinuation that had no follow up laboratory values documented in the case report forms.

In narratives for VTE, the applicant did not follow protocol and use the BMI at the baseline visit (V1), but used either the screening (V0) or baseline (V1) value, whichever was greater. For example, in the description of VTE for Subject (b) (6) in Study 300A, the applicant used her screening BMI (V0) of 29.1 kg/m^2 rather than the per-protocol baseline BMI (V1) of 28.5 kg/m^2. Further, the applicant notes in the narrative the subject's hospital BMI of 30.2 kg/m^2, but does not note the baseline BMI of 28.5 kg/m^2 nor the BMI of 28 kg/m^2 at the subject's clinic visit 5 days after VTE hospitalization. This documentation classified Subject (b) (6) as having a BMI >29 kg/m^2 and resulted in her being one of the two subjects on which the DSMB based their decision to exclude further enrollment of subjects >29 kg/m^2 from the clinical studies.

> ***Comment:*** *The applicant's assertion that there was a mare dly increased ris of VTE for women with a BMI > 29 kg/m^2 is not adequately substantiated by the data. The clinical review found that multiple BMIs were reported for individual subjects with VTEs over the course of the trial, and therefore the data does not support use of a single BMI cutoff to assess VTE ris . Furthermore, the applicant's suggested BMI cutoff of > 29 g/ m^2 does not correspond to any clinically utilized BMI category. Our assessment is that there is insufficient power from the database to draw conclusions about actual VTE ris. This VTE ris will be prominently included in the warnings section of labeling. The definitive ris of VTE across all BMI categories for this product needs to be further evaluated in a large required postmare ting study.*

10.3.2. Categorization of Adverse Events

The applicant defined an AE as any untoward medical occurrence in a subject who was administered the investigational product, regardless of causality assessment. An AE could include an abnormal laboratory finding and worsening of a pre-existing condition.

In the study, any event occurring after the clinical trial subject signed the study Informed Consent Form (ICF) and up to 14 days following last use of the CVS was recorded and reported as an AE. Treatment-emergent adverse events (TEAEs) were defined as AEs (including worsening of preexisting conditions) that began on or after first use of the CVS and up to 14 days after final CVS use.

The AEs from studies 300A, 300B, 300BEX, 300 PK, and 330 were coded by System Organ Class (SOC) and preferred term by using Medical Dictionary for Regulatory Activities (MedDRA) Version 9.1. MedDRA Version 14.1 was used for studies 180, 181, 204, 323, 174, and 175. Verbatim AEs were reviewed for consistency before pooled for the ISS using MedDRA 9.1 as the standard.

The TEAEs were summarized by SOC, preferred term and the percentage of subjects reporting at least 1 TEAE within each SOC for all subjects. Subjects reporting the same event more than once within each SOC and preferred term were only counted once.

The severity of the AEs was graded as mild, moderate, or severe based on whether routine

activities were unaffected, compromised, or interrupted, respectively. The Investigator documented AE relationship to the CVS based on temporal sequence, dechallenge response, and other factors (concomitant therapy, subject's clinical state) and categorized as not related, unlikely, possible, probable, and definite/highly probable. The Investigator also documented resolution or outcome of AE, and action taken with respect to continuation in the study.

Serious adverse events (SAEs) were defined as an AE that resulted in death, was life-threatening, required in-patient hospitalization, resulted in persistent or significant disability, or was a congenital anomaly/birth defect in the offspring of the subject. In addition, spontaneous abortion, cancer, and drug overdose were classified as an SAE. The SAE reporting time period was after signed ICF through 30 days after last CVS use. SAEs were followed to resolution or stabilization of the condition.

10.3.3. Routine Clinical Tests

Urine pregnancy tests (UPTs) were performed at each clinic visit. Clinical laboratory testing was performed, at a minimum, at the beginning and end of the one-year studies, and included hematology, clinical chemistry, Pap smears, Chlamydia and gonorrhea testing, and urinalysis. Physical and gynecologic examinations were also performed at the beginning and end of the one-year studies.

10.3.4. ISS Disposition

The primary ISS subjects' disposition is shown in Table 48.

Table 48. Disposition of Subjects in Primary ISS

Disposition	Primary ISS(N=2308)	Primary ISS BMI Subgroups	
		≤29.0 kg/m^2 (N=2099)	>29.0 kg/m^2 (N=209)
Completed the Study, n (%)	**1332 (58)**	**1296 (62)**	**36 (17)**
Discontinued Prematurely, n (%)[a]	**976 (42)**	**803 (38)**	**173 (83)**
Adverse Event	281 (12)	267 (13)	14 (7)
Lost to Follow-up	214 (9)	191 (9)	23 (11)
Withdrew Consent	197 (9)	184 (9)	13 (6)
Eligibility	147 (6)	31 (1)	116 (56)
Pregnancy	54 (2)	50 (2)	4 (2)
Compliance	49 (2)	47 (2)	2 (<1)
Expulsions	33 (1)	32 (2)	1 (<1)

Other	1 (<1)	1 (<1)	0

Source: ISS Table 1.1.1 and ISS Table 1.1.5
NOTE: Adverse events as a reason for discontinuation were mapped following a manual review of all reasons for discontinuation and include 3 cases that were not initially considered adverse events leading to discontinuation in the AE database.
[a] Reasons for discontinuation were coded to the following categories based on the verbatim reasons given in the individual studies:
Adverse Event = verbatim AE; Lost to Follow-up = lost to follow-up; Withdrew Consent = not sexually active, other medical problems, other mood change, other pelvic problems, other personal problems, planning pregnancy, relocation, or widowed, divorced, separated; Eligibility = eligibility criteria changed or other medical problems; Pregnancy = ectopic pregnancy or intrauterine pregnancy; Compliance = CVR remained out too long, difficulty following schedule, lost CVR, other user compliance problem, or used other contraceptives; Expulsions = repeated expulsions; Other = erroneous diagnosis of pregnancy

Source: NDA 209627, Module 5.3.5.3, ISS, Table 7-3, p 69/3781

Disposition of subjects in the secondary ISSs is shown in Table 49.

Table 49. Disposition of Subjects in Secondary ISSs

Disposition	**All SA/EE CVR (N=2843)**	**All SA/EE 150/15 CVR (N=2569)**	**SA-Only CVR (N=209)**
Completed the Study, n (%)	**1761 (62)**	**1546 (60)**	**155 (74)**
Discontinued Prematurely, n (%) [a]	**1082 (38)**	**1023 (40)**	**54 (26)**
Adverse Event	328 (12)	296 (12)	31 (15)
Withdrew Consent	228 (8)	214 (8)	9 (4)
Lost to Follow-up	220 (8)	218 (8)	2 (<1)
Eligibility	147 (5)	147 (6)	0
Pregnancy	63 (2)	56 (2)	3 (1)
Compliance	62 (2)	58 (2)	9 (4)
Expulsions	33 (1)	33 (1)	0
Other	3 (<1)	1 (<1)	0

Source: ISS Table 1.1.1 and ISS Table 1.1.3
NOTE: Adverse events as a reason for discontinuation were mapped following a manual review of all reasons for discontinuation and include 3 cases that were not initially considered adverse events leading to discontinuation in the AE database.
[a] Reasons for discontinuation were coded to the following categories based on the verbatim reasons given in the individual studies. Adverse Event = verbatim AE; Lost to Follow-up = lost to follow-up; Withdrew Consent = not sexually active, other medical problems, other mood change, other pelvic problems, other personal problems, planning pregnancy, relocation, or widowed, divorced, separated; Eligibility = eligibility criteria changed or other medical problems; Pregnancy = ectopic pregnancy or intrauterine pregnancy; Compliance = CVR remained out too long, difficulty following schedule, lost CVR, other user compliance problem, or used other contraceptives; Expulsions = repeated expulsions; Other = erroneous diagnosis of pregnancy.

Source: NDA 209627, Module 5.3.5.3, ISS, Table 7-4, p 70/3781

Comment: *Because the primary ISS made up the majority of the secondary ISSs with SA/EE CVS, there were no substantive differences in subject disposition between the primary and secondary ISSs.*

10.4. Safety Results

10.4.1. Deaths

There were no deaths reported in any studies.

10.4.2. Serious Adverse Events

In the primary ISS of 2308 subjects, 43 subjects (1.9%) experienced 47 SAEs. The SAEs experienced in the ISS all occurred in the two pivotal studies (300A and 300B) as shown in Table 50.

Table 50. SAEs in Pivotal Trials and Primary ISS

SOC Preferred Term	300A n subjects (N=1129)	300B n subjects (N=1135)	ISS n subjects (N=2308)
Subjects with any SAE, n(%)	21 (1.9)	22 (1.9)	43 (1.9)
Blood and Lymphatic System Disorders n(%)	1 (0.1)	1 (0.1)	2 (0.1)
Lymphadenitis	1	1	2
Ear and Labyrinth Disorders n(%)	1 (0.1)	0	1 (0.0)
Vertigo	1		1
Gastrointestinal Disorders n(%)	3 (0.3)	1 (0.1)	4 (0.2)
Abdominal Pain	2		2
Diarrhea/Nausea/Vomiting	1		1
Food Poisoning		1	1
General Disorders and Administration Site Conditions n(%)	0	1 (0.1)	1 (0.0)
Infusion Site Phlebitis		1	1
Hepatobiliary Disorders n(%)	0	1 (0.1)	1 (0.0)
Cholelithiasis		1	1
Immune System Disorders n(%)	3 (0.3)	0	3 (0.1)
Drug Hypersensitivity	1		1
Food Allergy	1		1
Hypersensitivity	1		1
Infections and Infestations n(%)	3 (0.3)	7 (0.6)	10 (0.4)
Amoebiasis		1	1
Appendicitis		2	2
Cellulitis		1	1
Dengue Fever		1	1

SOC Preferred Term	300A n subjects (N=1129)	300B n subjects (N=1135)	ISS n subjects (N=2308)
Influenza		1	1
Mastitis		1	1
Pneumonia	2		2
Pyelonephritis	1		1
Injury, Poisoning and Procedural Complications n(%)	0	3 (0.3)	3 (0.1)
Animal Bite		1	1
Back Injury		1	1
Ligament Injury		1	1
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) n(%)	3 (0.3)	0	3 (0.1)
Malignant Melanoma	1		1
Salivary Gland Adenoma	1		1
Uterine Leiomyoma	1		1
Nervous System Disorders n(%)	1 (0.1)	2 (0.2)	3 (0.1)
Cerebral Venous Thrombosis		1	1
Headache	1		1
Multiple Sclerosis		1	1
Pregnancy, Puerperium and Perinatal Conditions n(%)	0	3 (0.3)	3 (0.1)
Abortion Incomplete		1	1
Abortion Spontaneous		1	1
Ectopic Pregnancy		1	1
Psychiatric Disorders n(%)	2 (0.2)	2 (0.2)	4 (0.2)
Bipolar Disorder	1		1
Bipolar I Disorder	1		1
Mania		1	1
Suicide Attempt		1	1
Reproductive System and Breast Disorders n(%)	1 (0.1)	0	1 (0.0)
Uterine Spasm	1		1
Respiratory, Thoracic and Mediastinal Disorders n(%)	2 (0.2)	0	2 (0.1)
Pleural Effusion	1		1
Pulmonary Embolism	1		1
Skin and Subcutaneous Tissue Disorders n(%)	0	1 (0.1)	1 (0.0)
Urticaria		1	1
Social Circumstances n(%)	1 (0.1)	0	1 (0.0)
Drug Abuser	1		1
Vascular Disorders n(%)	2 (0.2)	0	2 (0.1)
Deep Vein Thrombosis	2		2

Source: NDA 208627, Module 5.3.5.2, 300A Study Report, Table 19 p 103/1147, 300B Study Report, Table 19 p 97/626; Module 5.3.5.3 ISS Table 2.5.5 p 2135/3781

In April 2018, the applicant submitted an updated SAE list which contained 10 additional SAEs that occurred more than 14 days after last drug use and had initially been considered nonemergent. Eight of the SAEs were pregnancies that ended in spontaneous abortion diagnosed after 14 days from last CVS use. One SAE was a pregnancy complicated by HELLP syndrome. These nine pregnancies were captured in the pregnancy data during efficacy review. The tenth SAE was pyelonephritis.

The SAEs included four VTEs (2 DVTs, 1 PE, 1 cerebral venous thrombosis) and two drug hypersensitivity reactions. These cases are described in detail in Section 10.5 Analysis of Submission-Specific Safety Issues.

The remaining SAEs of interest are discussed in detail below:

- one subject with vertigo but a history more consistent with transient ischemic attack (TIA)
- one subject with headache, nausea, vomiting, and diarrhea that resolved with discontinuation of the CVS
- one subject with vaginal bleeding and a fibroid
- two subjects with bipolar disorder that had worsening of symptoms
- one subject with a manic episode
- one subject with a suicide attempt

300A - Subject (b) (6): Vertigo/possible Transient Ischemic Attack (TIA)
A 25-year-old with Marfan syndrome used the CVS (b) (6) through (b) (6) removing the CVS on (b) (6) per protocol. On (b) (6), the subject had two episodes of vertigo, ataxia, weakness. She also had language problems and transient dizziness. On (b) (6), she presented to the emergency department where most of the symptoms resolved except for residual difficulty with balance. Physical examination showed trace intention tremor on the right and subjective feeling of unsteady gait. She was admitted to the hospital due to a concern for posterior circulatory TIA and vertebral artery dissection. TSH was elevated at 9.95 IU/ml. CT and MRI imaging of the head showed no abnormalities. EKG was normal. Echocardiography showed mitral prolapse with trace regurgitation. The subject was treated with SQ enoxapin, PO atorvastatin, aspirin, lansoprazole. Lab tests for protein C activity, protein S activity, Factor V Leiden and Prothrombin 2021GA Variant were within normal ranges. A neurologist determined the subject might have an inner ear imbalance. The subject was discharged from the hospital with no medication and was discharged from the study. The investigator ranked this treatment-emergent SAE as unlikely related to the CVS.

> ***Comment:*** *The narrative describes a subject with acute neurologic deficit that is not expected with an inner ear imbalance and was treated with VTE prophylaxis upon admission to the hospital. The event resolved and the subject was discharged from the*

hospital after 3 days with no medication. The subject continued to use the CVS for another 11 days until she was discontinued from the study. Marfan syndrome (MFS), an autosomal dominant disorder of the connective tissue, carries a significant ris of aortic dissection, especially with increasing aortic root dilatation in pregnancy among women with the disorder. The USMEC does not separately address MFS. An interdisciplinary working group on pregnancy and contraception for women with cardiac disease rates MFS without aortic root dilatation as a risk category 2.[17] This TEAE as possibly related to the CVS, due to the documented neurologic deficits and their transient nature, which is suggestive of a TIA.

300A - Subject (b) (6): Headache, Nausea, Vomiting, and Diarrhea
A 32-year-old with a history of hyperlipidemia and seasonal allergies started the CVS on (b) (6) On day 2 through day 4 after CVS insertion the subject experienced headache (with pain level reported as 7 out of 10), nausea, vomiting, and diarrhea. She discontinued the CVS permanently on day 6 with "relief of headache, nausea, and vomiting" in a few hours. By day 7 all symptoms had resolved. The investigator ranked these symptoms as possibly due to CVS use.

Comment: *The timing of the symptoms suggests a possible relationship and headache, nausea, and vomiting are AEs that are associated with CHCs. The resolution of symptoms after CVS removal also supports an association between the CVS and the subject's AEs.*

300A - Subject (b) (6): Worsening Submucosal Fibroid (menorrhagia)
A 28-year-old with known fibroids, including one submucosal fibroid, started the CVS on (b) (6) On (b) (6), the subject experienced continuous severe vaginal bleeding that was treated with progestin 5 mg twice daily from (b) (6) through (b) (6). Her hemoglobin was 8.3 g/dL on (b) (6). On (b) (6), she underwent a hysteroscopic resection of the submucosal fibroid. CVS use was interrupted (b) (6) and restarted (b) (6) until the end of the study, (b) (6). The investigator ranked the event as possibly related to the CVS.

Comment: *We agree with the applicant that the submucous fibroid becoming symptomatic might be related to the CVS. It is reassuring to note that after resection, the subject was able to continue use of the CVS for 7 more cycles.*

Bipolar Disorder/Depression
300A - Subject # (b) (6): Bipolar Affective Disorder, Mixed
A 25-year-old with a history of anxiety, anorexia nervosa, depression with suicidal thoughts, polysubstance dependence, irritable bowel syndrome and frequent urinary tract infections used the CVS (b) (6) through (b) (6). On (b) (6), the subject

[17] Contraception for the Medically Challenging Patient. Editors Rebecca Allen and Carrie Cwiak. Springer, Sep 3, 2014. Doi 10.1007/978-1-4939-1233-9

experienced symptoms of bipolar affective disorder. On [redacted], she was admitted to the hospital after purposefully cutting her leg and arm. History at admission included a prior episode of cutting one month previously, with gabapentin started [redacted]; both occurring presumably on treatment. The subject also complained of racing thoughts, severe insomnia and mood swings with no onset date given. Escitalopram had been started [redacted] (prior to CVS use) for depression and anxiety. She was treated with Neurontin, buspirone, valproate, and paroxetine at the time of discharge from the hospital [redacted]. She discontinued the CVS [redacted] and was discontinued from the study. The investigator considered the event to be unrelated to the study medication.

300A - Subject # [redacted] Bipolar Crisis

A 28-year-old a with history of bipolar disorder, anxiety disorder, and depression with 3 previous inpatient psychiatric hospitalizations started the CVS [redacted]. On [redacted], the subject was admitted for acute symptoms of bipolar illness and manic phase. She was paranoid, disorganized, hypomanic with pressured speech and racing thoughts. The subject had stopped taking her Abilify [redacted]. Her laboratory testing was normal except for positive cannabinoids on toxicology. The subject was started on Abilify and Vistaril and was discharged 5 days later. The narrative does not provide a stop date for the study drug. The investigator considered the event to be unlikely related to the study medication.

300 B - Subject # [redacted] Mood Disorder, Bipolar I with Manic Episode and Psychotic Symptoms

A 24-year-old with history of mood disorder (Bipolar I with manic episode), used the CVS from [redacted] through [redacted] She discontinued the CVS due to her husband's objection. On [redacted] the subject was admitted to the hospital with a manic episode with psychotic symptoms similar to an episode experienced in [redacted]. She underwent electroconvulsive therapy and was discharged [redacted] on therapy with trihexyphenidyl, risperidone, lithium, and chlorpromazine. The investigator considered the event unlikely related to the study medication.

300 B - Subject # [redacted] Suicide Attempt due to Worsening Depression

A 35-year-old with history of depression (on escitalopram), herniated disc, cystic ovaries and seasonal allergies started the CVS on [redacted]. On [redacted], the subject attempted suicide by swallowing a bottle of cyclobenzaprine after she was physically attacked at work and then not supported by her superiors. During this time, her brother was having legal problems while serving in Iraq. The subject called her mother after she swallowed the pills and the subject was hospitalized. She was discharged from the hospital nine days later on Depakote and Invega. She continued the CVS. The investigator considered the event unlikely related to the study medication.

> ***Comment:*** *All four subjects had underlying mental illness. In Study 300A, Subject # [redacted] had a history of inpatient psychiatric care and discontinued her bipolar medication two months prior to her acute bipolar episode which probably contributed to her acute*

episode. Subject # (b) (6) had an acute episode of bipolar affective disorder which temporally may have been related to CVS use, although with her extensive psychiatric history, the bipolar affective disorder may have been pre-existing. Subjects # (b) (6) and (b) (6) mae up 0.2% o f the study population in 300A, which had a 6.4% incidence of depression. In 300 B, Subject # (b) (6) continued using the CVS after in-hospital care and medication changes. Subjects # (b) (6) and (b) (6) mae up 0.2% of the study population in 300B, in which 2.6% of subjects had a medical history of depression. Ortho Evra had three depressive SAEs including one suicide attempt for an incidence of 0.1% of the study population. Quartette had seven depressive SAEs including 5 suicide attempts for an incidence of 0.2% of the study population. Therefore, the findings in the CVS pivotal trials are comparable to that of other CHCs. Regardless, the ris of mood disorders and exacerbations of such disorders is adequately addressed in class labeling for CHCs and will be included in the label for the CVS.

There were an additional 10 SAEs in the secondary ISS; 8 with a SA/EE CVS and 2 with a SA-only CVS. Thirty (30) more SAEs occurred in 28 subjects under 8 SA INDs which were not pooled in the ISS. These SAEs were also reviewed.

Comment: *From a clinical perspective, none of the SAE narratives indicate a new safety signal involving the various CVSs.*

10.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Early discontinuation due to AEs occurred in 11-12% of subjects in the two pivotal trials, the primary ISS, and the secondary ISS. The Reproductive System and Breast Disorders and Psychiatric Disorders SOCs contain the most frequent AEs leading to subject discontinuation.

Table 51. TEAEs Leading to >1% Subject Early Discontinuation by SOC

SOC1	300A n subjects (%) N=1129	300B n subjects (%) N=1135	Primary ISS n subjects (%) N=2308	All SA/EE ISS n subjects (%) N=2843
Total AEs Leading to Subject Discontinuation	127 (11.2)	144 (12.7)	275 (11.9)	323 (11.4)
Reproductive System and Breast Disorders	33 (2.9)	52 (4.6)	86 (3.7)	107 (3.8)
Psychiatric Disorders	29 (2.6)	24 (2.1)	54 (2.3)	63 (2.2)
Gastrointestinal Disorders	17 (1.5)	21 (1.9)	38 (1.6)	45 (1.6)
Nervous System Disorders	17 (1.5)	14 (1.2)	32 (1.4)	39 (1.4)
Infections and Infestations	8 (0.7)	13 (1.1)	21 (0.9)	27 (0.9)
Investigations	8 (0.7)	7 (0.6)	15 (0.6)	18 (0.6)

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, Table 14.3.2.3.1 p 574/1147, 300B Study Report, Table 14.3.2.3.1 p 485/626, Module 5.3.5.2, ISS Analysis Dataset Legacy, Medical Officer's analysis of the AE data set using JMP, and ISS Table 8-13 p 97/3781

The PTs for subjects' early discontinuation are shown in Table below. The results between analysis sets are consistent because 81% of the All SA/EE ISS is from the Primary ISS, and 98% of the Primary ISS is made up of subjects from 300A and 300B.

Table 52. AEs Leading to Early Discontinuation Occuring in ≥2 Subjects

Preferred Term	**300A n subjects (%) N=1129**	**300B n subjects (%) N=1135**	**Primary ISS n subjects (%) N=2308**	**All SA/EE ISS n subjects (%) N=2843**
Subjects with AE leading to Early Discontinuation	127 (11.2)	144 (12.7)	275 (11.9)	323 (11.4)
Metrorrhagia, Menstrual Irregular	12 (1.1)	15 (1.3)	27 (1.2)	31 (1.1)
Vaginal Discharge	1 (0.1)	14 (1.2)	15 (0.6)	21 (0.7)
Headache	11 (1.0)	6 (0.5)	18 (0.8)	24 (0.8)
Mood Swings, Mood Altered, Affect Lability	10 (0.9)	5 (0.4)	15 (0.6)	19 (0.7)
Nausea	8 (0.7)	11 (1.0)	19 (0.8)	24 (0.8)
Depression, Depressive Symptoms Or Mood	7 (0.6)	3 (0.3)	10 (0.4)	14 (0.5)
Vomiting	7 (0.6)	2 (0.2)	9 (0.4)	12 (0.4)
Libido Decreased	5 (0.4)	10 (0.9)	15 (0.6)	15 (0.5)
Vulvovaginal Mycotic Infection/Vaginal Candidiasis	5 (0.4)	9 (0.8)	14 (0.6)	14 (0.5)
Menorrhagia*, Vaginal Hemorrhage	4 (0.4)	10 (0.9)	14 (0.6)	15 (0.5)
Anxiety	4 (0.4)	3 (0.3)	8 (0.3)	8 (0.3)
Migraine	4 (0.4)	7 (0.6)	11 (0.5)	11 (0.4)
Weight Increased	4 (0.4)	6 (0.5)	10 (0.4)	10 (0.4)
Abdominal Pain	3 (0.3)	5 (0.4)	8 (0.3)	8 (0.3)
Acne	3 (0.3)	2 (0.3	5 (0.2)	6 (0.2)
Genital Pruritus Female	3 (0.3)	3 (0.2)	7 (0.3)	7 (0.2)
Blood Cholesterol Increased	2 (0.2)	0	2 (0.1)	2 (0.1)
Blood Triglycerides Increased	2 (0.2)	0	2 (0.1)	2 (0.1)
Deep Vein Thrombosis	2 (0.2)	0	2 (0.1)	2 (0.1)
Dysmenorrhea**	2 (0.2)	0	2 (0.1)	2 (0.1)
Fatigue	2 (0.2)	0	2 (0.1)	2 (0.1)
Insomnia	2 (0.2)	0	2 (0.1)	2 (0.1)
Premenstrual Syndrome	2 (0.2)	0	2 (0.1)	2 (0.1)
Urticaria	2 (0.2)	2 (0.2)	4 (0.2)	4 (0.1)
Vaginal Pain	2 (0.2)	1 (0.1)	2 (0.1)	3 (0.1)
Vulvovaginal Discomfort	1 (0.1)	3 (0.3)	4 (0.2)	4 (0.1)
Contraceptive/Medical Device Complication	1 (0.1)	2 (0.2)	3 (0.1)	3 (0.1)
Dyspareunia	1 (0.1)	2 (0.2)	3 (0.1)	6 (0.2)

Preferred Term	300A n subjects (%) N=1129	300B n subjects (%) N=1135	Primary ISS n subjects (%) N=2308	All SA/EE ISS n subjects (%) N=2843
Pain in Extremity	1 (0.1)	2 (0.2)	3 (0.1)	3 (0.1)
Urinary Tract Infection	1 (0.1)	2 (0.2)	3 (0.1)	3 (0.1)
Vulvovaginal Dryness	0	2 (0.2)	3 (0.1)	4 (0.1)
Back Pain	0	1 (0.1)	3 (0.1)	3 (0.1)

Terms used by applicant were*withdrawal bleed and **uterine spasm

Menstrual disorders make up the largest portion of AEs leading to CVS discontinuation. Metrorrhagia includes the verbatim terms of irregular bleeding, irregular spotting, breakthrough bleeding, breakthrough spotting, spotting, frequent spotting, and prolonged spotting. The preferred term "withdrawal bleed" includes the verbatim terms of heavy bleeding with menses, bleeding very much, prolonged bleeding with menses, and frequent bleeding with menses. However, review of data on AEs leading to early discontinuation shows all types of bleeding are categorized under metrorrhagia including 6 subjects with prolonged bleeding and prolonged menses.

> ***Comment:*** *Labeling of AEs leading to early discontinuation will group these terms together under menstrual disorders. This is also in concurrence with the draft guidance for Labeling for Combined Hormonal Contraceptives*[18]

The primary ISS combines both pivotal trials and gives an overview of AEs leading to early discontinuation in the primary study population. Overall 11.9% of subjects had early discontinuation due to an AE. The most frequent AEs were:

- Menstrual disorders 1.7%
- Nausea/Vomiting 1.2%
- Headache, including Migraine 1.3%
- Vaginal discharge, vulvovaginal mycotic infection, vaginal candidiasis 1.3%.

CVS expulsions as the reason for early discontinuation was not treated as a AE, but 33 subjects (1.4%) in the primary ISS population had early discontinuation due to expulsions (see Section 10.4.13 CVS Expulsions/Issues).

In comparison, the NuvaRing[19] clinical trial experience showed 13% of subjects had early discontinuation due to an AE with the most common being device-related events (2.7%), mood changes (1.7%), headache including migraine (1.5%), and vaginal symptoms (1.2%). Other CHC trials have noted subject discontinuation due to menstrual irregularities rates of 1.1% (Ortho Evra) to 4.9% (Quartette).

[18] Labeling for Combined Hormonal Contraceptives, Guidance for Industry. DRAFT GUIDANCE December 2017
[19] NuvaRing label 8/2017

Comment: *We conclude that rates of AEs leading to early discontinuation, and reasons for discontinuation, are sufficiently similar from a clinical perspective between the CVS and other CHCs that no specific safety concerns or trends were identified.*

Review of the SA-only CVS ISS showed similar patterns of AEs leading to early discontinuation with no unexpected AEs.

10.4.4. Significant Adverse Events

Significant adverse events considered to be submission-specific are described in Section 10.5 Analysis of Submission-Specific Safety Issues.

10.4.5. Adverse Events and Treatment Emergent Adverse Events and Adverse Reactions

Most subjects (87%) reported at least one AE. In the primary ISS, 69% of the AEs were considered by the Investigator to be related to CVS use and 15% were categorized as severe. The most frequent AEs occurred in the SOCs of Infections and Infestations and Reproductive System and Breast Disorders as shown in the table below.

Table 53. AEs by SOC Occuring in ≥10% of Subjects

SOC	300A n subjects (%) N=1129	300B n subjects (%) N=1135	Primary ISS n subjects (%) N=2308	All SA/EE ISS n subjects (%) N=2843
Total AEs	1003 (88.8)	972 (85.6)	2016 (87.3)	2466 (86.7)
Infections and Infestations	671 (59.1)	601 (53.0)	1302 (56.4)	1495 (52.6)
Reproductive System and Breast Disorders	480 (42.5)	549 (48.4)	1052 (45.6)	1415 (49.8)
Gastrointestinal Disorders	519 (46.0)	456 (40.2)	998 (43.2)	1137 (40.0)
Nervous System Disorders	565 (50.0)	370 (32.6)	962 (41.7)	1160 (40.8)
Musculoskeletal and Connective Tissue Disorders	295 (26.1)	145 (12.8)	448 (19.4)	483 (17.0)
Psychiatric Disorders	203 (18.0)	178 (15.7)	388 (16.8)	441 (15.5)
Respiratory, Thoracic and Mediastinal Disorders	188 (16.7)	75 (6.6)	267 (11.6)	282 (9.9)
Skin and Subcutaneous Tissue Disorders	122 (10.8)	132 (11.6)	257 (11.1)	291 (10.2)
Injury, Poisoning and Procedural Complications	170 (15.1)	79 (7.0)	256 (11.1)	265 (9.3)
General Disorders and Administration Site Conditions	167 (14.8)	73 (6.4)	244 (10.6)	279 (9.8)

NDA 209627, Module 5.3.5.2, 300A Study Report, Table 16 p 97/1147, 300B Study Report, Table 16 p 91/626, Module 5.3.5.3, ISS Table 8-3 p 74/3781, Table 8-5 p 79/3781

> ***Comment:*** *Overall, 87% of subjects experienced a AE. This is similar to Ortho Evra with 80% of subjects experiencing at least one AE and higher than NuvaRing with 38% of subjects experiencing at least one AE.*

The number of subjects with AEs by PT is shown in the table below. Overall, the proportion of subjects with AEs decreased over time with the nadir of AEs occurring at Cycle 10.

Table 54. AEs by PT Occuring in ≥2% of Subjects

Preferred Term	300A n subjects (%) N=1129	300B n subjects (%) N=1135	Primary ISS n subjects (%) N=2308	All SA/EE ISS n subjects (%) N=2843
Headache	494 (43.8)	312 (27.5)	829 (35.9)	1016 (35.7)
Nausea	244 (21.6)	257 (22.6)	514 (22.3)	572 (20.1)
Nasopharyngitis	212 (18.8)	242 (21.3)	475 (20.6)	494 (17.4)
Uterine Spasm~			281 (12.2)	307(10.8)
Dysmenorrhea	143 (12.7)	99 (8.7)	not reported	not reported
Vaginal Discharge	75 (6.6)	168 (14.8)	266 (11.5)	446 (15.7)
Upper Respiratory Tract Infection	204 (18.1)	41 (3.6)	247 (10.7)	249 (9)
Vulvovaginal Mycotic Infection*	142 (12.6)	84 (7.4)	232 (10.1)	259 (9)
Urinary Tract Infection*	97 (8.6)	109 (9.6)	211 (9.1)	229 (8)
Vomiting	117 (10.4)	60 (5.3)	182 (7.9)	201 (7.1)
Back Pain	114 (10.1)	63 (5.6)	181 (7.8)	197 (6.9)
Influenza	98 (8.7)	68 (6.0)	169 (7.3)	188 (6.6)
Diarrhoea	120 (10.6)	40 (3.5)	165 (7.1)	174 (6.1)
Metrorrhagia*	58 (5.1)	95 (8.4)	165 (7.1)	308 (10.8)
Breast Tenderness	69 (6.1)	72 (6.3)	142 (6.2)	153 (5.4)
Abdominal Pain Upper*	92 (8.1)	45 (4.0)	140 (6.1)	153 (5.4)
Pharyngolaryngeal Pain	95 (8.4)	41 (3.6)	138 (6.0)	138 (4.9)
Genital Pruritus Female	60 (5.3)	62 (5.5)	126 (5.5)	126 (4.4)
Dizziness	55 (4.9)	48 (4.2)	107 (4.6)	130 (4.6)
Migraine	58 (5.1)	38 (3.3)	104 (4.5)	112 (3.9)
Myalgia	82 (7.3)	18 (1.6)	101 (4.4)	105 (3.7)
Sinusitis	71 (6.3)	29 (2.6)	100 (4.3)	103 (3.6)
Insomnia	72 (6.4)	22 (1.9)	95 (4.1)	96 (3.4)
Abdominal Pain*	36 (3.2)	51 (4.5)	91 (3.9)	103 (3.6)
Abdominal Pain Lower*	30 (2.7)	55 (4.8)	89 (3.9)	145 (5.1)
Vaginal Candidiasis*	2 (0.2)	82 (7.2)	88 (3.8)	88 (3.1)
Pain in Extremity	55 (4.9)	28 (2.5)	84 (3.6)	86 (3.0)

Preferred Term	300A n subjects (%) N=1129	300B n subjects (%) N=1135	Primary ISS n subjects (%) N=2308	All SA/EE ISS n subjects (%) N=2843
Seasonal Allergy	67 (5.9)	16 (1.4)	83 (3.6)	84(3.0)
Vaginitis Bacterial	45 (4.0)	29 (2.6)	82 (3.6)	86 (3.0)
Acne	24 (2.1)	57 (5.0)	80 (3.5)	101(3.6)
Libido Decreased	28 (2.5)	48 (4.2)	78 (3.4)	81 (2.8)
Dyspareunia	39 (3.5)	34 (3.0)	77 (3.3)	86 (3.0)
Fatigue	53 (4.7)	23 (2.0)	77 (3.3)	89 (3.1)
Toothache	46 (4.1)	28 (2.5)	75 (3.3)	80 (2.8)
Dyspepsia	65 (5.8)	10 (0.9)	75 (3.2)	77 (2.7)
Vulvovaginal Discomfort	42 (3.7)	32 (2.8)	74 (3.2)	81 (2.8)
Cervical Dysplasia	35 (3.1)	35 (3.1)	70 (3.1)	80(2.8)
Mood Swings*	38 (3.4)	29 (2.6)	67 (2.9)	78 (2.7)
Pyrexia	47 (4.2)	19 (1.7)	66 (2.9)	76 (2.7)
Menorrhagia§	24 (2.1)	40 (3.5)	65 (2.8)	80 (2.8)
Arthralgia	50 (4.4)	14 (1.2)	64 (2.8)	69 (2.4)
Cough	47 (4.2)	17 (1.5)	64 (2.8)	67 (2.4)
Stomach Discomfort	59 (5.2)	2 (0.2)	62 (2.7)	62 (2.2)
Constipation	35 (3.1)	25 (2.2)	60 (2.6)	61 (2.1)
Neck Pain	46 (4.1)	10 (0.9)	56 (2.4)	60 (2.1)
Breast Pain	14 (1.2)	39 (3.4)	55 (2.4)	94 (3.3)
Gastroenteritis Viral	43 (3.8)	12 (0.1)	55 (2.4)	--
Herpes Simplex	26 (2.3)	25 (2.2)	52 (2.3)	--
Anxiety	29 (2.6)	21 (1.9)	51 (2.2)	--
Abdominal Distension	32 (2.8)	17 (1.5)	50 (2.2)	59 (2.1)
Depression	23 (2.0)	26 (2.3)	50 (2.2)	59 (2.1)
Procedural Pain	40 (3.5)	7 (0.6)	50 (2.2)	--
Rash*	35 (3.1)	14 (1.2)	50 (2.2)	--
Gastroenteritis	9 (0.8)	36 (3.2)	47 (2.0)	--
Vulvovaginal Dryness	25 (2.2)	22 (1.9)	47 (2.0)	64 (2.3)

~ uterine spasm includes dysmenorrhea; §withdrawal bleed = heavy bleeding; * see text in Reviewer's comment below. -- <2% incidence

Source: NDA 20627, Module 5.3.5.2, 300A Study Report, Table 17 p 99/1147, 300B Study Report, Table 17 p 93/626, Table 14.3.1.4.1 P 416/626, Module 5.3.5.3, ISS, Table 8-4 p 76/378, Table 8-16 ISS p 82/3781, and Medical Officer's analysis of ISS AE dataset using JMP

Comment: *The CVS AEs listed are consistent with other CHC clinical trials with no unexpected safety signals. The CVS has a higher incidence in some of the AEs (e.g. headache, dysmenorrhea) as compared with AEs identified with other labeled CHCs.*

Since the rate does not confer causation by the CVS and the majority of AEs are mild, the CVS AE profile is acceptable for a CHC product.

Analysis of AEs used MedDRA 9.1. The PT of uterine spasm included dysmenorrhea and the PT of withdrawal bleed was defined as heavy bleeding or menorrhagia. In addition, there were some conditions that were described using different terms. These terms include:

- vulvovaginal mycotic infection/vaginal candidiasis
- UTI/cystitis/genitourinary tract infection
- metrorrhagia/menstrual disorder
- mood swings/mood altered/affect lability
- depression/depressed mood/major depression/depressive symptom
- rash/papular/genital/generalized/macular/pruritic
- menorrhagia/withdrawal bleed

Comment: *We recommended that the applicant combine PTs that describe the same AE because it will give a more accurate picture of the given conditions. The Labeling for CHC Guidance[3] further recommends combining conditions that are found together (i.e. nausea and vomiting). The table below shows results of combining these PTs. Adverse events that occurred in 5% of subjects will be presented in Section 6.1 of the label.*

Table 55. Medical Officer's Analysis of ISS Combining Related Preferred Terms

Combined Terms	***n subjects***	***% (N=2308)***
headache/migraine	*933*	*40.4*
nausea/vomiting	*696*	*30.2*
vulvovaginal mycotic infection/vaginal candidiasis	*321*	*13.9*
abdominal pain/lower/upper	*321*	*13.9*
UTI/cystitis/genitourinary tract infection	*228*	*9.9*
breast pain/tenderness/discomfort	*220*	*9.5*
metrorrhagia/menstrual disorder	*167*	*7.2*
mood swings/mood altered/affect lability	*105*	*4.5*
depression/depressed mood/major depression/depressive symptom	*68*	*2.9*
rash/papular/genital/generalized/macular/pruritic	*67*	*2.9*
menorrhagia/withdrawal bleed	*66*	*2.9*

Source: NDA 209627, Module 5.3.5.3, ISS, Medical Officer's analysis of the AE data set using JMP

Within the primary ISS, the applicant presented the incidence of AEs based on BMI of ≤ 29 kg/m^2 and > 29 kg/m^2. The incidences of AEs were lower for the group with BMI >29 kg/m^2 than the group with lower BMIs.

The SA-only CVS ISS had 180 subjects with AEs. There were no new AEs identified with use of the SA-only CVS. Two of the AEs had a higher incidence than found in the SA/EE CVS; metrorrhagia (58%) and vaginal discharge (32%).

10.4.6. Laboratory Findings

Because this product contained a novel progestin, laboratory findings were evaluated to determine if there were any novel safety signals or trends in the data.

Hematology and serum chemistry laboratory parameters were evaluated at baseline, cycle 6 (Study 300A only), and cycle 13. Most subjects' laboratory parameters were within normal limits.

The largest hematology laboratory shifts involved <5% of subjects with a normal hemoglobin and hematocrit (H/H) at baseline who had a low H/H at final evaluation. Approximately 3% of subjects with a low H/H at baseline had a normal H/H at final evaluaton. Shifts in leukocyte and platelet counts were not clinically significant. The highest platelet count occurred at baseline.

> ***Comment:*** *Although there was irregular bleeding and spotting identified in the patient diaries and adverse events, the CVS does not appear to alter H/H to a clinically significant degree.*

The chemistry parameters of cholesterol, HDL, LDL, and triglycerides shifted from normal to high in >3% of subjects, with up to 11% of subjects having high cholesterol and HDL at the final evaluation.

There were four subjects who discontinued CVS use early due to elevated cholesterol and/or triglyceride levels. The table below shows the laboratory value at time of discontinuation.

Table 56. Discontinued Subjects due to Elevated Cholesterol/Triglyceride Laboratory Values

Subject ID	Cycle discontinued	Laboratory parameter	Laboratory value	Investigators relationship to CVS	Outcome
(b) (6)	6	cholesterol	248 mg/dL	possibly	ongoing
	7	triglyceride	471 mg/dL	not likely	ongoing
	6	triglyceride	415 mg/dL	possibly	ongoing
	6	triglyceride, cholesterol	140 mg/dL 300 mg/dL	possibly	ongoing

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, Medical Officer's analysis of the disposition and laboratory data sets using JMP

In addition, there was one extreme outlier, a triglyceride value of 1,243 mg/dL (Subject (b) (6))

which was not flagged as an AE. This subject discontinued the study due to vaginal soreness and no follow-up labs are noted in the submission. Her narrative does not mention her elevated triglycerides or cholesterol levels at her termination visit. In response to an IR, the applicant noted the triglyceride value of 1,243 was obtained at the subject's termination visit which was 6 weeks after last CVS use and at the time the subject was taking a COC. No further information was provided.

> ***Comment:*** *Mild elevations of cholesterol, HDL, LDL, and triglycerides occurred with the CVS. Adverse lipid and carbohydrate changes are a nown effect of CHCs and these changes will be labeled.*

In Study 300A over 5% of subjects had a creatinine shift from normal to high. This finding did not occur in Study 300B. The applicant noted that the abnormal creatinine flag for 300A was particularly low at 80 µmol/L (0.91 mg/dL). The value of 107 µmol/L equals 1.22 mg/dl. A total of 87 creatinine values were >80 and 4 subjects had creatinine values between 100 and 107. The applicant notes an elevation of creatinine is not found with the other CVS studies because the other CVS studies had higher normal creatinine values.

> ***Comment:*** *A creatinine of 0.6-1.2 mg/dl is considered normal by most laboratories and we agree with the applicant that the creatinine elevations are an artifact of the low normal range in the study.*
>
> *Mild adverse lipid changes are a nown effect of CHCs and these changes will be labeled. As for the outlier with elevated triglyceride levels six wee s after completing CVS use, it is no wn that pancreatitis and gallbladder disease can be initiated and/or exacerbated by CHCs. There is no indication that the CVS will have a different ris of these events from other CHC products. Therefore, the warnings on these events will be included in CVS labeling.*

There were eight subjects with an ALT and/or AST ≥ 2x normal; 0.3% of the ISS population. One of these subjects discontinued CVS use due to the laboratory abnormality. There were no BILI values >2x normal. The eight subjects' laboratory values are summarized in the table below.

Table 57. Subjects with ALT/AST >2 Times Upper Limit of Normal

Subject ID	Visit	Lab Parameter	Result U/L	Subject Disposition
(b) (6)	Visit 5	AST	100	completion of study
(b) (6)	Visit 5	AST	215	completion of study
(b) (6)	Visit 5	ALT	106	completion of study

(b) (6)	Visit 3	ALT	147	termination due to abnormal labs
		AST	90	
	Visit 5	ALT	127	
		AST	117	
(b) (6)	Visit 5	ALT	97	termination due to planning pregnancy
(b) (6)	Visit 5	ALT	110	completion of study
		AST	85	
(b) (6)	Visit 5	ALT	97	completion of study
		AST	95	
(b) (6)	Visit 5	ALT	87	completion of study
	Visit 6	ALT	115	

*confirmation that laboratory values returned to normal
Source: NDA 209627, Sequence 0019 Module 1.11.4, Response to Request for Information submitted 17 April 2018

Comment: *The liver enzyme abnormalities are mild and consistent with other CHCs. There do not appear to be any new safety concerns regarding liver toxicity and no labeling regarding these rare elevations are warranted.*

10.4.7. Vital Signs/Physical Examination

300A
Vital Signs

Systolic and diastolic blood pressures and pulse were assessed at baseline and at each clinical visit. The mean systolic pressures ranged from 107.5 to 108.5 mmHg and the mean percent change from baseline to final evaluation was 1.63% for all subjects. The mean diastolic pressures ranged from 68.8 to 69.8 mmHg and the mean percent change from baseline to final evaluation was 1.86% for all subjects. Mean pulse rate ranged from 74.0 to 76.6 beats/minute and the mean percent change from baseline to final evaluation was 4.7% for all subjects. There were 7 TEAEs due to elevated blood pressure.

Comment: *The vital sign data does not reveal any unexpected safety concerns compared with CHC users in general.*

Physical Examinations
Physical examinations were performed at baseline, Cycle 6, and Cycle 13. Abnormalities that were considered clinically significant by the investigator and that occurred after first use of the CVS were reported as AEs. Physical examination abnormalities occurring in >1% of subjects after initiation of the CVS were Skin, Breast, Vaginal Wall, and Vulva. Other than TEAES, findings at the Cycle 6 and Cycle 13 visits were reviewed. There were 35 skin abnormalities noted during the treatment visits that were primarily due to acne, bruising, and increased

pigmentation. The 40 abnormal breast findings were predominantly breast masses consistent with fibrocystic changes and breast implants. Out of 83 vaginal abnormalities, 56 involved discharge. Seven subjects had vaginal erythema without discharge and 4 subjects had excoriations and/or abrasions. Seventy-seven subjects had 94 vulvar abnormalities with the majority (48 events) being vulvar erythema. Other abnormalities included herpetic lesions, fissures, folliculitis, excoriations.

> ***Comment:*** *None of the findings in physical examinations are unexpected. The vaginal and vulvar findings reflect the TEAE findings of vaginal infections and discharge and vulvar irritation which are expected with ring insertion and removal and will be labeled.*

Urinalysis, Pap Smear, and STI Results

Urinalysis tests were performed at baseline with 15.8% having abnormal results and 3.8% clinically significant overall. Clinically significant abnormal findings on urinalysis after first use of the CVS were reported as a TEAE.

Abnormal Pap smear results were lower at baseline (31 subjects, 2.8%) than at final evaluation (67 subjects, 9.1%).

Positive Chlamydia tests were lower at baseline (5 subjects, 0.4%) than at final evaluation (14 subjects, 1.6%). Positive Gonorrhea tests were 0.1% at baseline and final evaluation.

> ***Comment:*** *The increased proportion of abnormal Pap smear results has been noted with other CHCs. It is still unclear if this relationship is causal because of associated HPV exposure[20]. Increased STIs are lie ly due to sexually activity without barrier protection and patients are reminded of this in labeling. In addition, participation in clinical studies provides regular screening for cervical cancer and STIs and this may increase the diagnosis of both entities. Labeling will include that the CVS does not protect against STDs.*

Weight and BMI

Height was measured once at baseline and weight was recorded at each clinic visit. Most subjects (63.7%) experienced a weight change of between -2.27 to +2.27 kg during the study. The mean change from baseline to final evaluation for all subjects was +0.26 kg. Approximately halfway through the study, 88 subjects with a BMI >29 kg/m^2 were discontinued and no further recruiting of subjects >29 kg/m^2 occurred. The majority for this subgroup (75.7%) had a weight change was -2.27 to +2.27 at Cycle 3, however, over the course of the

[20] UpToDate. https://www.uptodate.com/contents/risks-and-side-effects-associated-with-estrogen-progestin-contraceptives?search=vte%20and%20contraception&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2
Accessed April 13, 2018.

study, 69% of these subjects experienced weight change of between -4.54 to +4.54 kg. The mean change from baseline to final evaluation for all subjects who were discontinued early due to BMI>29 kg/m^2 was +0.27 kg.

> ***Comment:*** *The mean change of weight from baseline to final evaluation in all subjects of 0. 26 g is consistent with a weight gain of 0. 5 g noted in other studies[10]. In the subpopulation of subjects with BMI >29 g/ $m^2$the overall weight change was similar at +0.27 g. This weight change may be due to the length of the study or other factors, but does not appear to represent a concerning safety trend.*

300B

Vital Signs

Systolic and diastolic blood pressures and pulse were assessed at baseline and at each clinical visit. The mean systolic pressures ranged from 109.2 to 110.2 mmHg and the mean percent change from baseline to final evaluation was 0.9% for all subjects. The mean diastolic pressures ranged from 68.7 to 69.6 mmHg and the mean percent change from baseline to final evaluation was 1.6% for all subjects. Mean pulse rate ranged from 73.9 to 75.9 beats/minute and the mean percent change from baseline to final evaluation was 2.8% for all subjects. There were 5 TEAEs due to elevated blood pressure, one of which lead to early discontinuation.

> ***Comment:*** *The vital sign data do not reveal any unexpected safety concerns compared with CHC users in general.*

Physical Examinations

Physical examinations were performed at baseline and Cycle 13. Abnormalities that were considered clinically significant by the investigator and that occurred after first use of the CVS were reported as AEs. Physical examination abnormalities occurring in >1% of subjects after initiation of the CVS were Extremities, Skin, Breast, Cervix, Uterus, Vaginal wall, and Vulva. Most TEAEs in Skin SOC were acne with 56 subjects (4.9%), rash with 14 subjects (1.2%), and allergic dermatitis and urticaria with 7 subjects (0.6%) each. Abnormal findings in the data sets were also reviewed. The 23 subjects with abnormal extremity findings included scars, scratches, and bruises. Thirty-five (35) subjects had breast abnormalities, the majority were fibrocystic breast. Cervical findings in 45 subjects were mainly ectropion and "bleeds easily." Almost all of the 18 subjects with abnormal uterine findings had enlarged uterine size. All but four of the 99 subjects with abnormal vaginal wall findings had discharge or erythema. Most of the 78 subjects with abnormal vulvar findings had vulvitis and hyperemia.

> ***Comment:*** *None of the findings in physical examinations are unexpected from a gynecologic perspective. The vaginal and vulvar findings reflect the TEAE findings of vaginal infections and discharge and vulvar irritation and may result from repeated ring insertion and removal.*

Urinalysis, Pap Smear, and STI Results

Urinalysis tests were performed at baseline with 17.6% having abnormal results with 3.7% being clinically significant. Clinically significant abnormal findings on urinalysis after first use of the CVS were reported as a TEAE.

Abnormal Pap smear results were lower at baseline (40 subjects, 3.5%) than at final evaluation (77 subjects, 9.4%).

Positive Chlamydia tests were higher at baseline (48 subjects, 4.3%) than at final evaluation (3 subjects, 3.3%). There were 0.1% positive Gonorrhea tests at baseline and zero at the final evaluation.

> ***Comment:*** *The increase proportion of abnormal Pap smear results has been noted with other CHCs[10] and it is unclear if this is a causal relationship or related to HPV exposure. In addition, participation in clinical studies provides regular screening for cervical cancer and STIs and this may increase the diagnosis of both entities.*

Weight and BMI

Height was measured once at baseline and weight was recorded at each clinic visit. Most subjects (63.3%) experienced a weight change of between -2.27 to +2.27 kg during the study. The mean change from baseline to final evaluation for all subjects was +0.42 kg. Approximately halfway through the study, 52 subjects with a BMI >29 kg/m^2 were discontinued and no further recruiting of subjects >29 kg/m^2 occurred. Over 50% of this subgroup had a weight change between -2.27 to +2.27 at Cycle 3 and Cycle 6. The mean change from baseline to final evaluation for all subjects who discontinued early due to BMI>29 kg/m^2 was -0.77%.

> ***Comment:*** *The mean weight change from baseline to final evaluation in all subjects of +0.42 g is consistent with a weight gain of ≤ 0.5 kg noted in other studies[10]. In the subpopulation of subjects with BMI > 29 g/ m^2, the average overall weight change in g was not given, but 75% of the 48 subjects had < + 2.27 g change with the mean change reported at -0.77%.*

ISS

Combined data on vital signs, physical (and gynecological) examinations, weight and BMI, and urinalysis, pap smear, and STI laboratory results reported in the ISS were evaluated.

> ***Comment:*** *There were no new safety signals or trends noted in either of the two clinical studies or in the pooled ISS data for vital signs, weight/BMI or serum laboratory results. Vaginal infections and discharge were noted in both studies and these findings will be addressed in labeling.*

10.4.8. Electrocardiograms (ECGs)

ECGs were not done as part of the pivotal studies but were performed during QT evaluation studies discussed below.

10.4.9. QT

A thorough QT study (TQT; Study POP-648) was performed to evaluate the potential for QTc prolongation with use of this product. Study POP-648 was a single-center, double-blind, three-period, randomized, crossover study to evaluate the effect of supratherapeutic doses of intravenous (IV) SA on the QT/QTc interval in 44 healthy pre-menopausal female subjects. Subjects were randomized to either supratherapeutic dose IV SA or open-label moxifloxacin 400mg in each period. Thirty-nine subjects completed the study per-protocol. The study results demonstrated that the largest upper bound of the 90% CI for the mean difference SA administered by IV bolus and placebo were below 10ms, the threshold for regulatory concern as described in the ICH E14 guidelines. The Interdisciplinary Review Team for QT (IRT QT) studies was consulted and reviewed the TQT study results. In a review dated February 5, 2018 the IRT QT concluded: "no significant QTc prolongation effect of Nesterone [i.e. SA] was detected in this TQT study."[21] The IRT QT consult also provided suggested labeling language for Section 12.2 of the label (Pharmacodynamics), which will be incorporated into the final label.

10.4.10. Immunogenicity

See Section 10.5.2 Angioedema/Drug Allergy

10.4.11. Pregnancy Outcomes

There were a total of 86 pregnancies in the Primary ISS. Of the 61 pregnancies that occurred during the study, there were 30 livebirths (49%), 10 spontaneous abortions (16%), 15 induced terminations (25%), 1 ectopic pregnancy (2%), and 5 unknown outcomes (8%). Of the 25 pregnancies that occurred in the 6-month follow up, there were 3 livebirths (12%), 5 spontaneous abortions (20%), and 17 unknown outcomes (68%). No congenital abnormalities were reported. See Clinical Appendices, 22.6.1 Pregnancies, for the complete listing of pregnancies and outcomes.

> ***Comment:*** *We did not identify any pregnancy outcomes of concern during or after CVS use. See Section* 10.4.12 Return to Fertility *for comments.*

10.4.12. Return to Fertility

Subjects who wished to become pregnant or use non-hormonal contraceptives could enter a 6-month follow up to assess return to fertility after CVS use. Two hundred and ninety (290) subjects qualified for inclusion and provided data on return to fertility defined by menses or pregnancy. All subjects (100%) had return to fertility based on this definition. Twenty four subjects (8.2%) became pregnant within 6 months' post-treatment and the remaining 266 subjects reported menses occurring.

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[21] https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8047e456&_afrRedirect=1178869194318017

Comment: *The return to fertility data with the CVS show no safety concerns that women will require an extended timeframe if they decide that they wish to become pregnant or use another contraceptive method.*

10.4.13 CVS Expulsions/Issues

Expulsions of the CVS were self-reported by subjects on their diary cards. To be evaluable at least 15 of the first 21 days had to have a response (none, partial or complete) recorded. Of the 2096 subjects with evaluable diary cards, one completed expulsion occurred in 24.6% of subjects and in 7.0% of all treatment cycles. Expulsions occurred with the greatest frequency in the initial treatment cycles. Thirty-three (33) subjects or 1.4% discontinued the study due to CVS expulsions. There were seven subjects with device-related AEs which included vaginal discomfort (4 subjects), vaginal pain (1 subject), and urinary pressure (1 subject). By comparison, the NuvaRing label[4] reports the incidence of "device-related events" AEs of 6.3%. Device-related events include expulsion, discomfort, and foreign body feeling.

A summary of complete expulsions by cycle in the primary ISS is shown below.

Table 58. CVS Complete Expulsions occurring in the Primary ISS

Cycle	N[a]	Complete Expulsions[b] n (%)
1	2050	190 (9.3)
2	1994	120 (6.0)
3	1808	105 (5.8)
4	1751	90 (5.1)
5	1694	85 (5.0)
6	1561	66 (4.2)
7	1490	70 (4.7)
8	1445	61 (4.2)
9	1283	44 (3.4)
10	1185	42 (3.5)
11	1064	40 (3.8)
12	984	35 (3.6)
13	902	29 (3.2)
All Cycles[c]	21482	1509 (7.0)
All Subjects[d]	2096	515 (24.6)

Source: ISS Table 2.14

A cycle was deemed eligible for analysis of expulsions if the diary cards for that cycle had a proper response ('None', 'Partial', or 'Complete') recorded for at least 15 of the first 21 days.

[a] Count of eligible subjects or cycles. Because each subject could only have one of each numbered cycle, by-cycle counts also corresponded to subject counts.

[b] Count of eligible subjects/cycles during which at least 1 date on the diary card recorded an expulsion.

[c] All eligible cycles in the All QPharma NES/EE CVR Analysis Set, including cycles after Cycle 13.

[d] Subjects with at least one eligible cycle during the first 13 cycles. Data after Cycle 13 was excluded from this row.

Source: NDA 209627, Module 5.3.5.3, ISS, Table 6-5 ISS p 61/3781

Comment: *Although expulsions were not considered an AE, they are important information for prescribers and patients. The label will note that 25% of subjects reported at least one complete expulsion and 1.4% of subjects discontinued CVS use due to expulsions.*

10.5. Analysis of Submission-Specific Safety Issues

10.5.1. Venous Thromboembolism (VTE)

VTE is an AE of significant interest with CHC use. There were three VTEs in Study 300A and 1 VTE in Study 300B which are presented here. The VTEs occurred during cycles 2, 3, 6, and 7 of CVS use. All four subjects were past users of CHCs.

While Study 300A was ongoing, the Data Safety Monitoring Board (DSMB) met (August 22, 2007). At that time, two of the three VTEs (PE, DVT) had occurred and were reviewed. The meeting minutes are summarized below[33]:

> At the DSMB meeting two serious adverse events (SAEs), one pulmonary embolism (PE) in one subject and one deep venous thrombosis (DVT) in one subject; both with a BMI 29.3 kg/m^2 were reviewed. These two SAEs represented a larger rate of thrombosis than expected and were considered "not likely to be attributable to chance". The DSMB felt possible explanations of the thrombotic events were:
>
> - increased risk of thrombosis with increased BMI
> - higher than expected serum EE levels with the study ring during initial cycles (b) (4)
>
> The DSMB noted that the EE levels for the study CVS are higher than NuvaRing EE levels in the initial and third cycle, although less than daily serum levels for the OrthoEvra patch by cycle 4.
>
> The DSMB recommended against further enrollment of new subjects with a BMI >29 kg/m^2. For subjects of BMI >29 kg/m^2 and less than 35 y/o already in the study, the DSMB noted the greatest risk for elevated estrogen levels had passed and it was acceptable for these subjects to continue but that the study consents should be

reviewed to confirm there was adequate disclosure of possibly increased thrombosis risk.

After the recommendations, the applicant in agreement with DSMB decided to withdraw all subjects currently enrolled whose BMI was >29 kg/m^2 [22].

In the context of VTE and BMI, the applicant (b) (4)

Study 300A Subject # (b) (6) DVT, right calf
A 26-year-old nonsmoker with a screening BMI of 30.8 who had previously used COCs and a vaginal contraceptive ring, started the CVS (b) (6). Concomitant medications included Valtrex, taken (b) (6) through (b) (6). She experienced right leg pain and swelling on (b) (6) (Cycle 6 Day 3). On (b) (6), the subject went to the ER and had a lower extremity venous duplex performed showing acute deep vein thrombosis of the right popliteal and posterior tibial veins. Vital signs were normal. The subject was started on enoxaparin and warfarin, and was sent home with instructions to discontinue the CVS. The last day she used the ring was (b) (6). Follow-up laboratory testing after anticoagulant therapy was stopped was negative for lupus anticoagulant, Factor V Leiden and Factor II DNA mutation and showed normal activity in Antithrombin III, Protein C Activity, Activated Protein C Resistance, Protein S-Functional, Factor II activity and D-Dimer. This subject had a confounding factor of driving for five hours one week prior to the VTE event. The Investigator classified this AE as probably related to CVS use. The DVT resolved with treatment.

Comment: *Subject (b) (6) experienced a DVT while exposed to three ris factors for VTE. COC use increases risk of VTE 2-4 times compared to nonusers, obesity (>30 g/ m^2) further increases VTE ris in COC users 2.3-4.6 fold over non-obese COC users, and travel increases the relative ris of VTE by 2.8 compared to non-travelers[23]. We agree that all of these factors may have contributed to the VTE, however, we believe the emphasis on this subject's BMI is overstated. First, obesity is defined by >30 g/m^2 and the use of BMI > 29 g/m^2 is arbitrary and determined based on the VTEs experienced in the clinical study. Second, review of clinic data shows the subject's weight decreased during her use of the CVS. The day after her DVT was diagnosed (b) (6)), she was seen in the clinic and her BMI was 29.3 g/m^2. At her previous visit in (b) (6), her BMI was 30.1 g/m^2. Clearly, subject (b) (6) hovered at the overweight/obese cut off and the five pound difference between her April visit and July VTE event doesn't, physiologically speai ng, seem a*

[22] Application 209627 - Sequence 0007 - Report of DSMB Meeting Minutes for Protocols CCN006 (300A & 300B) - 22 Aug 2007

[23] https://www.uptodate.com/contents/risks-and-side-effects-associated-with-estrogen-progestin-contraceptives?sectionName=VENOUS%20THROMBOEMBOLIC%20DISEASE&topicRef=1361&anchor=H11&source=see_link#H11 UptoDate Risk and side effects associated with estrogen-progestin contraceptives. Accessed 6/13/18.

compelling factor of her VTE.

Study 300A Subject # (b) (6) Pulmonary Embolism
A 23-year-old with a screening BMI of 29.1, who had previously used COCs and transdermal contraception, started the CVS (b) (6). On (b) (6), the subject experienced numbness and tingling in the toes of both feet for a short time, but denied leg pain. On (b) (6) (Cycle 2) the subject experienced back and chest pain with difficulty breathing. On (b) (6), she was admitted to the hospital and computed tomography and pulmonary angiogram showed filling defects in the lingular segmental pulmonary artery, a subsegment of the posterior basal pulmonary artery in the right lower lobe, and the apical segmental pulmonary artery to the right upper lobe just past the bifurcation of the truncus anterior, giving a diagnosis of PE. Laboratory test results on admission were within normal range; tests for thrombophilia and for hemostatic factors were negative. She was treated with anticoagulants and discharged from the hospital on (b) (6). Her last CVS use was (b) (6) The applicant noted her screening BMI was 29.1. Her BMI at hospitalization was 30.2. The Investigator classified this AE as definite/highly probable in relation to CVS use. The PE resolved with treatment.

Comment: *Subject* (b) (6) *experienced an unprovoe d PE with a negative hypercoagulability worup du ring her second cycle of CVS use. The applicant notes her only ris factor was her BMI of > 29 g/m^2. We do believe that the patient's BMI alone precipitated her PE since her BMI was > 29 g/m^2 at baseline and she had no prior history of DVT/PE despite her previous exposure of COCs. Review of BMI measurements shows the following:*

Visit	***Date***	***BMI***	***Day of CVS Use***
V0	(b) (6)	*29.1*	*screening*
V1		*28.5*	*baseline day 1*
Hospital/PE		*30.2*	*day 42*
V5		*28.0*	*day 47*
V6		*27.8*	*day 54*

The applicant suggests that a BMI over 29 g/m^2 incurs a tenfold higher ris for VTE. Indeed, PE ris goes up as BMI increases beyond 22.5 kg/m^2 and the risk increases almost six fold at ≥35 g/m ^{2} compared to those with BMI<22.5 g/ m^2 (Kabrhel et al 2012).[24] From the subject's BMI measurements, her BMI was >28 g/ m^2 before initiation of CVS and her BMI change on CVS was not remarkable; therefore, a temporal association between exposure to CVS and the occurrence of PE cannot be excluded.

[24] Kabrhel C, Varraso R, Goldhaber S, Rimm EB, Camargo CA. Prospective study of BMI and risk of pulmonary embolism in women. *Obesity.* 2009;17:2040-2046

Study 300A Subject # (b) (6) DVT, Factor V heterozygous mutation
A 39-year-old with a baseline BMI of 24.7, history of hypothyroidism treated with Synthroid, and previous use of COC for 6 years (last use (b) (6) ago), and one pregnancy 15 years prior, started the CVS (b) (6) On (b) (6) (Cycle 3) she experienced left leg pain and swelling. On (b) (6) an "ultrasound scan" of leg was negative. The subject had increasing pain and difficulty walking and a second "ultrasound scan" was performed on (b) (6) with the diagnosis of acute DVT in left lower extremity involving the popliteal, peroneal and gastrocnemius veins at which time she discontinued the CVS. The subject was started on enoxaparin and warfarin and the CVS was discontinued. This subject was in the sub-study for hepatic factors and at baseline visit, (b) (6), her labs were normal. (b) (6) laboratory tests showed that she was positive for one copy Factor V mutation (heterozygous); the rest of thrombophilia labs were normal or negative. The Investigator classified this AE as possibly related to CVS. The DVT resolved with treatment.

> ***Comment:*** *Subject* (b) (6) *experienced a DVT and was found to have a Factor V Leiden mutation on subsequent thrombophilia laboratory testing. Presence of this mutation in women using OCs increases the ris of VTE 4-8 fold over women using OCs without the mutation. Screening for Factor V Leiden mutation prior to OC use is not recommended due to the prevalence (5% of women) and the low incidence of venous thrombosis-related mortality[33].*

Study 300B Subject (b) (6) Cerebral Venous Thrombosis
28-year-old former smoker (quit in (b) (6) with a history of depression and use of COC five weeks prior to study entry, started the CVS (b) (6) with a BMI of 25.0 kg/m^2. On (b) (6) (Cycle 7 day 24) during the ring-out period, the subject experienced a localized headache that progressed during the night and was accompanied with nausea and vomiting. The next day the pain returned and worsened. On (b) (6), a magnetic resonance angiography of the head "showed near total occlusive thrombosis of the left transverse sinus and no evidence of intracranial arterial aneurysm, occlusion or flow limiting stenosis". The subject was admitted to the hospital and treated with heparin. Laboratory tests on admission were within normal ranges. The subject was discharged from the hospital one week later on coumadin. Attempts to contact the subject by the study site were unsuccessful. The subject's physician verbally stated that the subject's coagulation profile laboratory tests were all normal. The Investigator classified this AE as possibly related to CVS use.

> ***Comment:*** *Subject* (b) (6) *experienced an apparent unprovoked cerebral venous thrombosis. The applicant was not able to obtain hospital records or follow up with the subject because the subject did not return calls nor had she given permission for medical records release. Her primary care physician verbally stated that "the subject was doing well and that her coagulation profile laboratory tests were all normal" to the Principal Investigator.*

The applicant acknowledges the observed rate of VTE in this program, four (4) VTEs in the primary ISS (All QPharma) was higher than other CHC programs. The applicant states this increased rate was due to the disproportionate rate of VTE in obese women (b) (4) By removing this population and two of the four VTEs, the applicant is able to calculate a VTE risk consistent with other CHC programs (Table 59).

Table 59. Summary of VTE risk by Analysis Sets and BMI

Rates by BMI Subgroup					
Baseline BMI (kg/m^2)	**N**	**VTEs Observed (n)**	**Exposure (cycles)**	**Cumulative Incidence Rate[a]**	**95% Confidence Interval**
All NES*/EE CVS (N=2843)					
≤29.0	2536	2	24190.9	10.78	(8.90, 13.07)
>29.0	307	2	2083.7	125.21	(103.34, 151.71)
Ratio (>29.0 vs. ≤29.0)				11.61	(8.85, 15.23)
All NES*/EE 150/15 CVS (N=2569)					
≤29.0	2312	2	21709	11.98	(9.82, 14.61)
>29.0	257	2	1590	163.52	(134.03, 199.50)
Ratio (>29.0 vs. ≤29.0)				13.65	(10.31, 18.09)
All QPharma NES*/EE CVS (N=2308)					
≤29.0	2099	2	20336	12.79	(10.39, 15.73)
>29.0	209	2	1254	207.34	(168.51, 255.11)
Ratio (>29.0 vs. ≤29.0)				16.22	(12.10, 21.74)
Source: ISS Table 1.1.6; ISS Table 2.7.14; ISS Table 2.7.15					

[a] incidence rate per 10,000 women-years
*NES=SA
Source: NDA 209627, Module 5.3.5.3, ISS, Table 8-15, p 108/3781

Comment: *We do not agree with the applicant's proposed* (b) (4) (b) (4)

[25] Report of DSMB Meeting Minutes for Protocol CCN006 (300A & 300B) 22 Aug 2007. Submitted NDA 209627 Modules 1.6.3 Correspondence Regarding Meetings.

(b) (4)

Based on clinical review,the CVS VTE ris should be evaluated including all subjects and cycles in the primary ISS, (b) (4) *Based on the primary ISS of 2308 women contributing 21,590 cycles with 4 VTEs, the cumulative incidence rate is 24.1 per 10,000 women-years (95%CI 6.6, 61.7). Although this is a somewhat higher incidence than noted in other recent CHC trials, the increased rate is due to one additional VTE event occurring in the trials. Further, these clinical studies were not powered to provide a precise estimate of the incidence of uncommon events such as VTEs, which is reflected in the wide confidence interval that speas to the considerable uncertainty associated with the VTE incidence rate estimate of 24.1 per 10,000 women-years estimate.*

There have been numerous studies on VTE risk in CHCs, especially in relation to type of progestin. FDA labels show the likelihood of developing a VTE for a CHC-user of 3-12/10,000 women-years. The American College of Obstetrician and Gynecologists Committee Opinion 540 (reaffirmed 2016) provides the risk of VTE among COC users as 3-9/10,000 women-years[26] while the EURAS Study[27] has 10.2/10,000 women-years for "other OCs" (other than LNG COCs and Yasmin).

In the past 10 years, approved CHCs with the highest VTE incidence per 10,000 women-years based on clinical trial data are 16.7 for Lo Loestrin Fe (EE/NETA) and 11.3 for Quartette (EE/LNG). The absolute numbers of VTEs were small with Quartette having 3 VTEs and the rest of the CHCs having 0-2 VTEs. NuvaRing clinical trials which excluded women with a BMI >29 kg/m^2 was approved in 2001 and had a VTE incidence of 5.3 per 10,000 women-years. The OrthoEvra patch clinical trials had 2 VTEs for a 11.7 VTE/10,000 women-years (approved 2001).

The applicant notes the mean BMI of 26.7 kg/m^2 for the CVS is higher than other CHCs, and this may have increased the number of VTEs in the pivotal trials. However, Quartette trial subjects had a mean BMI of 27.3 kg/m^2 and LoSeasonique trial subjects had a mean BMI of 26.8 kg/m^2. LoSeasonique had no VTEs in the clinical trials. Therefore, BMI is not the reason the VTE estimate appears high in this submission.

[26] https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Risk-of-Venous-Thromboembolism

[27] Dinger J, Heinemann L, Kühl-Habich D. 2007. The Safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception; 75(5): 344-354.

The applicant states that three of the four subjects with VTE had predisposing factors (driving for an extended time, positive Factor V, and BMI). While this is true, subject recruitment in this contraceptive study was consistent with other contraceptive studies. As in other contraceptive studies, in the studies for this application, subjects with known risks for VTE (i.e. family history or personal history of VTE, hypertension, migraines with focal symptoms, smokers over 35 years old) were excluded. These studies are designed to reflect how the contraceptive product will be used in practice, with the above exclusions listed as contraindications in the label. Since many women are not aware of their personal risk for VTE both in clinical studies and in clinical practice,this study design reflects real-world evidence. Of note, all 4 subjects had previously used CHCs and would be classified as "previous users" (4 weeks had elapsed since last use) and might be considered at lower risk than naïve subjects.

> ***Comment:*** *After discussions with the applicant, the identified VTE risk will be labeled in Warnings and Precaution (W&P) as in all CHCs. Within the W & P section, obesity as a risk factor for VTE is listed. I recommend discussion of the four (4) VTEs in the Clinical Trials experience. Whether to include subject level data, i.e. BMI and other risk factors, will be determined. Because we cannot draw a definitive conclusion about the actual VTE risk for the CVS based on the available data or how it would compare to other CHC products, we will require a postmar eting study to evaluate VTE ris with an appropriately powered required study to gain a more accurate ris assessment.*

10.5.2. Angioedema/Drug Allergy

Hereditary angioedema is a rare familial disorder that is associated with exogenous estrogens (i.e. CHCs) or high estrogen levels (as in pregnancy). Drug allergies with CHCs are more common and have diverse etiologies. Two SAEs in the Angioedema/Drug Allergy category occurred in the pivotal trials.

Study 300A Subject # (b) (6) Combination Drug Allergy, Angioedema
A 37-year-old who in the previous year used NuvaRing, used the CVS (b) (6) through (b) (6) and on (b) (6) experience angioedema, with throat constriction, respiratory wheezing and hives. She self-treated with Benadryl but later went to the emergency room and was treated with solumedrol and prednisone. She returned to the emergency room for the next 3 days (b) (6), was treated symptomatically and never admitted. The subject had been suffering from a viral illness and was using aspirin products. She had an evaluation by an allergist (b) (6) and the allergist made the diagnosis of angioedema/urticaria. The allergist felt the viral illness and use of NSAIDS and opioid therapy were contributing factors but that the reaction can be related to hormone therapy. The subject discontinued the CVS and restarted NuvaRing on (b) (6) with complete recovery from the event on (b) (6). The investigator classified this AE as probably related.

> ***Comment:*** *Angioedema is an uncommon but no wn event that occurs with the estrogen*

component of CHCs. This subject's symptoms of angioedema occurred within one month of starting the CVS and continued despite daily treatment until the CVS was discontinued. The episode resolved after the CVS was discontinued but while the subject was using NuvaRing. This is an interesting case because the symptoms of angioedema resolved despite using Nuvaring which contains the same estrogen component; therefore, it is possible the subject's angioedema is due to other components of CVS that is not ethinyl estradiol.

Study 300B Subject # (b) (6) Urticaria, Facial Edema, Asthmatic Attack
A 33-year-old with a history of asthma and several allergies including nickel and penicillin and past use of CHCs, started the CVS (b) (6). On (b) (6), she "got a cold" and increased her asthma medication. Two day later she experienced urticaria mainly on her arms one hour after eating cashews. She had no history of allergy to cashew nuts. She was treated with cortisone and antihistaminic medication with the rash decreasing on (b) (6) However, on (b) (6) her urticaria increased and she experience facial edema. She removed the CVS on (b) (6) With continued treatment for asthma and allergic reaction, she recovered. There were no genital symptoms suggesting a local allergic reaction. The applicant felt the nuts were more likely the causal factor and that a slow recovery from the allergic reaction most likely explained the clinical resolution rather than allergic reaction to the CVS with a positive dechallenge test.

Comment: *Hypersensitivity to the CVS or any of its components will be listed in the Contraindications section of the label. Angioedema will be labeled in the Warnings section.*

10.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no patient reported safety outcomes that required input from the clinical outcome assessment team regarding safety or tolerability.

10.7. Safety Analyses by Demographic Subgroups

The applicant presented MedDRA-based tables for their demographic subgroups of age, race, ethnicity and geographic region. There were no significant differences in the proportion or the types of TEAEs in any of the demographic subgroups.

Age was categorized by <36 years or ≥36 years. There were 1872 TEAEs in the <36 year group and 144 TEAEs in the ≥36 years group. Percentages for the different SOC and PT were similar between these groups.

Race was categorized by Caucasian, Black, and Other. There were 1429 TEAEs in the Caucasian, 261 TEAEs in the Black, and 287 TEAEs in the Other groups. Percentages for the different SOC and PT were similar for the three race categories.

The TEAEs between Hispanic and non-Hispanic, nulliparity and parity, US and non-US, and age of the CVS (<1.69 years, >1.69-1.99 years, ≥ 2 years) subgroups were similar.

10.8. Specific Safety Studies/Clinical Trials

Nested within Study 300A, were three sub-studies to explore the effect of the CVS on vaginal microbiology, endometrial histology, and four estrogen-dependent hepatic proteins. The sub-studies procedures and results discussed in this section (10.8 Specific Safety Studies/Clinical Trials) relate to the specific safety parameters.

10.8.1. Microbiology sub-study

The primary objective of the Microbiology sub-study was to evaluate changes in vaginal flora and risk of vaginal infection associated with use of the same CVS for 13 cycles.

The trial design was a single center sub-study of 300A where the subjects were also full participants in study 300A and included in the contraceptive efficacy and safety assessments in the main study. A separate and additional informed consent was obtained at enrollment into the microbiology sub-study.

In addition to the visits and procedures required for 300A, subjects in this sub-study had quantitative vaginal cultures, vaginal smear saline preparation, potassium hydroxide analysis, vaginal pH, Whiff test, gram stain, and temperature assessments at Screening (V0), cycle 6 (V3), and cycle 13 (V5). At Visit 5 (cycle 13) when the study ring was removed, quantitative culture of the vaginal ring was also performed. If subjects did not complete 13 cycles, they were to complete all of the cycle 13 assessments at their final study visit, regardless of when the final visit occurred. Visit 3 occurred on day 1-7 (in week 1 of CVS use) and Visit 5 occurred on day 21-27 (during last week of the last treatment cycle).

The endpoints for this sub-study were:

- the presence of bacterial vaginosis based on Amsels criteria and Nugent score

- presence of yeast based on KOH analysis
- presence and amount of WBCs
- presence or absence of trichomonads
- vaginal cultures presence of Lactobacillus, Gardnerella vaginalis, enterococcus, Staphylococcus aureus, E. coli, Candida albicans, other yeast, anaerobic gram-negative

Comparison between baseline (V0) and follow up visit (V6 and/or V13) was performed. Amsels and Nugent score were determined by the principal investigator. The criteria are presented in the Appendix (22.6.2 Microbiology Sub-study).

One hundred twenty (120) subjects were enrolled in the microbiology sub-study. One hundred and ten (110) subjects had a baseline and at least one follow-up visit and comprised the microbiology population. The disposition of the 120 subjects is shown in the table below.

Table 60. Disposition of Microbiology Population

Disposition	n subjects	% (N= 110)
Completed study	68	56.7
Discontinued study	52	43.3
Reason for Discontinuation		
Adverse event	18	15.0
Withdrew consent	17	14.2
Lost to follow up	6	5.0
BMI >29 kg/m^2	6	5.0
Compliance	3	2.5
Expulsion	1	0.8
Pregnancy	1	0.8

Source: NDA 209627, Module 5.3.5.2, 300A Microbiology Sub-study Clinical Study Report, Figure 1 p 34/58

The 120 subjects' demographics in this single site study were predominantly White (82.5%), not Hispanic (94.2%), never married (86.7%), had some college or higher (93.4%), and desired children after completing the study (76.6%). Most subjects were nulliparous with 23.3% of the 120 having at least one pregnancy.

The mean age was 24.5 years with 85.0% of subjects between 20 and 29 years. The mean BMI was 23.1 with 66.7% of subjects between BMI of ≥20 and <25 kg/m^2. Never smokers made up 62.5% of the population and 15.8% of subjects were current smokers.

Medical history for active conditions was present in 97.5% of the sub-study subjects. Compared with the general 300A study population, the sub-study population had a higher incidence of conditions in Nervous System Disorders (60.8% vs 35.3%) and Reproductive System and Breast Disorders (67.5% vs 20.0%) . Infections and Infestations was similar between the sub-study and main study (14.1% vs 15.8%). In this sub-study, there were 19 subjects (15.8%) who used fluconazole concomitantly.

The results of quantitative tests given in the report are presented in Table 61. Results for remaining microorganisms (enterococcus, E. coli, Gardnerella vaginalis, Staph aureus, Candida albican, or other yeast) did not indicate any significant changes or trends. There were no differences in the culture results between vaginal aspiration and CVS ring except for anaerobic gram negative rods that where not preserved in transport during the CVS ring culture process.

Table 61 Results of Microbiology Quantitative Tests

ASSESSMENT	V0	V6	V13	SIGNIFICANCE
Bacterial vaginosis	N=120 (%)	N=110 (%)	N=61 (%)	
Amsel	3 (2.5)	3 (2.7)	1 (1.6)	NS
	N=119 (%)	N=110 (%)	N=61 (%)	
Nugents score ≥7	15 (12.6)	12 (10.9)	5 (8.2)	NS
Yeast	N=120 (%)	N=110 (%)	N=61 (%)	
KOH	2 (1.7)	3 (2.7)	3 (4.9)	**
WBC	N=115 (%)	N=102 (%)	N=57 (%)	
moderate to many	6 (5.2)	4 (3.9)	0	NS
Vaginal culture	N=120 (%)	N=110 (%)	N=61 (%)	
Lactobacillus present	92(76.7)	91 (82.7%)	55 (90.2)	NS
Non H202 Lactobacillus	43 (35.8)	36 (32.7)	13 (21.3)	SS
Anaerobic gram negative rods (AGNR)	46 (38.3)	61 (55.5)	33 (54.1)	SS

NS=not significant, SS=statistically significant P<0.05, ** applicant separated symptomatic from asymptomatic yeast infections and stated there was no significance for symptomatic yeast infections. There was no calculation for all yeast infections.
Source: NDA 208627, Module 5.3.5.2, 300A Microbiology Sub-study Clinical Study Report p 41-43/58

Comment: *The mean concentration of anaerobic gram negative rods (AGNR) increased with CVS use with the median concentrations remaining at a low level (10^2) and no subjects with symptomatic infection suggesting that this increase is not clinically significant. The concentration of hydrogen peroxidase lactobacillus in vaginal flora cultures maintained high levels at all three assessments with no statistically significant changes based on shift tables. There was a decrease of non-hydrogen peroxidase lactobacillus between baseline and Cycle 13 that was statistically significant; this finding is not li ely to be clinically significant since hydrogen peroxide-producing lactobacillus helps provide a normal vaginal ecosystem. The KOH results reported by the applicant separate the KOH results into symptomatic and asymptomatic, which I have combined in the above table. It is difficult to ascribe clinical significance to such small numbers; 2 vs 3 subjects.*

Of concern is the concomitant use of fluconazole by 19 subjects during this study. It is unclear how this affects the results, especially for yeast. Also, the subjects of this sub-study, based on demographics, do not reflect the overall US population and it is

un nown if these results are generalizable to the US or global populations. In summary, none of the data obtained from this substudy shows a new trend or concern that would require specific labeling for vaginal infections.

10.8.2. Endometrial Safety Sub-Study

The primary objective of the Endometrial safety sub-study was to demonstrate the safety of the CVS on the endometrium after 1 year of use.

The trial design was a multicenter (6 US centers) sub-study of 300A where the subjects were also full participants in study 300A and included in the contraceptive efficacy and safety assessments in the main study. A modified informed consent form with risks and benefits of the endometrial biopsies was signed prior to subjects' entry into the sub-study.

In addition to the visits and procedures required for 300A, subjects in this sub-study had two endometrial biopsies. All subjects in this sub-study (after a negative UPT) had an endometrial biopsy at Screening (V0). If the subject was not on CHCs, the biopsy was performed between days 7-14 of the subject's cycle. If the screening biopsy showed hyperplasia or carcinoma, the subject was to be excluded from enrolling in both this sub-study and the main study (300A). After CVS treatment started, the first 25 subjects to reach Cycle 6 (V3) were to have a second endometrial biopsy on Days 20-24 of Cycle 6. The remainder of the subjects were to have a second biopsy at Cycle 13 (V5) during Days 20-24 or at the time of early termination (provided the subject had been enrolled for at least 3 months).

Three pathologists with expertise in gynecology pathology read each of the processed endometrial tissue in a blinded fashion. The most severe diagnosis was recorded if there were differing diagnoses.

Endpoints included:

- Endometrial histology data summarized by visit and hormonal contraception history
- Changes in endometrial patterns from baseline

A total of 156 unique subjects had baseline endometrial biopsies and 83 subjects had a follow-up endometrial biopsy. Twenty seven (27) subjects had biopsies at Cycles 5 to 6, 25 subjects had biopsies at Cycles 7 to 11, and 31 subjects had biopsies at Cycles 12 to 13 and one subject had a biopsy performed 2 cycles after she finished using the CVS for 14 cycles. The disposition of the 156 subjects is shown in Table 62.

Table 62. Disposition of Safety Population in the Endometrial Sub-Study

Disposition	**n subjects**	**% (N=156)**
Completed study	77	49.4

Discontinued study	79	50.6
Reason for Discontinuation		
Adverse event	23	14.7
Lost to follow up	22	14.1
Withdrew consent	17	10.9
Eligibility	15	9.6
Compliance	1	0.6
Pregnancy	1	0.6

Source: NDA 209627, Module 5.3.5.2, 300A Endometrial Safety Clinical Study Report, Figure 1 p 35/70

Six eligibility violations occurred; three due to abnormal baseline laboratory test results, two due to abnormal baseline Pap smears, and one due to the subject not having a history of regular menses.

The majority of the safety population's demographic and baseline characteristics were White (66.7%), non-Hispanic (92.3%), never married (68.6%), and 48.7% had some college or higher education. The majority, 55.8%, had a history of at least one pregnancy.

The majority of subjects (71.2%) were between 20 and 29 years of age, with the mean age of 27.2 years. The mean BMI (SD) was 24.2 (±11.5). Never smokers made up 71.2% of the population and 12.2% of subjects were current smokers.

Compared to the general 300A study population, medical history in the sub-study was similar , except that more subjects in the sub-study had a history of reproductive and breast disorders (32.7% vs 20.0%).

There were two cases of endometrial hyperplasia, both at baseline. One subject was allowed to continue in the study (b) (6), the other subject was discontinued from the study. There were two subjects where one of the three pathologists diagnosed a polyp; one at Cycle 5-6, the other at Cycle 12-13.

The histology results of the endometrial biopsies are shown in the applicant's table below.

Table 63. Summary of Endometrial Biopsies in Endometrial Safety Sub-Study by Cycle Window and Prior Use of CHC

	Safety Population[a]		Biopsy Population[b]			
				Post-Baseline Biopsies		
	Baseline N=156 n (%)		Baseline N=83 n (%)	Cycle 6 N=24 n (%)	Cycles 12-13 N=30 n (%)	Other N=29 n (%)
Normal Results						

Insufficient or No Tissue	14 (9.0)	4 (4.8)		3 (10.0)	1 (3.4)
Atrophic/Inactive	10 (6.4)	6 (7.2)	7 (29.2)	8 (26.7)	8 (27.6)
Proliferative	67 (42.9)	33 (39.8)	4 (16.7)	2 (6.7)	6 (20.7)
Secretory	43 (27.6)	25 (30.1)	7 (29.2)	11 (36.7)	1 (44.8)
Menstrual	2 (1.3)	2 (2.4)	1 (4.2)	2 (6.7)	
Mixed	13 (8.3)	9 (10.8)	4 (16.7)	3 (10.0)	1 (3.4)
Abnormal Results					
Hyperplasia[c]	2 (1.3)	1 (1.2)	0	0	0
Other Abnormal Results[d]					
Other	5 (3.2)	3 (3.6)	1 (4.2)	1 (3.7)	0

Source: Table 14.8.3; Listings 16.6.1, 16.6.3.1, and 16.6.6.2.
[a] All subjects with endometrial biopsy data, excluding 3 subjects (Subjects [redacted]) who were enrolled concurrently at two different sites.
[b] All subjects with both a baseline (Screening, Visit 0) and follow-up biopsy.
[c] At screening, 2 subjects were categorized as having a diagnosis of hyperplasia. One subject (Subject [redacted]) was permitted to remain in the study based on the Investigator's clinical judgment. The other subject (Subject [redacted]) was discontinued from the study due to the SAE of hyperplasia without a follow-up biopsy and was not included in the Endometrial Biopsy population.
[d] Includes one baseline reading of endometritis (Subject [redacted]; all others were single pathologist readings of an endometrial polyp (Subjects [redacted].
Cycle windows: baseline (Screening, Visit 0): Days ≤ 1; Cycle 6: Days 141–168; Cycles 12-13: Days 309-364; Other: Days 2–140, 169–308, and ≥ 365. During each window, only the most recent, non-missing result per subject was summarized.
Source: NDA 209627, Module 5.3.5.2, 300A Endometrial Safety Clinical Study Report, Table 10 p 46/70

Subjects using CHC prior to enrollment had endometrial biopsies taken at any time during their cycle with the majority of biopsies showing secretory endometrium. Subjects not on hormonal contraception had biopsies taken day 7-14 of their cycle and the majority of biopsies showed proliferative endometrium. The endometrial biopsy changes over time showed no consistency in the shifts between benign endometrial types. The one subject with endometrial hyperplasia at baseline who remained in the study had secretory endometrium at Cycle 6.

> ***Comment:*** *The difference in the baseline biopsy results is most likely due to cycle timing when biopsy was obtained. In this sub-study, there did not appear to be a shift towards atrophic/inactive endometrium with use of the CVS. Likewise, there was no evidence of premalignant/malignant changes of the endometrium with use of the CVS. Based on the findings, no additional labeling was required.*

10.8.3. Hepatic Factors Sub-Study

The primary objective of the hepatic factors sub-study was to evaluate the use of the CVS over 13 cycles on the effect of four (4) estrogen-dependent hepatic proteins: factor VIII, fibrinogen, Protein S, and sex hormone binding globulin (SHBG). Factor VIII, fibrinogen, and Protein S were selected due to their involvement in the coagulation system. The applicant notes that these

proteins may be associated with risk of thromboembolism although there is no biological marker established as an acceptable predictor of VTE risk.

The trial design was a two-center (both US) sub-study of 300A where the subjects were also full participants in study 300A and included in the contraceptive efficacy and safety assessments in the main study.

In addition to the visits and procedures required for 300A, subjects in this sub-study had an additional blood drawn of 10 cc for the hepatic markers at Screening (V0), Cycle 6 (V3), and Cycle 13 (V5). If subjects did not complete 13 cycles, at their final visit all of the Cycle 13 assessments were obtained. Visit 3 occurred on day 1-7 (in week 1 of CVS use) and Visit 5 occurred on day 21-27 (during last week of the last treatment cycle).

The endpoints for this sub-study were:

- Changes in each hepatic protein over time
- Compare values between the group of women with previous CHC use and the group of women without previous CHC use

One hundred twenty-nine (129) subjects were enrolled in the hepatic factors sub-study. One hundred and six (106) subjects had a baseline value, 104 subjects had a Cycle 6 value, and 61 subjects at Cycle 13 (or final visit) value. The safety population included all subjects enrolled who inserted the CVS. The hepatic-evaluable population included all treated subjects with at least one follow-up laboratory results.

The disposition of the 129 subjects is shown in the table below.

Table 64. Disposition of Safety Population in the Hepatic Factors Sub-Study

Disposition	**n subjects**	**% (N=106)**
Completed study	68	52.7
Discontinued study	61	47.3
Reason for Discontinuation		
Lost to follow up	17	13.2
Withdrew consent	15	11.6
Adverse event	14	10.9
BMI > 29 kg/m^2	7	5.4
Pregnancy	5	3.9
Compliance	2	1.6
Expulsions	1	0.8

Source: NDA 209627, Module 5.3.5.2, 300A Hepatic Factors Sub-study Study Report, Figure 1 p 31/57

A total of 12 protocol violations of eligibility in the study were allowed by physician's judgment. There were 8 subjects who were included despite abnormal baseline laboratory test results.

The majority of the safety population's demographic and baseline characteristics were White (69.0%), not Hispanic (93.8%), never married (63.6%), and had some college (46.5%).

The mean age was 26.5 years (range 18.2-39.5). The mean (±SD) BMI was 23.9 (±3.9) kg/m^2. Never smokers made up 62.8% of the population and 16.3% of subjects were current smokers

Active medical conditions for this sub-study subjects differed from the Study 300A population. The hepatic sub-study subjects had a higher incidence than the main population in Infections and Infestations (21.7% vs. 14.1%), Nervous System Disorders (72.9% vs. 35.3%), and Reproductive System and Breast Disorders (29.5% vs 20.0%).

Of the 129 subjects, 38 subjects had used CHCs within 30 days of enrollment.

The results of the mean value for each hepatic protein by cycle is shown in Table 65.

Table 65. Hepatic Factors Results by Cycle and Change from Baseline

Parameter	Screening mean (SD) N=106	Cycle 6 evaluation mean (SD) N=104	Final evaluation mean (SD) N=61	Normal range	Final Change from Baseline mean (SD)
Factor VIII (relative to RS~)	1.1 (0.4)	1.3 (0.6)	1.4 (0.6)	0.5-1.8	0.2 (0.5)*
Fibrinogen (g/L)	2.8 (0.7)	2.9 (0.6)	3.0 (0.6)	2.1-4.3	0.2 (0.7)*
Protein S (relative to RS)	0.85 (0.2)^	0.8 (0.2)^^	0.8 (0.2)	0.6-1.4	-0.08 (0.2)*
SHBG (nmol/L)	89.9 (62.3)^	172.8 (73.8)	171.6 (91.9)^^^	8-112	81.7 (94.3)*

Source: NDA 209627, Module 5.3.5.2, 300A Study Report, Table 14.5.2.1 p 897/1147
~ RS=reference standard. ^N=105, ^^N=103, ^^^N=60
*P<0.005

All four hepatic proteins showed a statistically significant change from mean baseline value to mean final evaluation value. SHBG was the only hepatic protein where the final mean value was above the normal range.

The 36 subjects who used CHC within 30 days of enrollment had higher baseline values of Factor VIII, fibrinogen, and SHBG and lower baseline values of Protein S than the subjects who did not use CHC within 30 days of enrollment. The mean laboratory values of these 36 subjects increased from baseline for Factor VIII, fibrinogen, and SHBG with only the SHBG value rising above normal range and Protein S not decreasing from baseline.

Comment: *The hepatic protein changes are consistent with nown changes that occur with CHCs.*

The SAEs and AEs are reported in the 300A Study report as all the subjects in this sub-study were enrolled in 300A. Subject (b) (6) was discontinued by the applicant from Study 300A due to a low Protein S level of 0.49 at Cycle 6 from a normal baseline of 0.74. Two subjects (Subjects (b) (6) and (b) (6)) in this sub-study had VTEs. Their baseline hepatic laboratory results for Subjects (b) (6) and (b) (6) were normal.

10.8.4. Colposcopy

Study 180, a 13-cycle, multicenter, randomized, dose finding and efficacy study performed vaginal/cervical colposcopy on subjects at 3 of the 5 sites. The colposcopic examinations were performed at pretreatment, cycle 3, and cycle 13. Evaluation of the vagina and cervix was for epithelial abnormalities (e.g. abrasion, ectropion, ulcer, acetowhite, punctuation, vascularity). No severe abnormality was found at any time. The only finding that occurred in >2% of the subjects on treatment was vaginal erythema in 6 subjects (4%) at Cycle 3 and cervical erythema in 5 subjects (3.3%). Findings suggestive of cervical intraepithelial abnormality were categorized as AEs and reported in the All SA/EE ISS.

Comment: *There does not appear to be any safety signal with the CVS use in regards to cervical and vaginal epithelial integrity.*

10.8.5. Lactation Studies

There are no lactation studies conducted with the CVS. However, three lactation studies with SA implants have been performed and are summarized here.

An early study[28] on 6 healthy lactating women using an implant with 20 mg SA evaluated the relationship between serum and breast milk SA levels. The average plasma concentration was 62 pg/ml and the average breast milk concentration was 38 pg/ml. The mean milk/plasma ratio was 0.6 with a range from 0.25 to 0.91.

Coutinho[14] studied lactating women with SA implants (50 mg) and their nursing infants for one year. On Day 75 mean maternal serum levels of SA were 381 pmol/L, mean maternal breast milk levels of SA were 373 pmol/L, and the mean infant serum levels of SA were 19 pmol/L.

[28] Lahteenmaki PLA, Diaz S, Miranda P, et al. Milk and plasma concentrations of the progestin ST-1435 in women treated parenterally with ST-1435. Contraception 1990;42:555-562

There were no safety signals in feeding, growth and development of the infants observed between the SA and control groups (who used a Copper T380 IUD)[29].

Massai[30] in a controlled study using SA implants delivering 100 µg/day studied lactation and infant growth. Mean SA levels in maternal serum were 175 pmol/L in the first months decreasing to 60 pmol/L at the end of the first year. The mean SA levels in the breast milk were 135pmol/L decreasing to 54pmol/L. It was estimated that the infants received 50 ng/day of SA through breast feeding. The body weight of infants was similar between the control group (copper IUD) and the SA group over the 1 year study period.

> ***Comment:*** *Although these studies were with SA-only implants and contained lower doses of SA than the CVS, the results of SA in lactating women, breast mil, and nursing infants showed no safety signals in feeding, growth, and development between the segesterone acetate implant group and the control group. This information is included in labeling in addition to the general recommendation against breast feeding with use of contraceptives containing EE.*

10.9. Additional Safety Explorations

10.9.1. Human Carcinogenicity or Tumor Development

None reported in this CVS database.

10.9.2. Human Reproduction and Pregnancy

There were 40 reported case of pregnancy during the CVS trials, all in the first trimester. Evaluation of these pregnancies is provided in Section 8 of this review.

10.9.3. Pediatrics and Assessment of Effects on Growth

The applicant submitted an initial Pediatric Study Plan (iPSP) on May 13, 2015, which was reviewed by the Pediatric Review Committee (PeRC) and agreed upon by the Division. The iPSP requested a waiver for males of any pediatric age and premenarchal females and assessment of extrapolation of data from adult women to post menarchal females to age (b) (4).

On July 18, 2018 PeRC agreed with the waiver for males and assessment from adult women to adolescent females.

[29] Coutinho EM, Athayde C, Dantas C, et al. Use of a single implant of elcometrine (ST-1435), a nonorally active progestin, as a long acting contraceptive for postpartum nursing women. Contraception 1999;59:115-122
[30] Massai MR, Diaz S, Quinteros, E, et al. Contraceptive efficacy and clinical performance of Nesteorone implants in postpartum women. Contraception 2001;64:369-376

10.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of toxicity due to overdose have been reported. The CVS is not believed to have any abuse or dependent potential. In addition, there is no evidence of impairment of fertility that would indicate a withdrawal-type phenomenon (See Section 10.4.12).

10.10. Safety in the Postmarket Setting

(b) (4)

Based on this information, there is no data from postmarketing that will add to the safety profile from the applicant's data.

Safety Concerns Identified Through Postmarket Experience Based on our review: Although the estimate for the VTE incidence rate has considerable uncertainty, it is possible that there may be a different or increased risk of thromboembolic disease with use of this CVS compared with other recently approved CHCs. However, the VTE risk should be further minimized with appropriate labeling, which can help prescribers select patients based on their low risk for VTE. The required postmarketing study will be necessary to determine whether the VTE risk with use of the CVS offers a different safety profile from that of other CHCs. At this time, labeling will reflect that the risk is likely comparable to that of other approved CHCs since the 95% CI of the CVS VTE incidence rate (6.6, 61.7) has some overlap with the 3-12 per 10,000 woman-years likelihood of developing a VTE for other CHC users.

[31] NDA 290627, Sequence 0018, submitted 4.26.2018, Response to IR, Module 1.11.4 p 10/11
[32] Email communication from Cherice Holloway CDER/OSE/OCT through Miriam Chehab OMPT/CDER/OSE/OPE/DPVII May 4, 2018

10.10.1. Expectations on Safety in the Postmarket Setting Based on the safety profile from subjects in the CVS trials, it appears that safety is expected to be similar to other approved CHC products. See Section 16.

10.11. Integrated Assessment of Safety

The safety assessment based on all submitted data (3,052 subjects with 26,794 cycles) for subjects treated with the TBM CVS and other formulations of SA and SA/EE CVSs indicates that the CVS has an acceptable safety profile. There were no new safety signals noted with the CVS which contains SA, an NME progestin. A post-marketing requirement (PMR) study to better characterize the VTE risk with use of the CVS is recommended because the submitted clinical trials are not powered for evaluation of VTE risk.

The safety findings in the TBM CVS population (primary ISS) with 2308 subjects contributing 21,590 cycles are summarized.

Subjects in the ISS were mostly Caucasian (71%), non-Hispanic (70%), nulliparous (64%), from the US (67%) with a mean age of 26.7 years and a mean BMI of 24.1 kg/m^2

No deaths occurred.

Forty-three subjects or 1.9% of the primary ISS experienced an SAE.

There were four VTEs. Two DVTs occurred in two subjects; one who had driven for 5 hours a week prior to diagnosis and the other in a subject subsequently found to be heterozygous for Factor V Leiden mutation. There was one PE in a subject with normal laboratory evaluation. Another subject experienced a cerebral venous thrombosis and had unconfirmed normal laboratory testing. All four subjects had histories of previous CHC use.

The four VTEs in the pivotal studies give a higher incidence of VTE than other contraceptive pivotal studies. However, this higher incidence is based on one additional VTE. Since the clinical trials were not powered to evaluate a relatively uncommon event (VTE), the risk estimate is imprecise. A PMR will be performed to provide a more accurate risk assessment.

VTE is a known risk of CHC use. Risk based on differences in COC formulations show VTE rates of 7.2-9.8 VTE/10,000 women-years with no statistically significant difference between types of progestin or days of use. The class labeling for VTE risk will be included in the CVS label. (b) (4)

The applicant's data on BMI and VTE risk (b) (4) Two VTEs occurred in subjects with a BMI 28-31 kg/m^2 and two VTEs occurred in subjects with a BMI 24-26 kg/m^2. Only one subject had a BMI >29 kg/m^2 at the time of VTE and

this BMI was 29.3 kg/m^2. Physiologically speaking this small difference in BMI should not increase VTE risk by tenfold.

There were four psychiatric events in four subjects with psychiatric history. There was one attempted suicide in a subject with depression. The remaining three events involved exacerbation of bipolar disorder. From a clinical perspective, the information in these events did not generate a new safety signal or trend for this CVS that required labeling that deviated from class labeling for CHCs.

Other SAEs included two subjects with drug hypersensitivity reactions (neither involved anaphylaxis), one subject with menorrhagia due to a worsening submucous fibroid, and one subject with headache, nausea, vomiting, and diarrhea.

Adverse events leading to discontinuation occurred in 275 subjects (11.9%) of the ISS. The most frequent AEs were vaginal symptoms (including discharge and infection) - 2.1%, menstrual disorders - 1.7%, mood changes - 1.4%, headache with migraine - 1.3%, nausea and vomiting - 1.2%. CVS expulsion was not considered an AE but was the reason 1.4% of subjects discontinued.

Common AEs experienced by CVS users did not show any additional safety issues that are noted in other CHCs although the incidences of many AEs were higher in CVS users. The frequency of the AEs are summarized in the table below.

Table 66. AEs Experienced by Subjects in Primary ISS

Preferred Terms	**n subjects**	**% (N=2308)**
Headache including migraine	933	40.4
Nausea/vomiting	696	30.2
Vulvovaginal mycotic infection/vaginal candidiasis	321	13.9
Abdominal pain/lower/upper	321	13.9
Dysmenorrhea	281	12.2
Vaginal Discharge	266	11.5
UTI/cystitis/pyelonephritis/genitourinary tract infection	234	10.1
Breast pain/tenderness/discomfort	220	9.5
Metrorrhagia/menstrual disorder	167	7.2
Genital pruritus	126	5.5
Mood swings/mood altered/affect lability	105	4.5
Acne	81	3.5
Libido decreased	78	3.4
Dyspareunia	77	3.3

Preferred Terms	n subjects	% (N=2308)
Vulvovaginal discomfort	74	3.2
Depression/depressed mood/major depression/depressive symptom	68	2.9
Rash/papular/genital/generalized/macular/pruritic	67	2.9
Menorrhagia/withdrawal bleed	66	2.9
Anxiety	51	2.2
Vulvovaginal dryness	47	2.0

Source: 10.4.5 ISS analysis of ARs

Comment: *AEs experienced by ≥5% of subjects will be labeled.*

At least one complete CVS expulsion was reported by 25% of subjects, however CVS expulsion was the reason for discontinuation of CVS use in only 1.4% of subjects..

Laboratory findings did not suggest any safety signals. There was no significant reduction or improvement of hemoglobin/hematocrit. There were elevations of cholesterol, HDL, LDL, triglycerides, and liver enzymes that were consistent with CHCs.

Physical examinations including vital signs did not show safety signals although findings of vaginal discharge and vaginal and vulvar erythema were noted.

There were no issues concerning pregnancy outcomes or return to fertility.

There were no differences in the safety profile of the CVS, based on TEAEs, within demographic subgroups of age, race, ethnicity, and geographic region. Safety profiles were similar between the ages of the CVS subgroups.

Specific safety studies were reviewed and did not show any new or unique concerns outside of those previously identified for CHCs.

- QT studies showed no significant QTc prolongation effect of SA
- Microbiology studies showed no increases in symptomatic bacterial vaginosis, yeast, or anaerobic gram-negative rods
- Endometrial biopsies did not find evidence of hyperplasia or malignancy
- Estrogen-dependent hepatic proteins showed the same trends as found in other CHCs
- Colposcopic evaluations did not find evidence of vaginal or cervical epithelial integrity abnormalities other than erythema in <5% of subjects

Comment: *The safety data was sufficient to conclude that the profile for this product does not appear to be significantly different from other CHCs except for the potential for a difference in VTE ris. A s previously stated, in order to better determine if this VTE ris is different from other CHC products, a large postmare ting required study will be*

necessary. The applicant understands this concern and has agreed to conduct this study using acceptable required milestones.

10.12. SUMMARY AND CONCLUSIONS

11.Conclusions and Recommendations

The review teams have concluded that the benefits of ANNOVERA for the prevention of pregnancy in females of reproductive potential outweight the risks when used according to labeling, and recommend approval. Refer to the benefit-risk section in Section 1 of this review for additional discussion.

12.Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was conducted for this application. No issues were identified during the review cycle that required expert input from an Advisory Committee.

13.Pediatrics

The applicant submitted an initial Pediatric Study Plan (iPSP) on May 13, 2015, which was reviewed by the Pediatric Review Committee (PeRC) and agreed upon by the Division. The iPSP requested a waiver for males of any pediatric age and premenarchal females and assessment of extrapolation of data from adult women to post menarchal females to age 18.

On July 18, 2018 PeRC agreed with the waiver for males and assessment from adult women to adolescent females.

14.Labeling Recommendations

14.1. Prescription Drug Labeling

The applicant's proposed Prescribing Information, submitted on April 5, 2018, was reviewed. The following significant revisions were recommended:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
Indications and Usage (Section 1)	(b) (4) BMI; (b) (4) indicating that this population has not been adequately evaluated	Applicant agreed.
Adverse Events (Section 6)	Utilize the combined pivotal trial data only to inform the label. (Do not include data from non-TBM CVS)	Applicant agreed.
Clinical Studies (Section 14)	Utilize the combined pivotal trial data to inform the PI	Applicant agreed

OPDP provided a consult containing recommendations on the prescription drug labeling. These comments were accepted by the reviewers and included in labeling to the applicant.

14.2 Carton and Container Labeling

The Division of Medication Error and Prevention has worked with the applicant on carton and container labeling. Agreement has been reached and there are no outstanding issues from the medication error perspective. Additional discussion with the applicant took place regarding labeling of the compact case used to store the CVS during the 7 days per cycle it is not in use. The applicant agreed to providing a label for the compact case containing information including

(b) (4) during a teleconference on July 25, 2018. This agreement resolved DMEPA's outstanding concern regarding labeling.

Please refer to the DMEPA consult in DARRTS dated June 8, 2018 and to supplementary memos dated June 19, 2018 and August 6, 2018.

15.Risk Evaluation and Mitigation Strategies (REMS)

DRISK, DBRUP and the applicant are in agreement that the benefit of the CVS can be adequately managed with labeling alone and that a REMS is not necessary to ensure that the product's benefit outweighs the risk.

Please see the consult from DRISK in DARRTS dated July 18, 2018.

16.Postmarketing Requirements and Commitment

It is expected that the CVS will be used chronically and that users will have a risk of thromboembolic disease. The size of the clinical trial for the CVS did not allow determination of whether this risk was different from the risks seen with other CHCs. The review team and the Division of Epidemiology agreed that this risk needed to be further characterized through a large epidemiologic study and communicated this to the applicant. The details of this study are outlined below:

1. A controlled, non-interventional, long-term cohort study that follows a series of cohorts comprising new users of your product (segesterone acetate and ethinyl estradiol vaginal system), new users of other ring contraceptives, new users of any intrauterine system, and new users of combined oral contraceptives containing other progestins. The primary objective of the study is to assess the risk for venous thromboembolism (VTE) and arterial thromboembolism (ATE) of short-term and long-term use of your product in a study population representative of actual users of the product in the United States and other countries where your vaginal system is prescribed.
    - The study should be sufficiently powered to rule out a 1.5 to 2-fold risk for VTE
    - (b) (4)

Two drug interaction studies were recommended by the Clinical Pharmacology and Clinical reviewers. These required studies are outlined below:

2. A clinical drug-drug interaction study to evaluate the effects of strong CYP3A induction and inhibition on the pharmacokinetics of SA and EE from your SA/EE contraceptive vaginal system (CVS) (See Section 6.3.1 for the rationale of this study request).
3. An (b) (4) study to evaluate the effects of tampons on the (b) (4) of SA and EE from your SA/EE CVS.

Postmarketing Commitments

The CMC review team determined that the Applicant had not fully characterized the in vivo release rate of the CVS based on residual drug collected at one time point at the end of 13 cycles. Therefore, to accurately determine the strength of the product for labeling, the "true" in vivo release rate should be calculated using data collected throughout the period of use. Under a PMC, (b) (4)

17.Appendices

17.1. Financial Disclosure

Table 67. Covered Clinical Study (Name and/or Number): 300B, 300PK, 330, 331, 323, 427, 571, 648, 300A (CCN006)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 132		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 9		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: X Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0_____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

17.2. Nonclinical Pharmacology/Toxicology

None.

17.3. OCP Appendices (Technical documents supporting OCP recommendations)

Refer to the clinical pharmacology review in DARRTS.

17.4. Additional Clinical Outcome Assessment Analyses

None.

17.5. Clinical Appendices

17.5.1. Pregnancies

Table 68. Table of Pregnancies

Protocol	Subject ID	Age	Treatment End	Conception Date	Outcome	Initial Determination per Applicant
300A on treatment pregnancies N=19						
300A	(b) (6)	26	(b) (6)	(b) (6)	Live Birth	During CVR use
300A		22			Induced Termination	During CVR use
300A		30			Induced Termination	During CVR use
300A		26			Induced Termination	During CVR use
300A		23			Spontaneous Termination	During CVR use
300A		28			Unknown	During CVR use
300A		30			Live Birth	During CVR use
300A		26			Induced Termination	During CVR use
300A		23			Spontaneous Termination	During CVR use
300A		22			Unknown	During CVR use
300A		22			Unknown	During CVR use
300A		26			Spontaneous Termination	During CVR use
300A		18			Live Birth	During CVR use
300A		30			Live Birth	During CVR use
300A		24			Spontaneous Termination	During CVR use
300A		23			Induced Termination	During CVR use

Protocol	Subject ID	Age	Treatment End	Conception Date	Outcome	Initial Determination per Applicant
300A	(b) (6)	22	(b) (6)	(b) (6)	Unknown	During CVR use
300A		23			Live Birth	1-7 days after CVR use
300A		21			Live Birth	8-14 days after CVR use
300A 8-14 days after last CVS use N=3						
300A	(b) (6)	26	(b) (6)	(b) (6)	Live Birth	8-14 days after CVR use
300A		23			Live Birth	8-14 days after CVR use
300A		23			Induced Termination	8-14 days after CVR use
300A 15+ days after last CVS use N=3						
300A	(b) (6)	31	(b) (6)	(b) (6)	Induced Termination	15+ days after CVR use
300A		29			Live Birth	15+ days after CVR use
300A		31			Induced Termination	15+ days after CVR use
300B on treatment pregnancies N=22						
300B	(b) (6)	21	(b) (6)	(b) (6)	Live Birth	During CVR use
300B		31			Spontaneous Termination	During CVR use
300B		25			Spontaneous Termination	During CVR use
300B		20			Live Birth	During CVR use
300B		21			Live Birth	During CVR use
300B		23			Live Birth	During CVR use
300B		24			Live Birth	During CVR use
300B		19			Induced Termination	During CVR use
300B		19			Live Birth	During CVR use
300B		21			Live Birth	During CVR use
300B		19			Induced Termination	During CVR use
300B		23			Spontaneous Termination	During CVR use
300B		19			Live Birth	During CVR use
300B		23			Live Birth	During CVR use
300B		25			Live Birth	During CVR use

Protocol	Subject ID	Age	Treatment End	Conception Date	Outcome	Initial Determination per Applicant
300B	(b) (6)	18	(b) (6)	(b) (6)	Induced Termination	During CVR use
300B		27			Live Birth	During CVR use
300B		38			Spontaneous Termination	During CVR use
300B		24			Live Birth	1-7 days after CVR use
300B		21			Unknown	1-7 days after CVR use
300B		29			Live Birth	1-7 days after CVR use
300B		24			Live Birth	1-7 days after CVR use
300B 8-14 days after CVS use N=2						
300B	(b) (6)	22	(b) (6)	(b) (6)	Spontaneous Termination	8-14 days after CVR use
300B		29			Induced Termination	8-14 days after CVR use
300B 15+ days after CVS use N=10						
300B	(b) (6)	27	(b) (6)	(b) (6)	Live Birth	15+ days after CVR use
300B		23			Live Birth	15+ days after CVR use
300B		33			Live Birth	15+ days after CVR use
300B		24			Live Birth	15+ days after CVR use
300B		18			Spontaneous Termination	15+ days after CVR use
300B		25			Induced Termination	15+ days after CVR use
300B		29			Induced Termination	15+ days after CVR use
300B		28			Induced Termination	15+ days after CVR use
300B		31			Ectopic	15+ days after CVR use
300B		29			Live Birth	15+ days after CVR use
Other protocol on-treatment pregnancies N=2						
300Ex	(b) (6)	21	(b) (6)	(b) (6)	Live Birth	During CVR use
300PK		29			Live Birth	During CVR use
300A Return to Fertility N=12						
300A	(b) (6)	25	(b) (6)	(b) (6)	Spontaneous Termination	Return to fertility
300A		27			Live Birth	Return to fertility

Protocol	Subject ID	Age	Treatment End	Conception Date	Outcome	Initial Determination per Applicant
300A	(b) (6)	28	(b) (6)	(b) (6)		Return to fertility
300A		24				Return to fertility
300A		21			Spontaneous Termination	Return to fertility
300A		26				Return to fertility
300A		35				Return to fertility
300A		31				Return to fertility
300A		28				Return to fertility
300A		38			Spontaneous Termination	Return to fertility
300A		24			Spontaneous Termination	Return to fertility
300A		28				Return to fertility
300B Return to Fertility N=12						
300B	(b) (6)	26	(b) (6)	(b) (6)		Return to fertility
300B		20				Return to fertility
300B		25				Return to fertility
300B		26			Spontaneous Termination	Return to fertility
300B		23				Return to fertility
300B		35				Return to fertility
300B		26				Return to fertility
300B		28				Return to fertility
300B		22			Live Birth	Return to fertility
300B		31				Return to fertility
300B		33				Return to fertility
300B		23				Return to fertility
Other protocol Return to Fertility N=1						
300PK	(b) (6)	25	(b) (6)	(b) (6)	Live Birth	Return to fertility

*subject excluded from efficacy population by applicant

17.5.2. Microbiology Sub-study

1. The diagnosis of bacterial vaginosis was determined by the Investigator utilizing the Amsel criteria. The presence of three of the following four criteria gave the diagnosis:
   - a homogenous excessive vaginal discharge
   - an alkaline vaginal pH (> 4.5)
   - a positive whiff test
   - the presence of 20% or more clue cells
   - [bacterial vaginosis was also categorized as symptomatic or asymptomatic]
2. The Investigator also determined the diagnosis of bacterial vaginosis utilizing the Nugent score. A score > 7 indicates bacterial vaginosis. The scores were categorized as:
   - Normal flora (Lactobacillus - predominant) - scores 0 to 3
   - Intermediate flora - scores 4 to 6
   - Bacterial vaginosis - scores 7 to 10

Source Microbiology Sub-study Clinical Study Report P6

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHELLE CAREY
08/09/2018

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08/09/2018