CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-187

MEDICAL REVIEW

HFD-580: DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review

NDA: 21-187 NuvaRing

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Key words: contraception, NuvaRing, etonogestrel, ethinyl estradiol, contraceptive vaginal ring

Sponsor: Organon Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Drug names:
Generic: etonogestrel and ethinyl estradiol
Trade: NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)
Chemical: etonogestrel chemical name:
(17α)-13-ethyl-17-hydroxy-11-methylene-18,19-dinorpregn-4-en-20-yn-3-one,
ethinyl estradiol chemical name:
19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol

Drug class: Progestin and estrogen (steroids)
Route of administration: Vaginal
Dosage form: Ring, one compartment, flexible
Strength: Ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol
Days 1-21 release: ~ 0.120 mg/day of etonogestrel + ~0.015 mg/day of ethinyl estradiol

Proposed indication: Hormonal contraception

Related INDs:

Related NDAs:
NDA 20-071 CTR 04 - Desogen® (desogestrel and ethinyl estradiol) Tablets - marketed product - Organon Inc.
NDA 20-301 CTR 04 - Ortho-Cept 21 and 28 (desogestrel and ethinyl estradiol) Tablets - marketed product - R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ
NDA 20-713 CTR 25 - Mircette™ (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets - marketed product - Organon Inc.

Executive Summary NDA 21-187 NuvaRing®

A. Recommendations

Approval of NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) as a vaginal combination hormonal contraceptive is recommended for prevention of pregnancy. The final printed label (FPL) should reflect the increased risk of venous thromboembolism (VTE) associated with combination hormonal contraceptives containing a so-called third-generation progestin such as desogestrel. Etonogestrel, the active progestin released from the ring, is the active metabolite of desogestrel. It is this reviewer's opinion that in addition to the class labeling for oral contraceptives, the FPL should also include some of the factual efficacy and safety data from the two large clinical trials, such as demographic information, number of subjects, cycles of exposure, pregnancies, common AEs and discontinuations due to AEs. This will help to better inform both healthcare providers and consumers about this new delivery system for combination hormonal contraception. The instructions to patients about how and when to use the ring are somewhat complicated, but well illustrated and acceptable. The FPL also addresses issues that are unique to this new delivery system, such as expulsion of the ring, prolonged use of the ring, and accidental removal.

Concerns about decreased efficacy due to interactions between the contraceptive steroids (progestin and estrogen) released by NuvaRing® and other drugs have been addressed. Other drug-drug interactions are also noted in the label. Chemistry stability of the ring in its foil sachet at room temperature has been established, but the actual serum levels of the steroids are noted to be highest (burst effect) in the first 24 hours after ring insertion, before the serum levels remain relatively constant for the next 20 days of normal ring use. It is uncertain if the burst effect may be altered by improper storage of the ring after purchase from a pharmacy where NuvaRing® is stored under refrigeration.

B. Phase 4 Studies

The vaginal administration of a single dose of 1200 mg of an oil-based miconazole nitrate increased the serum concentrations of etonogestrel and ethinyl estradiol by approximately 17% and 16% respectively. It is unknown if this change will impact the safety and efficacy of NuvaRing. Furthermore, the sponsor has no data on longer use (multiple doses) of miconazole nitrate (or any other oil-based products). Use of tampons could also impact the efficacy of NuvaRing by absorbing the contraceptive steroids released by the ring. Phase 4 commitments should be required for approval of NuvaRing: the sponsor should commit to completing further studies on the effect of commonly used oil-based vaginal drugs/products [such as miconazoles, Vaseline™, etc.] and different tampons on the PK/PD, efficacy and safety of NuvaRing.

C. Public Outreach or Information

The reviewer's primary concern is the increased risk of VTE associated with combination hormonal contraceptives containing a third-generation progestin, such as the etonogestrel in NuvaRing®. This issue is addressed in the review and the FPL.

D. Summary of Clinical Findings

Brief overview:

NuvaRing® is a new delivery system called a CCVR (combined contraceptive vaginal ring) for the prevention of pregnancy. It is a transparent, flexible one-compartment ring that releases on average per 24 hours approximately 0.120 mg of the "third-generation" progestin etonogestrel and 0.015 mg of the estrogen ethinyl estradiol once inserted in the vagina. Each ring is left in place for 21 consecutive days, removed for 7 days, and then a new ring is placed in the vagina.

This current NDA submission includes two large Phase 3 studies, 068003 and 034219, each designed to accumulate information about the contraceptive efficacy, vaginal bleeding patterns, and safety of the NuvaRing regimen in generally healthy women, age 18 to 41, who elected to use vaginal hormonal contraception for the prevention of pregnancy. Each study was a multicenter, open-label, non-comparative, 13-cycle efficacy and safety study of the CCVR. Study 068003 was conducted in 47 centers in the United States and 1 in Canada, while study 034219 was conducted in 53 centers in 11 European countries and Israel. **Since these studies were identical in design and the protocols were almost identical, the data from these two clinical studies have been analyzed separately and also pooled for a combined analysis in the NDA submission and in the medical officer's review.**

Study 68003 enrolled a total of 1,210 female subjects and treated (i.e. subject received at least one day's use of the study ring) 1,117 women for a total of 11,188 28-day cycles. Study 34219 enrolled a total of 1,182 female subjects and treated 1,145 women for a total of 12,109 cycles. The agency goal of a total of at least 10,000 evaluable cycles was easily achieved. In three smaller European metabolic studies, a total of 121 subjects were exposed to NuvaRing for 634 28-day cycles. In the local effects USA study 68004, 58 subjects were exposed to 460 cycles. The total extent of NuvaRing use in these six studies was 2,501 women treated for 24,391 cycles, comprising 1,870 woman-years of exposure.

Efficacy

The primary efficacy endpoint is in-treatment pregnancies in the sponsor's ITT evaluation group. This is in fact the all-subjects-treated (AST) group. One post-treatment pregnancy is reclassified by the medical officer as an in-treatment pregnancy. With this additional pregnancy, the Pearl Indices for the AST group increase from the sponsor's 1.75 to 1.86 for Study 68003, and from 1.18 to 1.23 for the combined studies. For the 1,920 women age 18-34 years, the Pearl Indices increase from 1.87 to 2.02 for Study 68003, and from 1.23 to 1.30 for the combined studies. The sponsor and reviewer Pearl Index for the combined 402 women age 35 to 41 years is 0.92; as expected, this result is lower compared to the younger age group because of lower fecundity (fertility) as women become older.

The medical reviewer added 4 pregnancies to the PP (per protocol) pregnancies. Therefore, the Pearl Indices for the PP subjects increase from the sponsor's 0.91 to 1.45 for Study 68003, from 0.40 to 0.53 for Study 34219, and from 0.62 to 0.92 for the combined studies. For women age 18-34 years, the Pearl Indices for the PP subjects increase from the sponsor's 0.93 to 1.61 for Study 68003, from 0.48 to 0.64 for Study 34219, and from 0.66 to 1.04 for the combined studies. The primary efficacy results [combined and by individual study; overall and by subsets for age and per protocol use] are within an acceptable range compared to other approved combination hormonal contraceptives. Use as directed (per protocol analysis) results in a range of 0.4 to 1.6 pregnancies per 100 women per year.

In spite of identical study designs and protocols, the compliance, efficacy, and cycle control results from the European Study 34219 were clearly better than the US Study 68003. The demographic categories noted in the first 6 rows in the table below probably reflect normal differences between the 12 European/ Israel countries versus the US/Canada. It is difficult to know whether these differences would influence compliance, discontinuation rates, and efficacy. Furthermore, it is difficult to know if the better European efficacy results (less pregnancies and better cycle control) are clinically significant. Some of the demographic and outcome differences are shown in the reviewer's table below:

DIFFERENCES Category	US Study 68003 N= 1177 treated	EURO Study 34219 N= 1145 treated	Comment
Caucasian subjects	88.7%	98.6%	
Black subjects	9.5%	0.5%	
Never pregnant	32.5%	46.4%	
Baseline body mass index	23.4	22.3	
Switch from OC use	41%	62%	
Switch from condom, foam	47%	21%	
Compliant cycles	79%	91%	
Discontinued study (13 cycles)	41%	30%	482 vs. 339
% Subjects per cycle with Breakthrough bleeding/spotting	7.2 to 11.7%	2.6 to 6.4%	No overlap between 2 studies
% Subjects per cycle with Absence of withdrawal bleeding (= amenorrhea)	2.3 to 3.8%	0.6 to 2.1%	No overlap between 2 studies
% with clinically significant (>7% change) ↑ in weight at EOT	18.1%	10.2%	US subjects were heavier at baseline
Pregnancies during study	16	6	
Overall Pearl Index (AST group)	1.86	0.65	Combined is 1.23

For cycle control claims, the sponsor's primary analysis centered on per cycle data rather than cumulative data per subject [called reference period analysis]. Furthermore, the sponsor wanted to include in the FPL comparative data from the 3 small, open-label studies that used an oral contraceptive containing 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol [total NuvaRing N= 135; OCs N= 129]. These studies were not designed to show superiority for cycle control and therefore cannot be used to make such claims. Daily recordings of vaginal bleeding were made for each of the 2,322 women who were treated from 1 to 13 cycles in the two large clinical trials. So the sponsor has ample data from which to make non-comparative statements about expected menstrual bleeding (cycle control) and what women should expect in terms of abnormal bleeding (breakthrough bleeding/spotting, amenorrhea, early withdrawal bleeding, and prolonged bleeding) while using NuvaRing for contraception.

Safety

With 2,501 women exposed to at least one day of NuvaRing use and 1,501 exposed to 13 cycles of NuvaRing use, there is a solid database of safety information. Subjects were seen at 3-month intervals during the two major 13-cycle trials. The 3 small European Metabolic Studies evaluated AEs and changes in lipid metabolism (N= 44), coagulation and fibrinolysis (N= 47), and carbohydrate, adrenal, and thyroid metabolism (N= 44). An additional US Local Effects Study 68004 evaluated colposcopic and vaginal microbiology findings, and cervical/ vaginal cytology in 58 subjects over 13 cycles: Cycle 3, 6, 9, and 13 assessments were completed by 48, 44, 43, and 41 subjects, respectively. Most of 2,586 women using NuvaRing were 18-35 year-old Caucasians in good health. A total of 1,870 woman years of exposure to NuvaRing® was accumulated by subjects in the six combined studies.

The single death reported was for a subject who died in a car accident. Of the 49 subjects (48 NuvaRing®, 1 LNG/EE OC) with serious adverse events (SAEs) reported during the in-treatment period (extended to 30 days after last ring use), 10 subjects had SAEs that were considered by the investigator or Organon to be possibly, probably, or definitely drug-related. One of these subjects, a 26-year-old non-smoker, had a deep venous thrombosis during her first cycle of NuvaRing use. Her VTE was diagnosed by venogram, treated in the hospital with anticoagulation, and she continued with oral anticoagulants at home for 3 ½ months. Special coagulation lab tests after discontinuation of anticoagulants were negative.

Of NuvaRing®-treated subjects, approximately 15% discontinued due to an AE, primarily due to ring specific-AEs related to device problems and vaginal discomfort. The most frequent system-organ class AEs (reported by ≥ 1% of subjects) leading to discontinuation included specifically: device related problems (2.5%), vaginal symptoms [discomfort, vaginitis, leukorrhea] (2.2%), headache (1.3%), emotional lability (1.2%), and weight increase (1.0%). The most commonly reported AEs in the AST group (≥5% in the trials, N= 2,501) were vaginitis (14.1%), headache (9.8%), upper respiratory tract infection (8.0%), leukorrhea (5.8%), sinusitis (5.7%), and nausea (5.2%). There did not appear to be an increased incidence of these common AEs with long-term NuvaRing use, and there were no clinically meaningful differences in the incidence of these AEs that could be attributed to differences in demographic characteristics, age, body mass index, race, and starter/switcher status.

Few subjects in either group had clinically significant abnormal values for hemoglobin, hematocrit, leukocyte count, and platelet count. Most of the clinically significant abnormal hematology values reported were for changes in leukocyte differential count parameters, but these changes were not considered to be clinically relevant. In the 3 small metabolic studies, notable downward shifts in hematocrit and hemoglobin were most commonly observed for the NuvaRing® group, but these shifts were not commonly seen in the 13-cycle large clinical studies. Few subjects had clinically significant abnormal blood chemistry values. In the combined studies, the most frequently occurring notable shifts in blood chemistry parameters were upward shifts in ALAT and ASAT, and downward shifts in total bilirubin. For all other parameters the incidence of notable shifts in blood chemistry values was very low.

The majority of subjects in all studies had no major changes in blood pressure during the studies compared to the screening assessment. An increase or decrease ≥ 7% from the baseline weight was considered to be clinically significant: such decreases in body weight were observed in 195 (9.3%) subjects, while increases in body weight were observed in 295 (14.1%) subjects. The incidence of clinically significant increases in body weight was higher in Study 068003 compared with Study 34219 (18.1% vs. 10.2%), while the incidence of decreases in body weight was comparable between the two studies (10.3% and 8.4%). The majority of subjects who received NuvaRing had no breast nodularity at screening and last assessment. The most significant shift to a higher category was for three subjects with no breast nodularity at screening and "+++" nodularity at last assessment.

The majority of subjects who received NuvaRing had normal pelvic examinations at screening and last visit. The most frequent shifts to abnormal occurred in the vagina and were mainly related to vaginitis. The majority of NuvaRing®-treated subjects had cervical Pap class I at screening and last assessment. Clinically relevant shifts of note occurred for a total of 8 subjects (all in the two large studies) with a normal Pap result at screening (Pap I, IIa or IIb) and a Pap class IIIb-IV (high grade SIL) at last assessment. At first impression this looks serious, but this represents only 0.30% of the 2,322 women in the two combined trials. This low percentage is acceptable in a population of sexually active women age 18-41.

In Study 34220, ten parameters of lipid metabolism were assessed during 6 cycles of NuvaRing® use in a comparative open-label study. NuvaRing® had generally favorable effects on HDL- and LDL-cholesterol relative to the comparator LNG/EE oral contraceptive (OC). The sponsor's analysis, however, focused exclusively on changes relative to the comparator and not relative to baseline values of each drug. This study was not blinded (a double-dummy design could have been easily used), was not designed to show superiority, and had only one OC comparative arm when additional arms may have shown very different results. The statistical and clinical significance of the results can also be questioned. It is this reviewer's opinion that the sponsor's conclusions are of limited value, of uncertain clinical significance, and should not be included in the FPL.

In Study 34221, the effects on hemostasis parameters [procoagulation, anticoagulation, profibrinolysis, antifibrinolysis, and fibrin turnover] seen in the NuvaRing® group were similar to the effects seen in the LNG/EE OC group, except for the relative higher increases of the procoagulation parameter Factor VII and the anticoagulation parameter Protein C, and the relatively less decrease of the profibrinolysis parameter activator t-PA

in the NuvaRing® group. The sponsor's analysis here is again comparative; more important, there were no major changes of concern in these hemostasis parameters seen in either group.

In Study 34222, the effects on carbohydrate metabolism and adrenal and thyroid function were assessed over 6 cycles. The measured parameters included:

- Carbohydrate metabolism: glucose (fasting), insulin (fasting), glucose tolerance test, glucose (AUC), insulin (AUC), glycosylated hemoglobin (HbA1c)
- Adrenal function: total cortisol, dehydroepiandrosterone sulphate (DHEAS)
- Thyroid function: TSH, T4

The effects on the carbohydrate metabolism parameters seen in the NuvaRing® group were not statistically different from the effects seen in the LNG/EE OC group. Of the adrenal function parameters, total cortisol was significantly less increased in NuvaRing® group as compared to the LNG/EE OC group. No significant treatment differences were observed for DHEAS. Of the thyroid function parameters, TSH level showed a significantly higher relative increase in NuvaRing® group at the Cycle 3 assessment, but not at the Cycle 6 assessment. In both treatment groups, the level of free thyroxine remained more or less unchanged compared to baseline.

Local Effects Study 68004 submitted interim data (cut-off date of 4/1/99; all subjects completed at least 6 cycles; expected completion 11/99).The data showed that NuvaRing® causes few abnormalities in cervical and vaginal tissue and has little effect on normal vaginal flora as assessed by cytology (Pap smears), colposcopy, and micro-biology [cultures were not obtained, but Gram stain interpretation using the widely accepted Nugent score was used].

Pregnancy outcome data showed: 2 unknown, 8 terminations, and 12 continuations. Outcome data from only three pregnancies is stated, and all 3 resulted in live births of healthy newborns. Although no human data is available regarding lactation, in animal studies only very small amounts of orally administered ENG and/or its metabolites were excreted in the milk of lactating rats.

The standard warnings and precautions for combination hormonal contraceptives should be followed in the FPL, with special attention to the fact that this will be the first vaginal delivery system marketed in the world for pregnancy prevention. Therefore, the FPL needs to state that it is unknown whether NuvaRing® is distinct for many of the specific listed parameters. Special information is included concerning the increased risk of venous thromboembolism (VTE or DVT) with third generation hormonal contraceptives.

Dosing

The dose and regimen have been adequately studied. The primary unresolved issues are 1) the clinical significance of the 17% and 16% respective increase in serum etonogestrel (ENG) and ethinyl estradiol (EE) levels seen following the single dose administration of an oil-based miconazole nitrate, 2) effect of tampon use on serum levels of ENG and EE, and 3) the factors that may influence the "burst" effect [high ENG and EE levels] during the first 24 hours after ring insertion. These will be addressed by a Phase 4 commitment. It is of note that there is limited data in Black and Asian women as these racial groups comprised only 4.9% and 0.7%, respectively, of the 2,322 women in the combined two large clinical trials.

Special Populations

No studies were carried out in special populations. The 2,501 women enrolled in the 6 studies were generally healthy, ages 18-41, and Caucasian (93.6%). Post-marketing data will be needed for any meaningful conclusions concerning special populations, women under age 18, and non-Caucasian ethnic groups.

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LIST OF NDA 21,187 ABBREVIATIONS/ACRONYMS

AE	adverse event
ACOG	American College of Obstetrics and Gynecology
AST	All-Subjects-Treated
BMI	body mass index
CCVR	combined contraceptive vaginal ring
CDER	Center for Drug Evaluation and Research
CI	Confidence Interval
COC	combined oral contraceptive [estrogen + progestin]
CRFT	case report form tabulation
CVR	contraceptive vaginal ring
DMEDP	Division of Metabolic and Endocrine Drug Products
DRUDP	Division of Reproductive/Urology Drug Products
DSG	desogestrel
DVT	deep vein thrombophlebitis
EC	emergency contraception
EDC*	estimated date of conception*
EE	ethinyl estradiol
ENG	Etonogestrel
EURO	European [refers to study 34219]
FDA	Food and Drug Administration
FPL	Final Printed Label
HIV	Human immunodeficiency virus
IND	Investigational New Drug
IRB	Institutional review board
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intent-to-treat
LMP	Last menstrual period
MO	medical officer
MOR	medical officer review
NDA	New Drug Application
NME	New molecular entity
Ob/Gyn	Obstetrics and gynecology
OCs	oral contraceptives
PP	Per Protocol
SAE	serious adverse event
STDs	sexually transmitted diseases
US	United States
VTE	venous thromboembolism
VVC	vulvovaginal candidiasis

1.0 INTRODUCTION

Since 1970, a series of studies have been conducted with contraceptive vaginal rings (CVR) releasing various progestins (norethisterone, norgestrel, chlormadinone acetate). Because of irregular bleeding with the progestin-only containing CVR, combined contraceptive vaginal rings (CCVRs) containing progestins and estrogens were developed. The three main advantages of the vaginal ring compared to oral contraceptives are the more constant steroid levels built up in comparison with oral formulations, the avoidance of the hepatic first-pass effects, and the potential for better patient compliance.

Organon Inc. has developed a transparent, flexible, colorless to almost colorless, one-compartment ring with an outer diameter of 54 mm and a cross-sectional diameter of 4.0 mm. This combined contraceptive vaginal ring, also known as NuvaRing®, has a declared daily in vitro release rate of 0.120 mg etonogestrel (ENG) and 0.015 mg ethinyl estradiol (EE). Each ring is to be used for one cycle; a cycle consists of three weeks with the ring in place and a one-week ring-free period.

The clinical program for NuvaRing® was designed and performed in accordance with the relevant FDA guidelines for oral hormonal contraceptive formulations. This provided the basis for the total number of cycles of exposure, the number of subjects exposed for at least 13 cycles, as well as monitoring of major clinical endpoints (pregnancy, bleeding patterns). Given the nature of the indication (contraception), placebo controlled efficacy trials were precluded. In addition, since no other CCVRs were available, limited comparative studies were performed with an oral contraceptive (OC) as comparator in three non-USA special metabolic and coagulation studies.

Exposure to first or second generation oral contraceptives containing the synthetic progestin levonorgestrel or norethindrone has been associated with androgen-dependent clinical and metabolic adverse effects. Oral contraceptives containing androgenic progestins induce changes in lipid/lipoprotein patterns that are considered undesirable in view of the epidemiological association of such changes with increased risk of coronary artery disease. In addition, androgenic progestins have been associated with adverse effects in users, such as weight gain and acne. Third generation OCs containing the newer progestins, desogestrel (DSG) or gestodene or norgestimate, were developed to obtain a higher ratio between the desired progestational effects and the undesired androgenic effects. The active metabolite of desogestrel (MW ~310) is etonogestrel (MW ~324), which is the progestin contained in NuvaRing.

This current NDA submission includes two large Phase 3 studies, 068003 and 034219, each designed to accumulate information about the contraceptive efficacy, vaginal bleeding patterns, and safety of the NuvaRing regimen in women who elected to use vaginal hormonal contraception for the prevention of pregnancy. Each study was a multicenter, open-label, non-comparative, efficacy and safety study of the CCVR. Study 068003 was conducted in 47 centers in the United States and 1 in Canada, while study 034219 was conducted in 53 centers in 11 European countries and Israel. **Since these studies were identical in design and the protocols were almost identical, the data from these two clinical studies have been analyzed separately and also pooled for a combined analysis in the NDA submission and in this review.**

> **Reviewer comment: where there are notable differences in the two major clinical trials, comments will be made throughout this review. In general, however, the combined (pooled) data was acceptable.**

2.0 BACKGROUND

OCs are divided into three generations:

1. First generation: high dose OCs with greater than 50 mcg estrogens were developed first in the 1960s (Enovid in 1960 contained 150 mcg mestranol and 9.85 mg norethynodrel).
2. Second generation: in the1970s, the dose-response relationship between adverse events and the amount of steroids in the pill was appreciated and "low dose" OCs with the progestins norethindrone or levonorgestrel (LNG) + 30-50 mcg of estrogens were developed.
3. Third generation: in the 1980s, the androgenic metabolic effects especially in terms of cardiovascular disease were recognized and low dose estrogen OCs with new progesterone components (gestodene, desogestrel, or norgestimate) were introduced. *The terms "third generation" progestin and "third generation" OCs derives from the fact that they appeared on the market at roughly the same time rather than from any pharmacological resemblance.*

The progestin component of NuvaRing is etonogestrel, a third generation progestin. Etonogestrel is the active metabolite of desogestrel (used in the OC formulations) and has a molecular weight 4.5% higher than desogestrel. Based on animal and human studies, etonogestrel has high progestational activity, no estrogenic activity and only weak androgenic activity, making it less likely than some other progestins to cause unfavorable effects on lipids. Organon Inc. in Oss, the Netherlands, discovered desogestrel and its active metabolite etonogestrel in the early 1970's. Organon Inc. first began clinical development of a monophasic OC containing 150 mcg DSG in combination with 30 mcg EE (CTR 04) in Europe. In 1981, West Germany was the first country to approve CTR 04 for the market (under the trade name of Marvelon®). Since early 1993, CTR 04 has been marketed in the United States as Desogen® by Organon Inc. and as Ortho-Cept® by Ortho Pharmaceutical Corporation. Currently on the USA market, there are two OC formulations (CTR 04 and CTR 25) and three brand name OCs (Desogen, Ortho-Cept, and Mircette) containing desogestrel. Outside the USA market, there are currently five desogestrel-containing OC formulations approved for marketing (see Table #1 on next page).

APPEARS THIS WAY
ON ORIGINAL

Table # 1-Formulation of Desogestrel (DSG)-containing OCs and Etonogestrel (ENG)-containing vaginal contraceptive ring

Brand name (code)	**Approved**	**days 1-21**	**days 22-23**	**days 24-28**
Marvelon (CTR 04) (21 and 28 day)	Outside USA **1981**	DSG 150/EE 30	Marvelon 28-placebo; Marvelon 21-no placebo	
Desogen (CTR 04) **Ortho-Cept**	**12/10/92** **12/14/92** **USA**	DSG 150/EE 30	placebo	
Mircette (CTR 25)	**4/22/98** **USA**	DSG 150/EE 20	placebo	EE 10
NuvaRing	**NDA 21,187**	**ENG 120/EE 15**	**Vaginal ring removed**	
Gracial (22 day)	Outside USA	DSG 25/EE 40 (D#1-7) DSG 125/EE30 (D#8-22)	no placebo (D#23-28)	
Mercilon (21 & 28 day)	Outside USA	DSG 150/EE 20	Mercilon 28-placebo; Mercilon 21-no placebo	
Ovidol (22 day)	Outside USA	EE 5 (D#1-7) DSG 125/EE 50 (D#8-22)	no placebo (D#23-28)	

Reviewer comment:

- **The development plan for the NuvaRing product is unclear. The NuvaRing formulation achieves a lower EE dose than the 30 mcg in Desogen. The desired advantage is a lower cardiovascular risk while maintaining efficacy and cycle control. The NuvaRing formulation results in a lower total cycle dose of ENG compared to the DSG in Desogen and Mircette (see Table # 2). The daily serum levels of EE resulting from the NuvaRing formulation are <u>probably</u> comparable to the serum levels achieved with an OCs containing ~20 mcg ethinyl estradiol. The sponsor performed limited PK/PD biopharmacology studies and further details are available in the Biopharmacology Review for this NDA.**

Exact comparisons cannot be made here because of several factors:

- **all OCs have daily serum peak levels, while NuvaRing's C_{max} level occur once a cycle**
- **vaginal bioavailability and oral bioavailability are not similar for DSG, ENG, and EE**
- **limited dose-ranging data is available**
- **a "burst" phenomenon is noted in the first 24 hours after ring insertion, followed by a very gradual decline in the daily serum levels**

Medical officer Table # 2 shows the total amount of DSG (or ENG) and EE administered during one 21-day cycle of the following combination hormonal contraceptive products. The NuvaRing data shows the total amounts presumed to be released during 21 days of ring use.

Table # 2-Total Cycle DSG and EE Content of DSG-Containing OCs and NuvaRing

Brand name	Total Cycle Dose DSG (in descending order)	Total Cycle Dose EE
Desogen®/Marvelon®/Ortho-Cept®	3150 mcg	630 mcg
Mircette®	3150 mcg	470 mcg
Mercilon	3150 mcg	420 mcg
NuvaRing	**~2520 mcg (ENG)**	**~420 mcg**
Gracial	2050 mcg	730 mcg
Ovidol	1875 mcg	785 mcg

Increased risk of venous thromboembolism (VTE):

Late in 1995, epidemiology reports were published linking combined oral contraceptives (COCs) containing desogestrel and gestodene with venous thromboembolism (VTE). VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). The WHO Study[1] (21 centers in 17 countries) matched controls to cases within 5-year age bands. This study found an Odds Ratio (OR) of 2.4 (CI 1.3-4.6) or a 2.4:1 increase in VTEs in COC users containing third generation progestins compared to first or second-generation progestins. The Transnational Study[2] used a protocol similar to that of the WHO study, but was specifically designed to compare the cardiovascular risks of combined OCs containing different progestagens (progestins) matched within 5-year age bands. The Transnational Study reported an OR of 1.5 (CI 1.1-2.2) or a 1.5:1 increase in VTEs when comparing DSG to LNG users. The Boston Collaborative Study[3] investigated the risks of cardiovascular death and nonfatal VTE among women who used different OCs through the General Practice Research Data Base of over 4 million people in the UK. Here the adjusted matched relative risk from a nested case-control analysis was 2.2 (CI 1.1-4.4) or a 2.2:1 increase in VTE when comparing DSG to LNG users.

The table below summarizes the odds ratio for VTE risk comparing OCs containing either desogestrel or levonorgestrel (a second generation progestin):

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[1] World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, effects of different progestagens in low estrogen OCs on venous thrombolic disease. *Lancet* 1995; 346: p. 1582-88.
[2] Spitzer WO et al., Third generation oral contraceptives and risk of thromboembolic disorders: an international case-control study. *BMJ* 1996; 312: p. 83-88.
[3] Jick H et al., Risk of idiopathic cardiovascular death and non-fatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995; 346: p. 1589-93.

Table # 3-VTE and OCs: Study Descriptions and Main Results[4]

Study	WHO[1]	Transnational[2]	Boston Collaborative[3]
Design	Case-Control	Case-control	Cohort
No. of centers	21 in 17 countries	10 in Germany and UK	370 general practices in UK
Cases/controls (n)	1143/2998	471/1772	75/300*
Odds Ratio (95% CI) DSG vs. LNG	2.4 (1.3-4.6)	1.5 (1.1-2.2)**	2.2 (1.1-4.4)

*nested case-control subgroup analysis
**compared with OCs containing all progestins other than DSG or GSD

On October 18, 1995, in response to the unpublished WHO, Transnational, and Boston Collaborative Drug Surveillance Program studies, **the United Kingdom (UK) Committee on Safety of Medicines (CSM) issued a warning advisory concerning OCs that contained DSG and GSD to all UK physicians:**

> For LNG-, norethisterone-[norethindrone], or ethynodiol-containing products "the excess risk of thromboembolism in users is around 5 to 10 cases per 100,000 women per annum" and "OCs containing DSG and GSD are associated with around a two-fold increase in the risk of thromboembolism compared with those containing other progestagens." "Women taking OCs that include DSG or GSD should be strongly urged to complete their current cycle and then discontinue the product." OCs that include DSG or GSD "should only be used by women who are: intolerant of other combined OCs and prepared to accept an increased risk of thromboembolism."

Some physicians interpreted this warning to mean that OCs containing DSG or GSD should not be prescribed, while others did not prescribe them as first line choices for women with no prior use of OCs, except occasionally to women with severe acne.

Additional Regulatory Agencies communications regarding OCs and nonfatal VTE soon followed:

- European Union's Committee for Proprietary Medicinal Products (CPMP)-Position Statement & CPMP Ad Hoc Expert Working Group Statement: (Oct. 27, 1995) "In view of its benefit/risk re-assessment, the CPMP did not consider it appropriate to withdraw combined OCs containing GSD or DSG." "[T]o date, there is no evidence to draw conclusions that the cardiovascular mortality is different for DSG- or GSD-containing combined OCs compared to LNG-containing combined OCs." Concerning the somewhat greater risk of VTE for DSG- or GSD-containing OCs compared to LNG-OCs it was stated: "there is no plausible biological explanation for the differences." "[T]he risk of VTE with all combined OCs is still substantially less than the risk of VTE in pregnancy."

- German Federal Institute for Drugs and Medical Devices (BfArM)-Press Release: (Nov. 6, 1995) "[C]ontraceptives with DSG and GSD cannot be prescribed to women under 30 years of age and using the pill for the first time." "For women who are happy with this pill and would like to continue with it, BfArM does not see any reason for them to change."

[4] Ory H, Epidemiology of Venous Thromboembolic Disease and OC Use. *Dialogues in Contraception* Fall 1996; Vol. 5, No. 1, p. 4.

- FDA-Talk Paper: (Nov. 14, 1995) "FDA has concluded from its review of three recent unpublished studies that the risk is not great enough to justify switching to other products." " FDA will work with the manufacturers to update this information in the product's labeling. The agency, however, does not recommend that women using the DSG containing products stop using them or change to another OC."

Of 16 regulatory decisions reviewed by Dr. Michael Lewis, 3 agencies (in UK, Germany, and Norway) restricted the use of third-generation oral contraceptives, 6 issued warnings, and 7 (including the European agency) took no action.[5] With their publications, it was apparent that the above 3 studies with their subsequent publications showed the incidence of venous thromboembolism among women who used third generation OCs to be higher than that among women who used second-generation products. Subsequently, the interpretation of the results of the 3 studies has been criticized primarily for bias and confounding factors [causal relationship vs. selection bias].[6]

In November 1997, The World Health Organization convened a meeting of scientific experts to consider the safety of the new progestins. They concluded that, "COC preparations containing desogestrel and gestodene probably carry a small risk of venous thromboembolism beyond that attributable to COC containing levonorgestrel. There are insufficient data to draw conclusions with regard to COC containing norgestimate." In addition, the group concluded, "The suggestion that gestodene- or desogestrel-containing low dose COC may carry a lower risk of myocardial infarction compared with low dose formulations containing levonorgestrel remains to be substantiated."[7] On December 19, 1997, the German ban was lifted.

In February 1999, Burnhill assessed the risk of thromboembolic events in 2,265,087 woman-years of OCs use in a group of Planned Parenthood Federation of America patients and found a statistically significant increase in the relative risk of pulmonary emboli in desogestrel users compared to norgestimate or norethindrone OC users.[8] In July 1999, Herings reported new use of third generation oral contraceptives was associated with a four-fold increased risk of VTE compared with users of second generation oral contraceptives, particularly among young, healthy women.[9] He had examined data from the [redacted] system, which included information of hospital admissions and drug-dispensing for all 450,000 residents of eight Dutch cities, to identify exclusive use of second or third generation oral contraceptives among new users. Bloemenkamp offered the biological explanation for the differences to be an interaction between types of oral contraceptives and an unidentified susceptibility factor that might be a prothrombotic mutation, such as factor V Leiden mutation.[10] In September 1999, Mellemkjaer reported a 16% increase in admission rates for VTE in a population study from Denmark that correlated with the increase in prescription of third generation contraceptives.[11] In June 2000, Parkin reported that in a national New Zealand case-control study of fatal pulmonary embolism in women of childbearing age, current users of OCs had a relative risk of 9.6; the relative risk was 5.1 for levonorgestrel OCs, and 14.9 for desogestrel or gestodene OCs.[12]

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[5] Lewis M, The epidemiology of oral contraceptive use: A critical review of the studies on oral contraceptives and the health of young women. *Am J Obstet Gynecol* Oct. 1998: Vol. 179, No. 4, p.1096-97.

[6] Lidegaard O and Milson I, Oral contraceptives and Thrombotic Diseases: Impact of new epidemiological studies. *Contraception* 1996; 53: p. 135-39.

[7] WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception, Report of a WHO scientific group. *WHO Tech Rep Ser* 1998; No. 877.

[8] Burnhill MS, The use of a large-scale surveillance system in Planned Parenthood Federation of America clinics to monitor cardiovascular events in users of combination oral contraceptives. *Int J Fertil Womens Med* 1999 Jan-Feb; 44 (1): p. 19-30.

[9] Herings R et al., Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999; 354: p. 127-28.

[10] Bloemenkamp K et al., Venous thromboembolism and oral contraceptives. (Letter), *Lancet* 1999; 354: p. 1469.

[11] Mellemkjaer L et al., Admission for and mortality from primary venous thromboembolism in women of fertile age in Denmark, 1977-95. *BJM* 1999; 319: p. 820-21.

[12] Parkin L et al., Oral contraceptives and fatal pulmonary embolism. *Lancet* 2000; 355: p. 2133-34.

Although there has been controversy and discussion about the third generation oral contraceptives, the authors of three of the four studies listed in the above table stand by their original conclusions. The four studies give a consistent picture: women using third generation OCs containing desogestrel or gestodene have about twice the risk of venous thromboembolism of women using OCs containing levonorgestrel.

2.1 Regulatory history

CTR 04 (Desogen and Ortho-Cept in USA, Marvelon outside USA)
This monophasic formulation contains 150 mcg desogestrel and 30 mcg ethinyl estradiol in a 21-day regimen. Organon Inc submitted it on 12/15/88 as [redacted] The NDA 20-071 for CTR-04 (Desogen) was submitted by Organon Inc. on 12/31/90 and was approved on 12/10/92. The Pearl index was 1.14, which was felt to be somewhat high but acceptable. Headaches and dysmenorrhea were more frequent than in other OC studies, but this was felt to be the result of ascertainment bias. On 10/8/92, Organon Inc. granted authorization for the agency to refer to the then pending NDA 20-071 for Desogen on behalf of The R.W. Johnson Pharmaceutical Research Institute. The NDA 20-301 for CTR-04 (Ortho-Cept) was submitted by The R.W. Johnson Pharmaceutical Research Institute on 10/8/92 and was approved on 12/14/92.

CTR 25 (Mircette)
This atypical biphasic formulation contains 150 mcg desogestrel and 20 mcg ethinyl estradiol for days 1-21, placebo for days 22-23, and 10 mcg ethinyl estradiol for days 24-28. Organon Inc. submitted CTR 25 as [redacted] on 8/26/93. NDA 20-713 for CTR 25 was submitted by Organon Inc. on 4/30/97 and approved on 04/22/98. The NDA included an open label non-comparative study of 1226 women at 33 sites in the U.S. for up to 18 cycles, with 327 women completing 13 cycles. The endpoints were efficacy, bleeding, and safety. The Pearl Index for this product using all 14,050 cycles of exposure was 1.11 pregnancies per 100 woman-years. The life table rate for the first 13 cycles of use was also 1.11. The pattern of AE was consistent with that seen with other OCs and did not raise safety concerns. No VTE's were noted in the clinical trial data submitted with the NDA.

The NDA included seven sub-studies that evaluated lipid profiles, endocrine effects, endometrial histology, carbohydrate metabolism, steady state pharmacokinetics, hemostasis/ fibrinolysis, and ophthalmic conditions.

The sponsor agreed to comply with a Phase 4 commitment noted in the NDA approval letter "to perform a clinical study to assess the risk of endometrial hyperplasia in women after one year of therapy," and to submit the study results by 4/22/01. Organon submitted a draft proposal of this Phase 4 study, Protocol 086007, on May 12, 1999. This submission (N-038) included plans to enroll 80 subjects in order to achieve 40 women completing the trial by February 2001.

NuvaRing (CCVR) (etonogestrel and ethinyl estradiol)

Pre-IND discussions were held with the agency on May 15 and July 18, 1991. In 1991 a Phase III efficacy study began in Europe with an [redacted] However, these studies had to be discontinued due to problems with the release of the two hormones and the type of ring used. Organon then decided in 1993 to concentrate on the development of an alternative design composed of EVA only and used for one cycle per ring.
Our Division File shows that on 7/1/97 we completed a biometrics review of the USA phase 3 protocol. In 10/97 the medical officer had concerns about excluding subjects with a BM index ≤ 18 and ≥ 29. On 9/21/98, Organon informed the agency of a larger than anticipated number of pregnancies reported for the US study 68003 as compared to the non-US study 34219. According to the sponsor, a follow-up teleconference was held on 12/2/98, and they were informed that until after the NDA was submitted, it would be premature to discuss the issue. It was concluded that a Pearl Index above 2 would require an explanation, but should not be a barrier to approval.

Reviewer comment:
Our division file notes a 11/30/98 meeting with the sponsor to discuss some preliminary trial issues: no meeting minutes are available from our Division files or from the NDA, but the following are topics that were listed for discussion with the sponsor on 11/30/98:

- **The higher pregnancy rates in the US trial compared to the European trial**
- **Sponsor should clarify the rationale and objectives of their proposed second PK/PD study**
- **An ex-vivo analysis of used rings will be performed on failure rings if possible**
- **Revised definition for post-treatment pregnancies based on data obtained in the European study**
- **Development of a regimen compliance aid for product marketing**

Further review of the sponsor's registration history and the division file confirms a Pre-NDA CMC meeting was held with the sponsor on 7/7/99. There is no record of a Pre-NDA clinical meeting. On 11/1/99, OPDRA has no objections to the proposed proprietary name "NuvaRing."

2.2 Preclinical studies
Please see pharmtoxicology review.

2.3 Human pharmacology studies
Please see clinical pharmacology and biopharmaceutics review.

2.4 International and US marketing experience
CTR-04 (monophasic 150 mcg DSG/30 mcg EE) was first approved on February 10, 1981, in Germany as Marvelon®. It has been approved in a total of 103 countries. In the United States, CTR-04 is marketed as Desogen® by Organon Inc. and as Ortho-Cept® by Ortho Pharmaceutical Corporation.

Ovidol (5 mcg EE on days 1-7 and 125 mcg DSG/50 mcg EE on days 8-22) was first approved in Germany on February 10, 1981. It has been approved in a total of 5 European countries.

Mercilon (monophasic 150 mcg DSG/20 mcg EE) was first approved in Great Britain in 1986. It has been approved in a total of 54 countries.

Gracial (biphasic 25 mcg DSG /40mcg EE on days 1-7 and 125 mcg DSG/30 mcg EE on days 8-22) was first approved in Belgium in 1988. It has been approved in a total of 21 countries.

CTR-25 (biphasic 150 mcg DSG/20 mcg EE on days 1-21, placebo on days 22-23, and 10 mcg EE on days 24-28) has been approved only in the United States in January 1998 as Mircette™.

NuvaRing® is not approved in any country and therefore not marketed in any country.

3.0 NDA CLINICAL SECTION

3.1 Summary of trials- Table # 4 below, tabulated by the MO:

Table # 4- All the Major Studies incorporated into this NDA submission.

Study #	# Sites Location	1° Objective (2° objective)	Study design	# subjects cycles (women-yr)	Age range (Mean)	Medical Officer Comments
068003	48 USA- 47 Canada- 1	**Efficacy/Safety** (Cycle control)	**Open-label** **Non-comparative** **Multicenter**	N= 1,117 11,188 (858)	18-41 (28.1)	Phase III Vol. 109-20
34219	53 in 11 Euro countries + Israel	**Efficacy/Safety** (Cycle control)	**Open-label** **Non-comparative** **Multicenter**	N= 1,145 12,109 (928)	18-41 (28.2)	Phase III Vol. 121-30
34220	3 Finland	**Lipid metabolism** (Safety; control)	Open-label Group comparative 1:1 Ring or OC	N= 44- Ring N= 45- OCs 6 cycle/patient	19-39 18-35 (25)	69 completed Vol. 83-7
34221	1 Iceland	**Coagulation and Fibrinolysis** (Safety; control)	Open-label Group comparative	47- Ring 43- OCs 6 cycle/patient	19-35 18-33 (24)	65 completed Vol. 88-91
34222	3 UK and Holland	**Carbohydrate, adrenal/thyroid** (Safety; control)	Open-label Group comparative	44- Ring 41- OCs 6 cycle/patient	18-39 18-40 (27)	69 completed Vol. 92-96
68004	2 USA	**Local effects and efficacy** (Safety; control)	Open-label Non comparative	N= 58 44 at ≥ 6 mo 14 at ≥ 9 mo	21-40 (30)	13 cycle study; **Interim report 4/1/99** Vol.131+
85012	1 Finland	Dose-finding	Open-label Comparative (3 arms crossover)	11 1 cycle/arm	20-36 (24.4)	**1985-86 study** Vol. 135
86016	1 Finland	Dose-finding	Open-label Comparative	12- Ring 12- OCs 1 cycle/patient	24-38 (30)	**1986 study** Vol. 135
34218	1 Utrecht, Holland	PK/PD Bioavailability	Open-label Randomized Crossover- 2 arms	N= 16- Ring, OCs, iv arms	18-30 (~25)	Phase I ABC or BAC Vol. 76
		Effect on BMD	Comparative to an IUD	N= 35- IUD		
34225	1 Utrecht, Holland	PK with single dose N-9 or 1200 mg miconazole	Open-label	N-9 arm: 12 Miconazole arm: 12	18-35	Vol. 97
34226	1 Utrecht, Holland	PK/PD	Open-label	N= 45 3 arms 2 cycles	18-35	Window for the removal of ring. Vol. 102

Reviewer comment:
There were no controlled, blinded, large Phase III clinical trials submitted in this NDA. Three small open-label comparative trials were performed to evaluate metabolic, endocrine, and coagulation changes + cycle control due to NuvaRing versus a second generation OC containing 0.150 mg levonorgestrel + 30 µg ethinyl estradiol. The specific reasons for the choice of the one OC product are not clear in the NDA submission. None of the trials were designed to show superiority, so no superiority claims can be made in the Final Printed Label for, or marketing of NuvaRing®.

3.2 Summary of uncontrolled trials

There were two large Phase 3 trials submitted in this NDA: Protocol 068003 and 34219. The first subjects were enrolled in both trials in November 1997 and the last subjects completed the studies in June 1999. Both trials were non-comparative, multi-center, open-label, safety and efficacy studies of NuvaRing. Identical protocols were used for both trials.

Protocol 68003 enrolled a total of 1,210 female subjects and treated (i.e. subject received at least one dose of study medication) 1,117 women for a total of 11,188 28-day cycles. Protocol 34219 enrolled a total of 1,182 female subjects and treated 1,145 women for a total of 12,109 cycles. The goal of a total of at least 10,000 evaluable cycles was easily achieved.

In the three European metabolic studies, a total of 121 subjects were exposed to NuvaRing for 634 28-day cycles. In the local effects USA study 68004, 58 subjects were exposed to 460 cycles. The total extent of exposure to NuvaRing in these seven studies is summarized in the reviewer table below:

Table # 5- Exposure to NuvaRing

Study(s)	Subjects treated	28-day Cycles	Woman years	Reviewer Comments
68003	1117	11,188	858	**Large USA study**
34219	1145	12,109	928	**Large European study**
34220, 34221, 34222	121	634	49	3 "metabolic" studies
68004	58	460	35	Local Effects study
TOTALS	2,501	24,391	1,870	Exceeds the # required

4.0 PROTOCOLS 68003 and 34219: Open-Label, Multicenter, Non-Comparative Study in Healthy Female Subjects to Evaluate Contraceptive Efficacy, Cycle Control, and Safety of NuvaRing®.

4.1 Objectives

The study objectives were to evaluate the safety, contraceptive efficacy, and cycle control seen with the use of NuvaRing for a duration of treatment of 13 consecutive cycles. Each cycle consisted of a 21-day period with the ring remaining in the vagina, followed by a 7-day ring-free period.

4.2 Design

Studies 68003 and 34219 were open-label, non-comparative studies conducted in 48 centers in the United States/Canada [68003] and 53 centers in Europe/Israel [34291]. No positive control group was included in either study.

4.3 Study population

A total of 2,322 female subjects were treated at 101 different centers in the 2 large studies. The subjects were recruited and treated between November 1997 and June 1999. These subjects received at least one day of the study medication (see reviewer Table # 6).

Table # 6- Exposure to NuvaRing in 2 Large Clinical Trials

Study	Subjects treated	28-day Cycles	Woman years	Reviewer Comments
68003	1177	11,188	858	Large USA study
34219	1145	12,109	928	Large European study
TOTALS	2,322	23,297	1,786	

4.3.1 Demographics

Demographic data including date of birth, race, height, body weight, and a general medical and gynecological history (including menstrual bleeding characteristics, gravidity, and parity) were recorded during the screening period. Descriptive summaries of demographic characteristics (age, race, body mass index [BMI]), obstetric history (gravidity, parity), menstrual bleeding characteristics (usual duration of flow, usual volume of flow), and contraceptive history (last contraceptive method used) are presented for the two large studies individually and for the two studies combined. Information on social-economic background was also recorded in the two large studies and is presented by study and by the two studies combined.

For both studies combined, the subjects had a mean age of 28.2 years (range of 18 years to 41 years). The majority of subjects (77.1% in combined studies) ranged in age from 21 years to 35 years of age. The majority of subjects were Caucasian. A lower percentage of Caucasians in Study 068003 (88.7%) than in Study 34219 (98.6%) reflected a greater percentage of Blacks in Study 068003 (9.2%) than in Study 34219 (0.5%). Combined, NuvaRing racial distribution was Caucasian 93.6%, Black 4.9%, Asian 0.7%, and Other 0.8%. Mean BMI for the combined studies was 22.85 kg/m^2. The two studies were comparable to each other with respect to age, and BMI was slightly different between the two studies, namely, women in Study 068003 tended to be heavier than women in Study 34219, since both the mean and median BMI was higher for Study 068003 than Study 34219. The average mean coital frequency was not reported.

The obstetric history of subjects was comparable in the two studies, except the percentage of subjects who had never been pregnant was greater in Study 34219 (46.4%) than in Study 068003 (32.5%). In combined studies, 39.4% of subjects had never been pregnant and 52.7% of subjects were nulliparous.

Menstrual bleeding characteristics at screening were similar in the two studies. Under menstrual characteristics, the screening history asked for the "usual duration of flow" [# of days] and "usual volume of flow" [scanty (1-2 pads per day), moderate (3-4 pads per day), or heavy (>4 pads per day)].The combined studies showed a mean usual duration of flow of 4.7 days; the majority of women (61.1%) reported the usual volume of flow as "moderate."

The most frequently used "last contraceptive method" differed in the two studies. The most frequently used last contraceptive method was foam, condom, etc. in Study 068003 (46.8%) versus OCs in Study 34219 (67.4%). The second most frequently used last contraceptive method was OCs in Study 068003 (37.4%) versus foam, condom, etc. in Study 34219 (20.5%).

Reviewer's comment:
The two studies were well matched with regard to age and number of subjects enrolled. Despite this fact and identical study protocols, it is interesting to note that the following differences are found in the two study populations (US study versus Euro study), although the clinical significance of these differences is unclear:

- **Black subjects---------- 9.5% vs. 0.5%**
- **Heavier subjects (baseline BMI)-- 23.4 vs. 22.3**
- **No prior pregnancy---------- 32.5% vs. 46.4%**
- **OC as last contraceptive---------- 37% vs. 67%**
- **Foam, condom as above---------- 47% vs. 21%**
- **Usual menstrual flow "moderate"- 55% vs. 68%**
- **Usual menstrual flow "heavy"----- 29% vs. 19%**

It is difficult to know if some of these above differences were major contributing factors in the difference in compliance, discontinuation, and efficacy results that are discussed later in this review. Despite the much higher percentage of European women using an OC as their last contraceptive method, the mean days duration of menstrual flow at screening was virtually the same for the 2 study populations (4.7 vs. 4.8) and the median was 5 days for both study groups.

4.4 Inclusion and exclusion criteria: identical for both the large clinical studies

Inclusion Criteria

1. Women at risk for pregnancy and asking for contraception
2. Between 18-40 years of age at the time of screening
3. Cycles with a usual length of between 24 and 35 days and an individual variation of +/- 3 days
4. Body mass index ≥ 18 and ≤ 29
5. Willing to give written informed consent to participate in the study

Exclusion Criteria

1. Cervicitis, vaginitis, or a bleeding erosion
2. A cervical smear Papanicolau Class III, IV, or V, in the history or diagnosed in the screening phase [US study: smear of low grade SIL or higher in the Bethesda System]
3. Contraindications for contraceptive steroids:
   - known or suspected pregnancy
   - history of, or existing thrombophlebitis or thromboembolic cardiovascular or cerebrovascular disorders
   - a known defect in the blood coagulation system
   - the presence of more than one risk factor for vascular disease
   - hypertension
   - known or suspected estrogen-dependent tumors or endometrial hyperplasia
   - undiagnosed abnormal vaginal bleeding
   - cholestatic jaundice of pregnancy or jaundice with prior pill use
   - porphyria
   - a history during pregnancy or previous estrogen use of severe pruritus, herpes gestationis or deterioration of otosclerosis
4. Use of an injectable hormonal contraceptive within the past six months, or those who had used an implant or hormone-mediated intrauterine device (IUD) within the past two months
5. Women who were breast-feeding or within two months after stopping breast feeding
6. Status post-partum or post-abortion within a period of two months prior to the start of the study medication
7. Women who required concomitant use or use within the two months prior to study medication of the following drugs: [redacted] barbiturates, primidone, carbamazepine, [redacted] topiramate, rifampin, griseofulvin

8. Prolapse of the uterine cervix, cystocele, and/or rectocele
9. Severe or chronic constipation
10. Dyspareunia or other coital problems
11. Any woman who had taken an investigational drug within two months prior to the start of the study
12. A history of (within 12 months) alcohol or drug abuse

Reviewer's comment:
The inclusion criteria "women within the age range of 18-40 years inclusive" differs from the majority of previous United States OC investigations, which have studied women in the age range of 18-35 (or 38) years inclusive. Accepting females up to age 40 into the clinical trial potentially introduces the bias of decreased fertility due to maternal age. The value, however, is the information gained concerning efficacy and safety in women ≥ 35. Numbers and percentages of all-subjects-treated from age 18-34 and age 35-41 are shown shaded below.

Table # 7-Age Demographics by Age Group
(All-subjects-treated Group)

Trial	68003		34219		Combined studies	
	N	%	N	%	N	%
Age < 35 years	963	81.8	957	83.6	1920	82.7
Age ≥ 35 years	214	18.2%	188	16.4%	402	17.3%
TOTAL	1177	100%	1145	100%	2322	100%

4.5 Procedures

4.5.1 Screening period

The study design and purpose were explained at the Screen Visit, and the volunteers were assessed for eligibility. Written informed consent was obtained. The requirements of participation were thoroughly explained to the subject, including the use of home pregnancy test, compliance with back-up contraceptive methods (if used), returning used and unused NuvaRings, and availability for scheduled visits. A medical and gynecological history, pretrial medications (recreational, prescription and OTC) history, and the existence of any relevant pre-existing conditions were obtained. General characteristics including smoking, alcoholic beverage consumption and need for contraception were recorded. Vital signs and a complete physical examination (including breast, pelvic exam, and cervical Pap smear) were performed. Subjects had blood drawn for β-hCG level (pregnancy), routine biochemistry and hematology (CBC) testing at a central laboratory. Starter subjects were instructed to insert the first ring on Day 5 of the menstrual cycle and to use a back-up method (condoms without spermicides) during the first seven days of ring use. Direct OC switch subjects were instructed to start using the ring after a 7 day tablet-free period. Women who were switching from progestin-only oral contraception use were to continue pill intake until the day before ring insertion. Verbal and written instructions for the insertion and removal of the ring were given.
Four NuvaRings were dispensed at the Screening Visit. Each subject performed a home urine pregnancy test immediately before inserting the first ring of the study. The NuvaRing could be left in the vagina during intercourse. If necessary, the ring could be removed before intercourse, but it was to be reinserted within three hours. Instructions were given in case of non-adherence to the recommended regimen of use.

Reviewer comment: per protocol, switchers were those subjects who used hormonal contraception in the two months before the start of the ring, whereas non-switchers did not. In the US study, 41% were switchers, while in the European study 62% were switchers.

4.5.2 Admission period: there was no official admission period after the screening visit.

4.5.3 Treatment period

Subjects were seen in the first week following Cycles 3, 6 and 9. At each of these visits, blood pressure, weight, and interim history were performed, the daily diaries (or IVRS data) and product sachets were reviewed and collected, and AE and concomitant therapies were reported. A gynecological exam and Pap smear were repeated at the Cycle 6 and 13 Visits and also in case of early discontinuation. Routine laboratory parameters were repeated after completion of Cycle 13 or in case of early discontinuation. Each subject was contacted by telephone approximately one month after her completion of participation in the study for a Post-Treatment Evaluation. At this evaluation, post-treatment medications, evaluations, and AEs were reported. If a subject was not reached by telephone, she was contacted by mail.

A pregnancy test was also done whenever pregnancy was suspected during the study period. Pregnancy testing was prompted by failure of withdrawal bleeding. Testing was not done at each visit. All pregnancies reported during the study and post-treatment period were followed for pregnancy outcome and a pregnancy follow-up form completed.

The table below shows the flow chart of subject assessments:

Table 8: Assessment Schedule for Adequate and Well-Controlled Studies

Assessment	Screening	Cycle 3	Cycle 6	Cycle 9[a]	Cycle 13[b]	Post[c]
Informed consent	•					
Medical and gynecological history	•					
Physical examination	•				•	
Vital signs[d]	•	•	•	•	•	
Gynecological examination	•		•		•	
Cervical cytology	•		•		•	
Routine laboratory parameters	•				•	
NuvaRing® acceptability		•	•		•	
Urine pregnancy test	•[e]					
Vaginal bleeding		•[f]	•[f]	•[f]	•[f]	
NuvaRing® compliance		•[f]	•[f]	•[f]	•[f]	
Drug accountability	•	•	•	•	•	
Pre-trial and concomitant medication	•	•	•	•	•	•
Pre-treatment signs and symptoms	•	•				
Adverse events		•	•	•	•	•

[a] In anticipation of the discontinuation of study treatment at the end of Cycle 13, contraceptive counseling was to be given to the subject and post-treatment contraception prescribed.

[b] Assessments were to be performed after completion of Cycle 13 and also in case of early discontinuation.

[c] The post-treatment evaluation was to be performed by interviewing the subjects. Inquiries were to be made regarding menstrual cycle, possible return of fertility, and possible use of contraceptives. This evaluation was to be performed within 1 month following completion of Cycle 13, but preferably in the last week (fourth week) of this period.

[d] Blood pressure, body weight, and (at screening only) height.

[e] Home pregnancy tests were to be performed by the subject just before the first ring insertion. The results were to be recorded via Interactive Voice Response System (Study 068003) or diary cards (Study 34219) and subjects were to start with study medication only if the test was negative.

[f] Daily by use of Interactive Voice Response System (USA Study 068003) or diary cards (Euro Study 34219).

4.6 Evaluation criteria (methods)

4.6.1 Contraceptive Efficacy

The sponsor classified pregnancies into three categories: pretreatment, in-treatment, or post-treatment. Pretreatment pregnancies were those in which conception occurred prior to the first start of study drug (ring insertion). In-treatment pregnancies were those in which conception occurred after the first ring was inserted and prior to discontinuation of the study ring. Post-treatment pregnancies were those in which conception occurred after

discontinuation of the study ring. Pregnancy tests were not done at every visit. Pregnancy tests were performed only at Screen Visit, at home immediately before inserting the first ring for the first cycle, at Cycle 13 Visit or in case of early discontinuation. If pregnancy was suspected during the study period, then pregnancy testing was performed.

> **Reviewer's comment:**
> **Many contraceptive trials include subjects who become pregnant within 7-14 days of the last study dose as "in-treatment" pregnancies. This issue is discussed later in this review in the Section titled Pregnancies conceived POST discontinuation of study drug.**

The date of conception was determined by using the following information, if available:

1. ultrasound,
2. quantitative serum β-hCG determination,
3. qualitative urine β-hCG determination,
4. estimation of gestational age based on pelvic and/or abdominal examination or pregnancy outcome,
5. daily diary information (e.g. absence of withdrawal bleeding, subjects complaints), or
6. investigator's estimation in the absence of the above criteria for the determination of the conception date.

In the case of conflicting information, the more accurate method of estimation was used. If a range was reported (e.g. 18-20 weeks on ultrasound), the midpoint was used. In the case of multiple ultrasounds, the results of an ultrasound performed between 5 and 12 weeks of gestational age was recorded on the Pregnancy Determination Form and used for calculating the estimated date of conception (EDC).

4.6.2 Bleeding patterns

The evaluation of bleeding patterns was based on bleeding and spotting information recorded by the subjects on daily diary cards. Bleeding was defined as any bloody discharge requiring more than one sanitary napkin or tampon per day. Spotting was any bloody discharge that did not require more than one napkin or tampon per day. For definitions of additional bleeding/spotting terms see pages 32-33 of the sponsor's ISE. Bleeding patterns were evaluated by individual cycle control analysis. In the cycle control analysis, the first 7 days of only the first cycle were excluded and the incidence of bleeding events such as intermenstrual bleeding, breakthrough bleeding, breakthrough spotting, and absence of withdrawal bleeding were displayed. Duration of withdrawal bleeding, early withdrawal bleeding, continued withdrawal bleeding, and the number of breakthrough bleeding-spotting days were also calculated.

> **Reviewer comment:**
> **One other method of bleeding or cycle analysis is called "reference period analysis" where the data is evaluated in a block of time such as three menstrual cycles [e.g., a "reference period" of 90 days]. Both methods are valid, but the reference period data allows for much better information over time. The sponsor's cycle control analysis gives valuable information for what happened each cycle 1 through 13, but no insight into whether the same subjects are having the same bleeding patterns each cycle or different subjects are contributing each cycle.**

4.6.3 Safety evaluation

Safety evaluation was based on the incidence of adverse experiences (AEs), discontinuations due to AEs, changes from screening to last assessment in vital signs, physical examination findings (including breast and pelvic exam and cervical Pap smear), laboratory results and pregnancy outcome. Adverse experiences and serious adverse experiences were categorized by the study period in which they occurred: pre-treatment, in-treatment, or post-treatment. Serious adverse experiences were defined as an event that was fatal or life-threatening, was permanently

disabling, required an inpatient hospitalization, was a congenital anomaly, was cancer, or was caused by an overdose (whether or not it was related to the study drug). Relationship of AE to study drug was defined as:

- None-no relationship to study drug
- Unlikely-a relationship is not likely, but not impossible
- Possible-a relationship is not likely, but may exist
- Probable-a relationship has not been clearly demonstrated but is likely
- Definite-a reaction which follows a reasonable temporal sequence from administration of study drug and which is confirmed by improvement on stopping the drug and reappearance of the reaction on repeated exposure

Reviewer's comment:
It is not likely that repeated exposure ("rechallenge") would occur in the context of this study. Therefore, the designation of "definitely related" is not likely to have been made in most cases. Thus, those events which are "probably related" may be more meaningful.

4.7 All-Subjects Disposition: enrollment, withdrawals, compliance and discontinuations

Study 68003: 1210 subjects were enrolled at 48 sites in the US and Canada. 1177subjects were enrolled at 47 US sites and 33 subjects at one Canadian site. **1177 subjects were included in the All-Subjects-Treated Group for NuvaRing,** of which 59% were starters and 41% were switchers.

1177 subjects were exposed to NuvaRing for a total of 11,188 cycles
695 (59%) were Starters
482 (41%) were Switchers
482 (41%) discontinued during the study:
-178 due to SAEs
-18 due to pregnancy
-10 due to bleeding irregularity
-276 due to other reasons

Study 34219: 1182 subjects were enrolled at 53 sites in Europe and Israel. 1145 subjects used the ring and were included in the All-Subjects-Treated Group for NuvaRing, of which 38.3% were starters and 61.7% were switchers.

1145 subjects were exposed to NuvaRing for a total of 12,109 cycles
439 (38.3%) were Starters
706 (61.7%) were Switchers
339 (29.6%) discontinued during the study
-173 due to AEs/SAEs
-4 due to pregnancy
-9 due to bleeding irregularity
-153 due to other reasons

Reviewer's comment:
In the All-Subjects Treated Group from the combined data, 821 (35.4%) of the subjects discontinued prematurely from the study. This is a relatively good discontinuation rate given the fact that this was a 13-cycle trial. The percentage of subjects who discontinued was greater in the US study 68003 (41%) than the European study 34219 (29.6%). There is no specific explanation for this fact except to note that in the US trial there was also a higher percentage of protocol violations, irregular ring use, and pregnancies, suggesting that the US subjects were not as compliant as the European counterparts.

Dosing compliance

Trial 68003 subjects were to document on a daily basis, via IVRS (interactive voice retrieval system), the daily number of hours of ring use as well as the dates of insertion of new rings. Trial 34219 subjects used a booklet with diary cards for the same documentation. This information was used as a measure for the extent of exposure and dosing compliance. Two types of compliance were calculated per cycle as well as over all cycles per subject, namely,

1) compliance to the 21/7 day regimen, and
2) compliance to ring-use during the ring periods (temporary ring removal).

Reviewer's comment:
A detailed 24-hour recording system was used throughout the trials, and a fairly complex analysis used to determine ring compliance. The analysis plan used by the sponsor was fair and accurate.

In the two studies combined, 89.9% of AST cycles complied with the dosing schedule. The dosing compliance differed in the two studies (79.1% of compliant AST cycles in Study 068003 versus 90.8% of compliant cycles in Study 34219). In the combined studies, the incidence of prolonged ring-free period was 4.8% and the incidence was comparable for the two studies (5.5% versus 4.1% for Studies 068003 and 34219, respectively).

For the combined studies, at least 75% of all subjects never had a temporary ring removal during each of Cycles 1-13. The 90th percentile of the number of temporary ring removal hours for the combined studies ranged from 4 to 29 hours. In study 34219, during each cycle (except Cycles 1 and 3), 90% of subjects never removed the ring temporarily.

Reviewer's comment:
This level of compliance is very good for a 13-cycle hormone contraceptive study involving the 21-day use of a vaginal ring. The compliance was clearly better in the 34219 trial, but this is probably not clinically significant.

Discontinuation Reasons- see table # 9 below:

Table # 9. All-Subjects-Treated Group, Percentage Discontinuing: Primary Reason for Discontinuation

Primary reason for discontinuation	Study 068003 (N = 1177)		Study 34219 (N = 1145)		Total (N = 2322)	
	n	% of total	n	% of total	n	% of total
Adverse event / Serious adverse event	178	15.1	173	15.1	351	15.1
Bleeding irregularities	10	0.8	9	0.8	19	0.8
Pregnancy	18	1.5	4	0.3	22	0.9
Other[a]	276	23.4	153	13.4	429	18.5
Total	**482**	**41.0**	**339**	**29.6**	**821**	**35.4**

N = number of subjects in the study; n = number of subjects with a particular reason for discontinuation

[a] "Other" includes unspecified reasons and "Non-acceptance of the CCVR concept" as listed as a separate category on the End of Trial case report form.

Reviewer's comment:
The most common reason for discontinuation (failure to complete the study) was Other. The second most common reason for discontinuation was Drug Related AEs. The Drug Related AE discontinuation rates were not unusually high. Further discussion is found under section 4.9.1 of this review on page 47.

4.8 Contraceptive Efficacy Analysis
Contraceptive efficacy was evaluated based on the occurrence of pregnancy during the study drug administration (or "in-treatment") period.

Forty-two subjects became pregnant in the two large studies:

- 26 pregnancies occurred prior to the first ring insertion/pill intake (16 in the 68003 Group and 10 in the 34219 Group,
- 21 pregnancies occurred during the drug administration period (15 in the 68003 Group and 6 in the 34219 Group), and
- 27 pregnancies (12 in the 68003 Group, and 15 in the 34219 Group) occurred after the discontinuation of study drug.

Pregnancy Determination Forms were completed for a total of 74 subjects with suspected or confirmed pregnancies.

Table # 10. Protocols 68003and 34219: Pregnancies (By Study and Combined Total)

	68003	34219	**Total**
Total Pregnancies Confirmed	43	31	**74**
Pregnancy Prior to Start of Study Drug	16	10	**26**
Pregnancy During Study Drug Administration	15	6	**21**
Pregnancy After Discontinuation of Drug	12	15	**27**

Reviewer's comment:
The efficacy analysis does not include data available from the 3 metabolic and 1 local effects studies, although this data is available. In these studies there were 3 pre-treatment pregnancies, no during-treatment pregnancies, and no post-treatment pregnancies.

During a clinical quality assurance audit of Study 68003, it was discovered that in some of the later months of the study, the first ring day was incorrectly represented in the database. Subsequent to this discovery, the sponsor carried out a complete reanalysis of study 68003 which resulted in the following changes [not considered to be clinically significant]:

- **extent of exposure for the PP group and compliance were slightly increased**
- **temporary ring removal hours were decreased in Cycles 12 and 13**
- **the Pearl Index was slightly decreased**
- **incidence of non-evaluable cycles was decreased in Cycles 11-13**

This review will use the revised figures submitted by the sponsor in their July 6, 2000 submission to this NDA. The reviewer agrees that the revised database is not clinically significant.

4.8.1 Pregnancies conceived while on (during) study drug

From the sponsor's ISE, there were 21 pregnancies conceived during the treatment period [between the day of first ring insertion and the 7 days after the last ring removal]. In Study 068003, there were 15 in-treatment pregnancies reported, 5 of which were considered PP [per protocol or "perfect use"] pregnancies as defined by the sponsor in Section 8.1.1. Study 34219 had 6 in-treatment pregnancies, 3 of which were considered PP pregnancies. The difference in AST [All-Subjects-Treated] Pearl Indices between both studies was not statistically significant (P=0.0522). With a total of 23,298 28-day cycles, equivalent to 1,786 woman years, the combined AST Pearl Index is estimated to be 1.176 (95% CI: 0.728-1.797). The difference in PP Pearl Indices between both studies was not statistically different (P=0.3983). With a total of 17,049 28-day cycles, equivalent to 1,311 woman years, the sponsor's combined PP Pearl Index is 0.610 (95% CI: 0.266-1.216).

Ultrasound data used to calculate dates for conception was available for all subjects who became pregnant during treatment in both studies. The following two tables list the reviewer's analysis of the during-treatment pregnancies.

Table # 11. Combined Sponsor and MO: Pregnancies Conceived DURING the Treatment Period in Study 68003 (All Subjects Treated Group)

Study 68003 Subject #	Age/ Parity	Last ring removal	LMP[a] date Cycle of Conception	Method Estimated conception date	Estimated: gestational age (weeks); date of determination	Pregnancy Outcome	PP User? (per protocol) MO comment
⊕1934	26/G0P0	2/7/99	12/16/98 Cycle 12-13	US 1/17/99	(6) 2/18/99	Not stated	⊕Yes Took LoOvral 4/13/98 for EC[b]
2432	*39/G1P1	1/13/99	12/17/98 Cycle 12	US 12/29/98	(7) 2/3/99	Not stated	Yes
2459	28/G0P0	5/28/98	4/15/98 Cycle 2	US 5/1/98	(7) 6/1/98	Abortion 6/1/98	No
2908	31/G3P1	1/4/99	11/10/98 Cycle 11	US 11/18/98	(14) 2/9/99	Continue pregnancy	Yes
3001	*35/G3P2	7/28/98	3/15/98 Cycle 4	US 3/30/98	(19) 7/28/98	Abortion 8/5/98	No
3003	26/G4P1	7/19/98	3/14/98 Cycle 5	US 3/30/98	(18) 7/20/98	Continue pregnancy	Yes
3014	33/G2P0	12/22/98	11/11/98 Cycle 11	US 11/21/98	(6 ½) 12/22/98	Abortion 12/30/98	No
3209	26/G5P4	6/30/98	5/12/98 Cycle 7	US 6/28/98	(5) 7/20/98	Continue pregnancy	No
3430	26/G2P1	8/25/98	7/12/98 Cycle 5	US 7/22/98	(14) 10/13/98	Continue pregnancy	Yes
4131	29/G0P0	1/27/99	12/17/98 Cycle 11	US 12/30/98	(6) 1/27/99	Continue pregnancy	No
4214	19/G1P0	5/23/98	4/27/98 Cycle 6	US 5/11/98	(7) 6/9/98	Abortion 6/25/98	Yes
4342	22/G1P1	4/7/98	3/12/98 Cycle 1	US 3/10/98	(28) 9/9/98	Continue pregnancy	No
4350	22/G0P0	6/29/98	5/27/98 Cycle 4	US 6/10/98	(9) 7/31/98	Continue pregnancy	No
4407	22/G0P0	2/1/98	12/16/98 Cycle 1	US 12/31/97	(13) 3/13/98	Abortion 3/14/98	No
⊕4820	29/G4P4	11/16/98	10/4/98 Cycle 8	US 10/24/98	(5) 11/17/98	Abortion 12/2/98	⊕Yes

[a]LMP=last menstrual cycle Day 1 [b]EC=emergency conception

* these subjects are highlighted only because of their age. Women ≥ age 35 are also evaluated separately (see pg. 38)

⊕Reviewer's comments:

The reviewer and the sponsor disagree on the determination of PP vs. non-PP for two of the listed subjects (#1934 and 4820). The sponsor considered them to be non-PP and the reviewer concluded they had used the product properly and should be counted as PP pregnancies.

Subject 1934 was considered by the sponsor as non-PP because she used emergency contraception on Day 65 (Cycle 3) earlier in the trial. She conceived between Cycle 12 and 13, used

the ring correctly, and should be counted as a PP pregnancy. The earlier "protocol violation" had no bearing on her conception.

Subject 4820 used the ring between 9/17 and 10/08 (21 days), had 15 days of bleeding between 10/04 and 10/18, inserted a new ring on 10/15 (7 days after the previous ring) and left it in place for 23 days (until 11/07). Her LMP was light between 11/06-9. She inserted a new ring on 11/12 (5.4 days after the previous ring). An ultrasound on 11/17 estimated the conception date as 10/24. The sponsor considered the subject to be non-compliant because the ring-free interval was shortened to 5.4 days. The shortened interval per se would NOT diminish contraceptive efficacy; furthermore, it was after the date of conception. The reviewer's determination is that ring use prior to and after the conception date was correct and that the subject should be counted as a PP pregnancy.

Table # 12. Combined Sponsor and MO: Pregnancies Conceived DURING the Treatment Period in Study 34219 (All Subjects Treated Group)

Study 34219 Subject #	Age/ Parity	Last Day ring use	LMP[a] date Cycle of Conception	Method Estimated conception date	Estimated: gestational age (weeks); date of determination	Pregnancy Outcome	PP User? MO comment
0128	29/G2P2	11/21/98	LMP not stated Cycle 8	US 10/20/98	(7) 11/22/98	Abortion 12/11/98	Yes
⁴0524	27/G0P0	1/24/98	LMP 1/04/98 Cycle 2	US 1/25/98 MO 1/19/98	(7) 2/23/98	Normal delivery @ 38 weeks	⁴Yes Ring inserted 1/24/98 Sponsor NO
0830	27/G3P2	8/23/98	LMP not stated Cycle 5	US 8/10/98	(8) 9/18/98	Normal delivery @ 39 weeks	Yes
0968	33/G2P0	5/10/99	4/15/98 Cycle 11	US 4/10/99	(6) 5/21/99	Continue pregnancy	Yes
1090	33/G1P1	12/15/98	11/30/98 Cycle 8+	US 11/30/98 MO: 12/18/98	(6) 1/15/99	Continue pregnancy	No Very irregular ring use
1316	37 G1P0	3/05/98	3/14/98 Cycle 1	US 2/12/98	(4) 3/16/98	Normal delivery on 11/2/98	No

* this subject is highlighted only because of her age. Women ≥ age 35 are also evaluated separately.

⁴Reviewer's comment:

The reviewer and the sponsor disagree on the determination of PP vs. non-PP for one of the listed subjects (# 0524). Subject 0524 used the ring between 12/13 and 1/01 (20 days), had a spontaneous period 1/04-7, inserted a new ring on 1/08 (7 days after the previous ring) and left it in place for 15 days (until 1/25). Her LMP was 1/04 and a serum pregnancy test was positive on 2/20. An ultrasound on 2/23 (7 weeks gestation) estimated the date of conception as 1/25 [per sponsor] and 1/19 [per reviewer]. Ring use and removal was correct past the time of conception, so this subject should be counted as a PP pregnancy.

The sponsor's definition of in-treatment pregnancies included only the subjects listed in the above table. Careful analysis of the post-treatment pregnancies in Study 34219 follows in this review and does not change the number of pregnancies [during] in-treatment from Study 34219.

Table # 13. Treatment Cycle for 21 Pregnancies Conceived DURING Treatment Period

Study ⇒	68003 USA	34219 European	**Total per cycle**
Cycle 1	2	1	3
Cycle 2	1	1	2
Cycle 3			
Cycle 4	2		2
Cycle 5	2	1	3
Cycle 6	1		1
Cycle 7	1		1
Cycle 8	1	2	3
Cycle 9			
Cycle 10			
Cycle 11	3	1	4
Cycle 12	2		2
Cycle 13			
TOTALS	**15**	**6**	**21**

Reviewer's comment:
This pattern of pregnancies during the trial appears to be random. Roughly half of the pregnancies occurred during the first 6-7 cycles, and half occurred during the last 6-7 cycles. There is no particular pattern and no findings of major concern.

4.8.2 Pregnancies conceived prior to administration of study drug

Pre-treatment pregnancies are those pregnancies that occurred before the first ring insertion/pill intake or for which dispensed study medication was returned unused to the clinic. A summary of the pre-treatment pregnancies is described below. The sponsor provided adequate details of all pre-treatment pregnancies and associated subjects' characteristics for the large Phase III studies and in the four individual clinical study reports.

In Study 68003, there were 16 pre-treatment pregnancies reported. Of these, 12 subjects were enrolled in the study but were discontinued before inserting the first ring. The reason for discontinuation was pregnancy. All dispensed rings were returned unused. The other 4 subjects had estimated dates of conception, as recorded by the investigator, before the start of the study and were lost to follow-up or did not have complete information regarding the use/return of the NuvaRings.

In Study 34219, there were 10 pre-treatment pregnancies reported. All but one of these subjects discontinued the study before inserting the first NuvaRing; 8 of these subjects returned all dispensed NuvaRings® unused and 1 of these subjects discarded the study medication as dispensed to her by the investigator after the screening visit. According to the investigator, this subject never inserted any ring and, therefore, she was considered to be a non-treated subject and "Pregnancy before start" was the reason given for discontinuation. The pre-treatment pregnancy of the remaining subject ended in a spontaneous abortion. Two months after the spontaneous miscarriage, she started with the study medication and completed the study. For 8 of the 9 non-treated subjects, pregnancy was reported as the reason for discontinuation.

In the four smaller metabolic and local effects studies, there were a total of 3 pre-treatment pregnancies, all of which occurred in the NuvaRing-treated group of the coagulation and fibrinolysis Study 34221 (Subjects 0007, 0040, and 0047). All three subjects discontinued the study before inserting the first NuvaRing and returned the medication unused. Detailed descriptions of all pre-treatment pregnancies are found in the integrated contraceptive efficacy and cycle analysis report as well as in the clinical study report 34221.

Reviewer's comment:
After careful review of the subject narrative summaries, the MO concurs with the sponsor's list of 29 pregnancies conceived prior to starting study drug. It is fair to conclude that all of these 29 women probably conceived PRIOR TO starting the study drug. Therefore, they were not counted as pregnancies in any of the sponsor's or reviewer's calculations for efficacy (Pearl Index, Life Tables, etc.).

4.8.3 Pregnancies conceived POST discontinuation of study drug

From the sponsor's ISE, there were 12 post-treatment pregnancies reported in Study 68003 and 15 post-treatment pregnancies reported in Study 34219.

In Study 68003, of the 12 post-treatment pregnancies reported, 1 subject completed the study, 8 subjects discontinued for other reasons (non-compliance, desire for pregnancy, and personal reasons), and 1 subject discontinued due to an adverse event (heart palpitations). In addition, 2 subjects were discontinued from the study due to pregnancy, and an ultrasound assessment determined the conception to be after discontinuation of study medication. In all of these 12 pregnancies, the estimated gestational age, and consequently, the estimated conception date were based on ultrasound assessment.

In Study 34219, of the 15 post-treatment pregnancies 9 had estimated dates of conception based on ultrasound assessment. For 4 other subjects, the estimated date of conception was based on pelvic examination. One subject discontinued the study after 6 cycles of treatment because she wanted to become pregnant. At the post-treatment interview (by telephone), 2 months after the subject's last ring removal, the subject informed the investigator that she was pregnant. This subject was subsequently lost to follow-up. The remaining subject with a post-treatment pregnancy discontinued the study after 7 cycles of treatment because of "non-compliance" as mentioned under "other reasons" on the End of Trial CRF. Approximately 2 months after last ring removal the subject returned to the clinic for her last assessments. The blood sample, as collected during this visit, was positive for β-hCG. The subject was subsequently lost to follow-up. It was assumed that, based on the approximately 2-month interval between last ring removal and the β-hCG positive blood sample, the pregnancy occurred after discontinuation of treatment.

The estimated dates, relative to the date of last ring use, indicate that pregnancy occurred after discontinuation of treatment. These post-treatment pregnancies are evidence of the rapid return to fertility after discontinuation of NuvaRing® treatment.

Reviewer's comment:
Another interpretation is that some of these women actually conceived while using study drug. This probably occurred with subject # 4321 in the US trial 68003 and is discussed below.

This "rapid return to fertility" is fine for anyone wishing to become pregnant, but must be a cause for concern for anyone discontinuing use of NuvaRing for any reason and NOT desiring to become pregnant; such a person should initiate a method of contraception within 7 days of ring removal.

Table # 14. Combined Sponsor and MO: Pregnancies conceived POST Study Treatment Period in US Study 68003 (All Subjects Treated Group)

Study 68003 Subject #	Age/Parity	Last day ring use	LMP[a] date Cycles Completed	Method[b] Estimated conception date	Estimated gestational age (weeks) Date of US	Pregnancy Outcome	MO comment[c] MO eval: # days removal to conception
1106	29/G4P1	7/5/98	LMP 8/4/98 Cycle 6	US 8/16/98	(9) 10/5/98	Continue pregnancy	Urine + 9/7/98 41 days
1216	28/G4P2	7/21/98	LMP 7/23/98 Cycle 7	US 8/7/98	(8) 9/18/98	Continue pregnancy	Urine + 8/26/98 16 days
1622	31/G2P2	1/5/99	LMP 1/5/99 Cycle 10	US 1/16/98	(8) 3/4/98	Continue pregnancy	Urine + 2/4/99 11 days
2304	41/G4P1	10/11/98	LMP 1/1/99 Cycle 11	US 1/13/99	(8) 2/25/99	Continue pregnancy	87 days*
2616	25/G1P1	12/21/98	LMP 12/26/98 Cycle 10	US 1/12/99	(4) 1/26/99	Continue pregnancy	22 days*
4004	21/G0P0	1/6/98	LMP 1/10/98 Cycle 2	US 1/26/98	(3) 2/3/98	Continue pregnancy	20 days
4321	20/G0P0	12/14/98	LMP 12/16/98 Cycle 1	US 12/27/98	(8) 1/30/99	Abortion 1/30/99	MO conception 12/18 = 4 days Sponsor 13 days
4338	19/G2P1	3/11/98	LMP 3/3/98 Cycle 1	US 4/9/98	(17) 7/23/98	Continue pregnancy	29 days
4606	22/G0P0	7/23/98	LMP 7/26/98 Cycle 8	US 8/7/98	(6) 9/4/98	Continue pregnancy	15 days
4614	25/G4P1	7/19/98	LMP 8/17/98 Cycle 8	US 8/26/98	(9) 10/13/98	Continue pregnancy	38 days
4760	19/G0P0	4/12/98	LMP 4/13/98 Cycle 6	US 5/1/98	(6) 5/28/98	Continue pregnancy	19 days
5104	25/G0P0	2/15/98	LMP 2/17/98 Cycle 1	US 3/4/98	(6) 3/30/98	Continue pregnancy	17 days

[a]LMP=last menstrual cycle Day 1
[b]Method: US = ultrasound results
[c] **Sponsor consistently had 7 days <u>less</u> for the # of days from last ring use to conception, except Subject # 4321.**
*this subject is highlighted only because of her age.

Reviewer's comments:
One subject completed the study (13 full cycles of treatment), while three subjects completed only 1 or 2 cycles. The remaining 8 subjects completed between 6-11 cycles. Ultrasound findings were available on all 12 subjects, so relatively accurate estimation of the conception date is possible.

The subject narratives and case report form tabulations (CRFT) were carefully reviewed for all 12 subjects. With the exception of patient 4321, each patient had a sonogram placing the date of conception at least 11 days after ring removal, the date of last study drug use. The far right column gives the medical officer's assessment of the # of days that conception occurred after the last day of study drug (the day of ring removal). The variable degree of accuracy with conception dating by sonogram measurements makes it difficult to make an absolute assessment.

If we <u>use 7 days since the last ring use as a window of pregnancy failure</u>, then subject 4321 would be counted as a during treatment pregnancy for the following reasons. Subject 4321 inserted the first ring on 12/29/97. She used the ring correctly throughout cycles 11, 12, and 13.The last day of ring use (Cycle 13) was 12/14/98 and she had a normal menstrual period between 12/16-21. A urine pregnancy test was positive on 1/22/99 and an ultrasound on 1/30/99 estimated the fetal gestational age as approximately 8 weeks; this corresponds with a conception date of 12/18/99, NOT 12/27/98 as stated by the sponsor's analysis.

Adding subject 4321 as an in-treatment failure would make a total of 16 NuvaRing pregnancies in the US trial and would increase the All-Subjects-Treated Pearl index for this trial from the sponsor's 1.749 to the reviewer's 1.860. This should be considered a per protocol (PP) pregnancy as the subject used the ring correctly for the last 3 cycles. The other 11 subjects listed in the above table would remain as post-treatment pregnancies.

The post-treatment pregnancies reported in the European Study 34219 are listed in the following Table # 15.

Table # 15. Combined Sponsor and MO: Pregnancies Conceived POST the Treatment Period in Study 34219 (All Subjects Treated Group)

Study 34219 Subject #	Age/Parity	Last day ring use	*LMP[a] date Cycles Completed	Method[b] Estimated conception date	*Estimated gestational age (weeks) Date of eval	Pregnancy Outcome	*MO comment Sponsor eval: # days removal to conception
0082	31/G0P0	12/17/98	12/20/98 Cycle 13	Pelvic 1/3/99	(8) 2/24/99	Continue pregnancy	Urine + 1/27/99 17 days
0195	28/G1P1	7/21/98	7/25/98 Cycle 4	US 8/20/98	(6) 10/2/98	Normal 38 wk delivery	Urine + 10/2/98 30 days
0210	23/G0P0	2/6/99	2/9/99 Cycle 13	Urine hCG No US/pelvic 2/22/99	(6) 3/22/99	Continue pregnancy	Urine + 3/18/99 16 days
0346	27/G1P1	12/19/98	12/21/98 Cycle 13	US 1/3/99	(7) 2/22/99	Outcome unknown	Urine + 2/22/99 15 days
0387	24/ G1P0	6/15/98	Unknown Cycle 7	Serum hCG Not available	(?) 8/11/99	Lost to follow up	Serum + 8/11/99 Unknown
0642	24/G1P1	5/16/98	5/18/98 Cycle 2	US 6/2/98	(5) 6/26/98	Abortion 8/18/98	Urine + 6/15/98 17 days
0649	29/G2P2	8/23/98	9/19/98 Cycle 5	US 10/3/98	(4) 10/22/98	Continue pregnancy	41 days
0691	26/G1P1	6/30/98	6/24/98 Cycle 4	US 7/30/98	(7) 9/3/98	Normal 37 wk delivery	30 days
0707	24/G4P1	5/13/98	5/6/98 D3/Cycle 1	US 5/20/98	(6) 6/23/98	Normal 37 wk delivery	***Irregular ring use x 3 days only*** 7 days
0757	29/G0P0	5/20/98	5/22/98 Cycle 3	Pelvic 6/10/98	(8) 7/20/98	Abortion 7/20/98	21 days
0778	26/G3P2	6/25/98	6/27/98 Cycle 3	US 7/11/98	(8) 8/20/98	Normal 40 wk delivery	16 days
0800	26/G0P0	10/22/98	11/24/98 Cycle 6	Not given NoUS/pelvic 12/8/98	(4) 12/22/98 Phone only	Pregnancy outcome unknown	Urine + 12/22 @ home 47 days
0810	24/G1P1	4/12/98	7/4/98 Cycle 1	Pelvic 7/18/98	(6) 8/10/98	Abortion 9/3/98	Urine + 8/10/98 98 days
0839	28/G0P0	7/30/98	9/21/98 Cycle 3	US 10/5/98	(5) 10/28/98	Continue pregnancy	67 days
0922	34/G5P2	2/14/98	12/20/98 D17/Cycle 1	US 1/4/99	(8) 2/9/99	Continue pregnancy	Almost 1 year

[a]LMP=last menstrual cycle Day 1
[b]Method: US = ultrasound results
***Subject narratives did not provide LMP and gestational age data, but the CRF tabulations did.**

Reviewer's comments:
Three subjects listed above completed the study (13 full cycles of treatment), while four subjects completed less than 3 cycles. Five subjects completed 3-4 cycles, and three subjects completed 5-7 cycles. Ultrasound findings were available on only 9/15 (60%) subjects, so relatively accurate estimation of the conception date is not as good compared to the USA study where 100% had ultrasound evaluations.

The subject narratives and case report form tabulations (CRFT) were carefully reviewed for all 15 subjects. With the exception of patients 0387, 0707, and 0800, each patient had sufficient information to place the date of conception at least 15 days after the date of last study drug use. The far right column gives the sponsor's assessment of the # of days that conception occurred after the last day of study drug (the day of ring removal). The variable degree of accuracy with conception dating by sonogram measurements and pelvic examinations makes it difficult to make an absolute assessment. Careful review of each subject does not raise any significant doubt that 12 of the 15 subjects conceived at least 15 days after the last day of ring use. The remaining 3 subjects are discussed here:

Subject 0387 was lost to follow-up; because of the lack of accurate information, one simply cannot evaluate her date of conception.

Subject 0707 used the ring very sporadically (< 6 hours/day) for only 3 days of study Cycle 1. She should be considered a POST-treatment pregnancy because she never received appropriate drug.

Subject 0800 voluntarily discontinued the study after 6 cycles of correct ring use because she wanted to become pregnant. Because of lack of accurate information, her date of conception cannot be accurately determined, but it is most probably POST-treatment.

The overall reviewer conclusion is that all 15 of the 15 subjects listed above in Study 34219 should be considered as post-treatment pregnancies, and therefore should not be included in the contraceptive efficacy calculations. As discussed above, there is one post-treatment subject (# 4321) in Study 68003 that is included in this reviewer's contraceptive efficacy calculations.

4.8.4 Pearl Index and Life Table pregnancy rate

Pearl Index

From the sponsor's ISE, assessment of contraceptive effectiveness is based on In-treatment pregnancies, as defined below: In-treatment pregnancy: Pregnancies with an estimated day of conception (EDC) in the in-treatment period (the period from first ring insertion up to and including 7 days - the scheduled ring-free period - after the day the ring was last removed). Such pregnancies are referred to as ITT pregnancies.

A further distinction of in-treatment pregnancies is made between PP pregnancies and non-PP pregnancies, as follows: Per Protocol and non-Per Protocol in-treatment pregnancies: In-treatment days and/or cycles were excluded from the PP analysis according to the major and minor protocol violations criteria specified in Section 7.1.4 of the individual clinical study reports, pertaining, for the most part, to non-compliance. In-treatment pregnancies with an EDC not excluded from the PP analysis were classified as a PP pregnancy. Those pregnancies that were excluded from the PP analysis were classified as non-PP pregnancies.

Reviewer's comments:
The sponsor uses the term ITT incorrectly in most of their analyses. The true ITT group is all subjects enrolled in a study, whether any study drug is received or not. The sponsor is actually using the numbers for all-subjects-treated (AST) in almost every place where they state ITT throughout the NDA.

Table # 16 (from Sponsor). Contraceptive Efficacy: Pearl Index with 95% Confidence Interval – Large Clinical Studies (Intent-to-Treat and Per Protocol Groups)

Group	Study number	N	Total extent of exposure		Number of in-treatment pregnancies	Pearl Index estimate	95% Confidence interval	
			Number of 28-day cycles	Number of woman years			Lower	Upper
ITT[a]	068003	1,177	11,188.1	857.7	15	1.749	0.979	2.885
	34219	1,145	12,109.4	928.3	6	0.646	0.237	1.407
	Combined	2,322	23,297.6	1,786.0	21	1.176	0.728	1.797
PP[b]	068003	966	7169.4	549.6	5	0.910	0.295	2.123
	34219	1,049	9,879.6	757.4	3	0.396	0.082	1.158
	Combined	2,015	16,912.1	1,296.5	8	0.617	0.266	1.216

ITT = Intent-to-Treat; N = Number of treated subjects in a particular group; PP = Per Protocol

[a] Test for homogeneity of ITT Pearl Indices: P=0.0522 [95% Confidence Interval for ratio of Pearl indices equals (0.1175, 1.008)].

[b] Test for homogeneity of PP Pearl Indices: P=0.3983 [95% Confidence Interval for ratio of Pearl indices equals (0.0663, 2.1952].

Note: The data in this table were obtained from the revised data submitted 9 June 2000

Reviewer's comment: the above table and calculations by the sponsor are based on the total cycles of exposure divided by 13 pill cycles per year divided by 100 to obtain the Pearl index per 100 woman-years. The only pregnancies that are counted in their calculations are those considered to have happened while on (during) study drug.

Reviewer's comment: the MO table below shows the difference in the Pearl Indices between the MO and sponsor due to the previously noted interpretation of Study 68003 Subjects # 4321, 1934, and 4820, and Study 34219 subject # 0524.

Table # 17 (from MO). ITT/AST* and PP Pearl Indices in Studies 68003 and 34219

Study population	N	Cycles	Woman-years	MO failures	Sponsor failures	MO Pearl Index	Sponsor Pearl Index	MO evaluation comments
68003 US ITT/AST*	1,117	11,188	860	16	15	1.860	1.749	Subject 4321 added
PP (per protocol) % of total	966 **82%**	7,169	551	8	5	1.452	0.910	Subjects 4321, 1934, 4820 added as PP.
Non-PP	18%			8	10			
34219 EUR ITT/AST*	1,145	12,109	931	6	6	0.644	0.646	MO has 3 more woman-years
PP (per protocol) % of total	1049 **91.6%**	9,880	760	4	3	0.526	0.396	Subject 0524 added
Non-PP	8.4%			2	3			

*Throughout the NDA the sponsor uses ITT (intent-to-treat), but in fact this is the AST group (All-Subjects-Treated)

Reviewer's comment:

The sponsor's Pearl Index calculations are consistently the same or lower than the reviewer's because the reviewer had one more pregnancy during treatment (16 vs. 15 in the US trial) and 3 more per protocol pregnancies in the US trial and 1 more per protocol pregnancy in the European trial. In the worst case scenario, the Pearl Index is 1.860 in the reviewer's interpretation of the All-Subjects-Treated population in study 68003. In the best case scenario, the Pearl Index is 0.396 in the sponsor's calculation for the Per Protocol population in study 34219. What is of general concern is the difference in the Pearl Index results between the two large trials. The reviewer's analysis shows almost a three-fold higher Pearl Index for the AST and PP groups in the US trial compared to the European trial. The sponsor's analysis shows at least a two-fold difference.

Although the data presented here by the sponsor for the "per protocol" population clearly is much better than the "ITT" population, it is the Pearl Index of the Intent-to-Treat Group or the All-Subjects-Treated Group that is traditionally used by the FDA. Furthermore, according to the reviewer's analysis there were three more NuvaRing subjects (# 4321, 1934 and 4820) added to the 68003 study "per protocol" population, and one more NuvaRing subject (# 0524) added to the 34219 study "per protocol" population which lessens the difference between the PP and non-PP Pearl Indices. Because of the definite difference in all the Pearl Indices between the two large pivotal studies, this reviewer favors noting that difference in the final printed label so that healthcare providers and consumers will be more fully informed. Since the study protocols are virtually identical, the reason(s) for the difference in Pearl Indices is unclear. It could be due to differences in drug compliance, study completion rates, and data recording by the subjects in the two study populations, or differences in overall investigators' strictness in carrying out the two studies.

The sponsor's results for the Pearl Index for the combined data from the two large trials are found above in Table # 16. The MO results are shown in the following Table # 18:

Table # 18 (from MO). ITT/AST* and PP Pearl Indices in Combined Studies 68003 and 34219

Study popu-lation	N	Cycles	Woman -years	MO failures	Sponsor failures	MO Pearl Index	Sponsor Pearl Index	MO evaluation comments
68003 and 34219 ITT/AST*	2,322	23,297	1792	22	21	1.228	1.176	Subject 4321 added
PP (per protocol) % of total	2,015 86.8%	17,049	1311	12	8	0.915	0.617	Subjects 4321, 1934, 4820, 0524 added as PP by MO.
Non-PP	13.2%			10	13	N.A.	N.A.	

*Throughout the NDA the sponsor uses ITT (intent-to-treat), but in fact this is the AST group (All-Subjects-Treated)

Reviewer's comment:

The sponsor's Pearl Index calculations are consistently the same or lower than the reviewer's because the reviewer had one more pregnancy during treatment (16 vs. 15 in the US trial) and 4 more per protocol pregnancies in the combined trials. The combined Pearl Index is acceptable. Labeling recommendations are made in the preceding reviewer's comments because of the marked difference in the Pearl Index results from the two large trials as shown in Table # 17.

Efficacy by Age < 35

In the sponsor's June 9, 2000 submission to the NDA, data was presented in a table format for efficacy by age < 35 and ≥ 35. The Table 1(19) below is copied [as a graphic] from the submission and shows the Pearl Index calculations for the two age groups for the studies separately and combined.

Efficacy by Age <35

Table 1 Contraceptive Efficacy: ITT Pearl Index by Age Category - Adequate and Well-Controlled Studies (Intent-to-Treat Group)

Trial	Age-category[a]	N	Total extent of exposure		No. of ITT	Pearl Index	95% CI	
			28-day cycles	(woman years)	Preg-nancies	estimate	Lower limit	Upper limit
068003	≥ 35 years	214	2164.1	165.9	2	1.206	0.148	4.355
	< 35 years	963	9024.0	691.8	13	1.879	1.001	3.214
34219	≥ 35 years	188	2080.1	159.5	1	0.627	0.016	3.494
	< 35 years	957	10029.3	768.8	5	0.650	0.211	1.518
Combined	≥ 35 years	402	4244.2	325.4	3	0.922	0.190	2.695
	< 35 years	1920	19053.4	1460.6	18	1.232	0.730	1.948

a) Testing homogeneity of ITT Pearl Indices across age-categories:
- Trial 068003: P = 0.8462 (95% CI for ratio of Pearl indices equals (0.0703, 2.8336)).
- Trial 34219 : P = 1 (95% CI for ratio of Pearl indices equals (0.0204, 8.6177)).
- Combined : P = 0.9025 (95% CI for ratio of Pearl indices equals (0.1412, 2.5629)).

The MO analysis is presented in Table # 20 below:

Table # 20 (from MO). ITT/AST* Pearl Indices in Studies 68003, 34219, and Combined by Age Category

Study popu-lation	N	Cycles	Woman -years	MO failures	Sponsor failures	MO Pearl Index	Sponsor Pearl Index	MO evaluation comments
68003 US ≥ 35 years	214 (18%)	2,164	166	2	2	1.205	1.206	
68003 < 35 years	963 (82%)	9,024	694	14	13	2.017	1.879	Subject 4321 added in.
34219 EUR ≥ 35 years	188 (16%)	2,080	160	1	1	0.625	0.627	
34219 < 35 years	957 (84%)	10,029	771	5	5	0.648	0.650	
Combined ≥ 35 years	402	4,244	326	3	3	0.92	0.92	
Combined < 35 years	1,920	19,053	1,465	19	18	1.30	1.23	Subjects 4321 added in.

*Throughout the NDA the sponsor uses ITT (intent-to-treat), but in fact this is the AST group (All-Subjects-Treated)

Reviewer's comment:

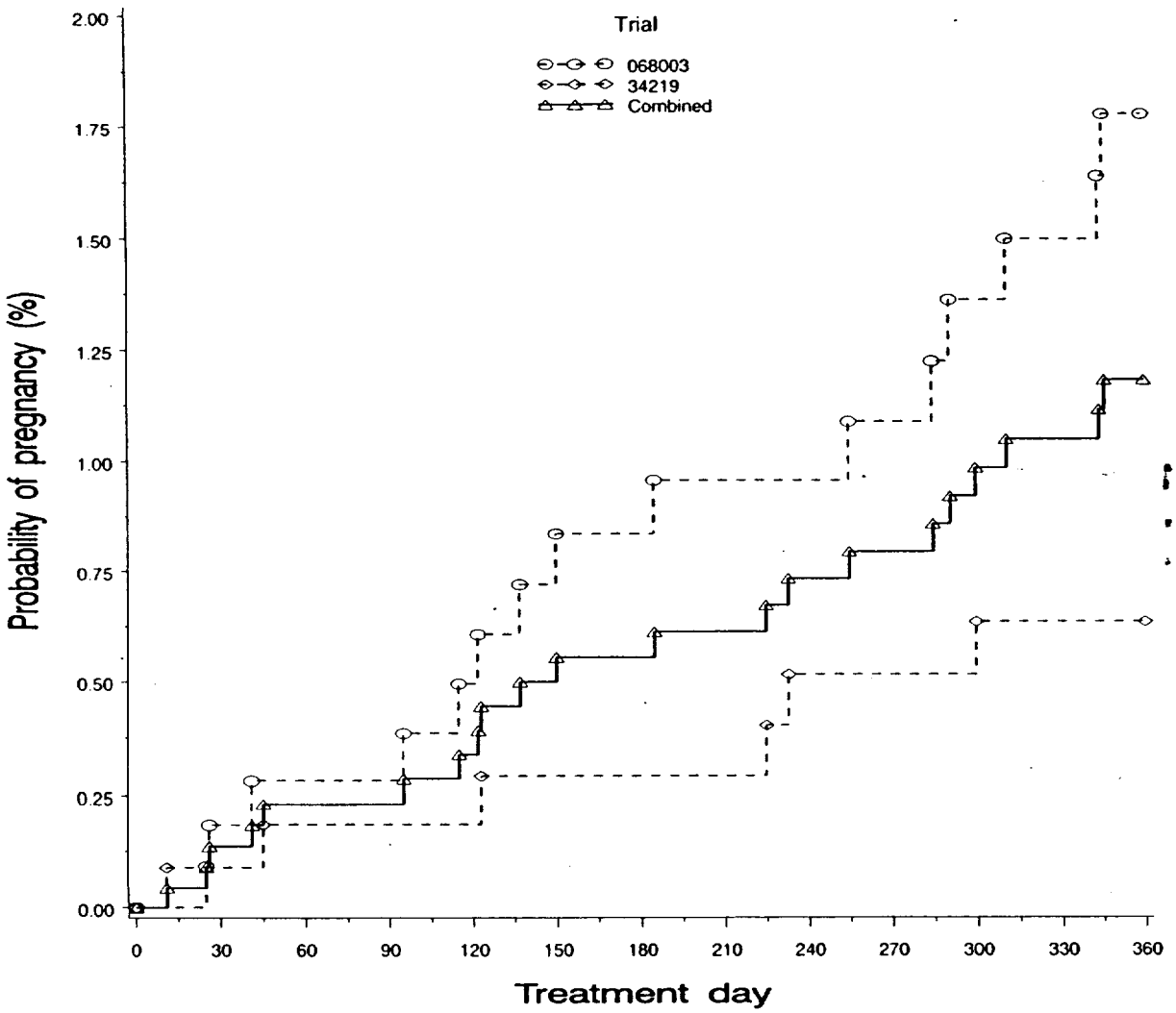
The reviewer had one more pregnancy during treatment (16 vs. 15 in the US trial) and 4 more per protocol pregnancies in the combined trials. The combined Pearl Index for All-Subjects-Treated is acceptable for both age groups. Because fertility is believed to decrease with age, especially with age ≥ 35, we would expect a corresponding decrease in the Pearl Index. Both the reviewer's and the sponsor's table show this to be true in the 68003 study. In the 34219 study, however, the sponsor's Pearl Index is virtually the same for both age groups. Both studies had similar total enrollments (1175 vs. 1145) and age distributions (82% < 35 year vs. 84%); the reason for the similar Pearl Index by age category in the European study is not apparent and is not discussed in the NDA.

The sponsor also analyzed the per protocol contraceptive efficacy by age category. It is the Pearl Index of the Intent-to-Treat Group (or the All-Subjects-Treated Group) that is traditionally used by the FDA for contraceptive approval and labeling. The larger ITT group clearly represents what is called "typical use" or "actual use" or "user failure," so the Pearl Index in this group is more realistic for both the patient and healthcare provider to use. The reviewer Pearl Index of 2.02 in the ITT group < 35 years old in the US 68003 study is borderline high compared to oral contraceptive data from large controlled clinical trials. The reviewer's combined Pearl Index of 1.30 in women < 35 years is obviously better and acceptable.

Life Table Estimates

In Figure 2 on the next page, the cumulative ITT pregnancy-probabilities associated with Studies 68003 and 34219 are graphically displayed. The overall cumulative probability of an ITT in-treatment pregnancy after one year of NuvaRing® use is estimated to be 1.18% (95% CI: 0.68-1.69; Analysis 8.1.3.A.3 in Appendix B).

Figure 1 Cumulative Probability of ITT In-Treatment Pregnancy by Trial – Studies 68003 and 34219 (Intent-to-Treat Group)



Data is from Appendix B, Figure 8.1.3.A.

The 13 cycle Life-Table cumulative pregnancy rate for NuvaRing is estimated as 1.18%. Cumulative pregnancy rates for each cycle are provided above by the sponsor. These data are based on the Intent-to-Treat Evaluation Group, which included all subjects who contributed information on extent of exposure.

Reviewer's comment:
The above graph is another representation of the overall difference in the two large trials in terms of the subjects' probability of becoming pregnant. The sponsor offers no explanation for the marked difference between the two studies.