CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-187

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA:	**21-187**
Compound:	11.7 mg etonogestrel/2.7 mg ethinyl estradiol vaginal ring, NuvaRing®
Sponsor:	Organon Inc.
Type of Submission:	New Drug Product; Classification, 1,4 S
Date of Submission:	August 2, 2001, labeling
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the Clinical Pharmacology and Drug Interactions sections of NDA 21-187's labeling submission dated August 2, 2001. OCPB/DPEII has no changes to recommend for this August 2, 2001 labeling.

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

FT signed by Ameeta Parekh, Ph.D., Team Leader 9/ /2001
cc: NDA 21-187, HFD-870 (H. Malinowski, A. Parekh, J. Lau), HFD-580 (D. Davis, J. Mercier), CDR (B. Murphy for Drugs)

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA:	**21-187**
To:	**HFD-580**
Place:	PKLN 17B43
Compound:	etonogestrel/ethinyl estradiol ring, NuvaRing®
Sponsor:	Organon Inc.
Date:	February 24, 2000 9:00 a.m.
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background:

NDA 21-187 (NuvaRing®, [redacted]) for a combined contraceptive vaginal ring was submitted on December 28, 1999. NuvaRing® contains 11.7 mg etonogestrel (ENG) and 2.7 mg ethinyl estradiol (EE). It releases daily 0.12 mg ENG and 0.015 mg EE for 21 days. Each ring should be used for 1 cycle. A cycle is 21 days of ring use followed by a 7-day ring-free period. ENG is a new molecular entity.

Comments:

1. Sponsor conducted 3 non-U.S. studies (34218, 34225, and 34226) to assess the clinical pharmacokinetics (PK) and pharmacodynamics (PD) of ENG and EE for NDA 21-187 (Attachment).
2. Study 34218 **i)** assessed the PK of ENG and EE upon NuvaRing® administration, **ii)** assessed the absorption rate and absolute bioavailability (BA) of ENG and EE for NuvaRing®, **iii)** compared the PK of ENG and EE for NuvaRing® with those upon oral administration of 0.15 mg desogestrel and 0.03 mg EE (Marvelon® tablet), and **iv)** evaluated the effects of NuvaRing® on ovarian function (PD). 2 groups of randomized subjects participated in this study. Group 1 treatment consisted of 21 days of Marvelon® intake, a 7-day pill-free period, 35 days of NuvaRing® use, a 3-day ring-free period and an ENG/EE (0.15 mg/0.03 mg) intravenous injection. Subjects in Group 2 received the same treatment, except they started with NuvaRing®, then had their Marvelon® treatment followed by the ENG/EE IV injection.
3. Study 34225 assessed the effect of either nonoxynol-9 (spermicide) or miconazole nitrate (antimycotic) on the PK of ENG and EE upon coadministration with NuvaRing®. Duration of treatment was 2 cycles. Each cycle consisted of 21-day ring use followed by 7-day ring-free period. Randomized subjects received either treatment A (spermicide) or treatment B (antimycotic). Within each treatment, subjects were randomized to either group I or Group II. Group I started with control cycle followed by interaction cycle, whereas Group II used the reverse order. Control cycle was the 21-day ring use followed by 7-day ring-free period. In the interaction cycle, either spermicide or anti-mycotic was administered on Day 8 of the cycle. Serum ENG and EE concentrations were measured throughout the 2 cycles of each treatment.
4. Study 34226 **i)** assessed the time to ovulation after removal of NuvaRing®, **ii)** evaluated whether further development of follicles with a diameter of at least 13 mm could be blocked by NuvaRing® treatment, and **iii)** assessed a window for removal of NuvaRing® within the period of 21 days. Randomized subjects were assigned to 3 treatments. Treatment of all subjects consisted of 1 control cycle (21-day NuvaRing® use and 7-day ring-free use) and then 1 intervention (2nd) cycle.

Treatment 1's 2nd cycle consisted of 3 days of NuvaRing® use. After ring removal on Day 4, subjects were followed up until ovulation. Treatment 2's 2nd cycle consisted of 21-day ring use after which subjects were followed up until ovulation. Subjects in treatment 3 were not inserted a 2nd NuvaRing® until their follicles with diameter of at least 13 mm were present. After insertion of a 2nd ring, these subjects were followed up for a total of 21 days of NuvaRing® use. PK and PD assessments were performed on the 1st cycle of only treatment 3 and the 2nd cycle of all treatments.

5. Bioanalytical reports for ENG and EE together with validation reports for studies 34218, 34225, and 34226 are provided.
6. Final study report for studies 34218, 34225, and 34226 are also provided.
7. Draft annotated labeling for the Clinical Pharmacology section is provided.
8. In vitro amounts of released ENG and EE are correlated with in vivo serum ENG and EE concentrations (IVIVC). Discussion on IVIVC was provided.
9. Since ENG is a new molecular entity and only information on in vitro human hepatic microsomes study was provided in the original NDA, information on human mass balance of ENG, on specific human enzymes/pathways that metabolizes ENG, and on the induction or inhibition potential of ENG in humans should be submitted by the sponsor as private reports or published literature.
10. Sponsor stated "The formulations used in all clinical trials were identical and the same as the proposed market formulation." in the Human PK/BA summary. However, changes in [redacted] occurred (page 2 of the application cover letter). The validity of whether the clinically-tested formulation is identical to the to-be-marketed formulation needs to be confirmed.
11. Proposed in vitro release method was mentioned in the Human PK/BA summary. However, details of the method such as content of release media and method conditions were abscent. No proposed specifications for the in vitro release of ENG and EE were stated.
12. PK and PD data for studies in electronic diskettes (ASCII format) with user guide should be provided to aid the review.
13. The sponsor is encouraged to provide the labeling and Human PK/BA summary sections of the NDA in electronic Word for Windows files to aid the review. Sponsor provided these sections in Adobe PDF files, which cannot be edited.
14. The potential partner exposure to ENG and EE issue was discussed with the medical reviewer, Jerry Willett, and deemed not clinically significant.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) finds that the Human Pharmacokinetics and Bioavailability section of NDA 21-187 is fileable. Comments 9 to 13 should be conveyed to and addressed by the sponsor.

/S/ February 25, 2006

S.W. Johnny Lau, R.Ph., Ph.D.
(OCPB/DPEII)

FT signed by Ameeta Parekh, Ph.D., Team Leader /S/ 2/25/06

cc: NDA 21-187, HFD-870 (S. Huang, A. Parekh, J. Lau), HFD-580 (G. Willett, J. Mercier), CDR (B. Murphy for Drugs)

Attachment

Table 1 List of NuvaRing® Human Pharmacokinetics and Bioavailability Studies

Study number (Number of sites) Country: Principal investigator (Site #) Start Date End Date Reports Publications	Study design	Age range (Mean) (years)	Treatment and dose	Number of subjects enrolled/ days of exposure	Maximum duration of drug treatment	Batch number */ Plant/ Date manufactured	Location of report Vol/path	Location of CRF tabs Vol/path	Location of CRF Vol/path
HUMAN PHARMACOKINETIC AND BIOAVAILABILITY STUDIES									
34218 (1) Netherlands: Haring (1)	Open-label, randomized, cross-over, pharmacokinetic/ pharmacodynamic, bioavailability	Group I: 22-30 (26.5)	NuvaRing® with a declared daily release rate of 0.120 mg ENG and 0.015 mg EE vaginal	16/ 576 days	35 days	CP 097055/ [redacted] The Netherlands/ May, 1997	1.56-1/62/ hpbio\ hupharm\ 34218	Data Listings crt\domain\ 34218 CRF Tabs ---	---
		Group II: 18-26 (23.0)	Reference therapy: Marvelon®: 0.150 mg desogestrel + 0.030 mg EE tablets po	16/ 335 days	21 days				
Start: January, 1998 End: May, 1998 Publication: None			0.150 mg ENG + 0.030 mg EE ampoule iv	16/ 16 days	1 injection				

Table 1 (continued) List of NuvaRing® Human Pharmacokinetic and Bioavailability Studies

Study number (Number of sites) Country: Principal Investigator (Site #) Start Date End Date Reports Publications	Study design	Age range (Mean) (years)	Treatment and dose	Number of subjects enrolled/ days of exposure	Maximum duration of drug treatment	Batch number */ Plant/ Date manufactured	Location of report Vol/path	Location of CRF tabs Vol/path	Location of CRF Vol/path
HUMAN PHARMACOKINETIC AND BIOAVAILABILITY STUDIES (Continued)									
34225 (1) Netherlands: Haring	Open-label, randomized, within treatment cross-over, pharmacokinetic interaction	A-I: 18-32 (25.5)	Group A: NuvaRing® with a declared daily release rate of 0.120 mg ENG and 0.015 mg EE vaginal	12/ 525 days	2 cycles	CP 097171/ [redacted] The Netherlands/ April, 1998	1.63-1/67/ hpbio\ hupharm\ 34225	Data Listings crt\domain\ 34225 CRF Tabs ---	---
		A-II: 21-35 (25.8)	Spermicide: 4% nonoxynol-9, water-based, gel vaginal	12/ 12 days	1 application				
		B-I: 19-31 (23.0)	Group B: NuvaRing® with a declared daily release rate of 0.120 mg ENG and 0.015 mg EE vaginal	12/ 528 days	2 cycles				
Start: January, 1999 End: May, 1999 Publication: None		B-II: 18-35 (24.5)	Anti-mycotic: 1200 mg miconazole nitrate, oil-based, capsule, vaginal	12/ 12 days	1 application				

Table 1 (continued) List of NuvaRing® Human Pharmacokinetic and Bioavailability Studies

Study number (Number of sites) Country: Principal Investigator (Site #) Start Date End Date Reports Publications	Study design	Age range (Mean) (years)	Treatment and dose	Number of subjects enrolled/ days of exposure	Maximum duration of drug treatment	Batch number */ Plant/ Date manufactured	Location of report Vol/path	Location of CRF tabs Vol/path	Location of CRF Vol/path
HUMAN PHARMACOKINETIC AND BIOAVAILABILITY STUDIES (Continued)									
34226 (1) Netherlands: Haring (1) Start: January, 1999 End: June, 1999 Publication: None	Open-label, single center, pharmacokinetic, pharmacodynamic	Group I: 20-35 (26.5) Group II: 20-35 (25.3) Group III: 18-32 (22.2)	NuvaRing® with a declared daily release rate of 0.120 mg ENG and 0.015 mg EE vaginal	19/ 390 days 17/ 660 days 15/ 660 days	1 cycle followed by 3 additional days of treatment 2 cycles 1 cycle followed by no treatment until follicle size ≥13-15 mm, then 1 cycle	CP 097171/ [redacted] The Netherlands/ April 1998	1.68-1/73/ hpbio\ hupharm\ 34226	Data Listings crt\domain\ 34226 CRF Tabs ---	crt\34226

EE = Ethinylestradiol; ENG = Etonogestrel; IND = Investigative New Drug application; iv = Intravenous; NA = Not applicable; NDA = New Drug Application; po = per os (oral)

* Complete information on batch No., plant of manufacture and date manufactured can be found in Item 3 of this NDA

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA:	**21-187**
Compound:	11.7 mg etonogestrel/2.7 mg ethinyl estradiol vaginal ring, NuvaRing®
Sponsor:	Organon Inc.
Type of Submission:	New Drug Product; Classification, 1,4 S
Date of Submission:	Original, December 28, 1999; B2, April 21, 2000; Amendment August 11, 2000; Amendment October 6, 2000; Chemistry Amendment November 14, 2000; Industry Meeting November 16, 2000; Telephone Conference December 11, 2000.
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Synopsis

NDA 21-187 (NuvaRing®, [redacted] for a combined contraceptive vaginal ring (CCVR) was submitted on December 28, 1999. NuvaRing® contains 11.7 mg etonogestrel (ENG) and 2.7 mg ethinyl estradiol (EE). It nominally releases 120 µg ENG and 15 µg EE daily for 21 days. Each ring should be inserted for 1 cycle. A cycle is 3 weeks of ring use followed by a 7-day ring-free interval. ENG (Org 3236) is a new molecular entity and a biologically active metabolite of desogestrel (DSG), which is a progestin. Sponsor submitted results for 7 studies (34218, 34225, 34226, 85012, 86016, SDG RR 2601, [redacted] and 1 submitted publication manuscript to support the Human Pharmacokinetics and Bioavailability section of NDA 21-187. This is a question-based review.

The vaginal EE dose was based on clinical experience with EE oral contraceptive and absolute vaginal bioavailability. The vaginal ENG dose was based on clinical experience with 3 Silastic® prototype vaginal rings. The clinically-tested drug formulation is identical to the to-be-marketed drug formulation.

Study [redacted] was originally submitted for NDA 20-713's Phase IV commitment mass balance study for Mircette™/Organon (DSG/EE and EE oral tablets). [redacted]

Studies 34218 and 34226 provided the single dose and multiple dose pharmacokinetics, respectively, for NuvaRing®. ENG and EE do not accumulate upon repeated cycles of CCVR administration. Only 1 dose strength of NuvaRing® is being sought for approval. Studies 34226 and 34218 provided pharmacodynamic data for NuvaRing®.

Sponsor conducted Study 34225 to assess the interaction potential of NuvaRing® with nonoxynol-9 (spermicide in a water-based formulation) and miconazole nitrate (anti-mycotic in an oil-based formulation). Miconazole nitrate increased area under the serum ENG and EE concentration-time curves (AUC) by about 17% and 16%, respectively. Nonoxynol-9 did not affect the serum ENG and EE AUCs. During the Clinical Pharmacology and Biopharmaceutics Briefing on August 31, 2000, medical officer suggested that sponsor should conduct in vitro dissolution tests to characterize the dissolution of NuvaRing® in the presence and absence of the oil-based different doses of

miconazole nitrate vaginal capsule and other oil-based vaginal products. Sponsor agreed to conduct in vivo drug interaction studies of oil-based vaginal anti-mycotic preparation with NuvaRing® as postapproval Phase IV commitment, per telephone conference on December 11, 2000. Hence, the in vitro dissolution tests become unnecessary.

ENG and EE are primarily metabolized via cytochrome P450 3A4 isoenzyme (CYP3A4). Sponsor did not conduct any study to address the interaction potential of NuvaRing® with systemic CYP3A4 inducers and inhibitors as well as the inducing and inhibiting potential of both ENG and EE on CYP3A4 and conjugation enzymes. Sponsor did not conduct studies for NuvaRing® in any special populations and did not submit any population pharmacokinetic analysis.

Sponsor did not provide either internal or external validations for the ENG and EE IVIVC. Hence, the proposed ENG and EE IVIVC for NuvaRing® are not acceptable yet.

The recommended in vitro release specifications for ENG and EE from NuvaRing® and acceptance criteria are in the response of Question 22 below (pages 30 to 31).

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 21-187 dated December 28, 1999. OCPB/DPEII finds that the submitted information supports the Human Pharmacokinetics and Bioavailability section of NDA 21-187. However, the following comments should be communicated to the sponsor:

- Sponsor is strongly encouraged to conduct in vivo and in vitro drug interaction studies for etonogestrel and ethinyl estradiol with systemic cytochrome P450 3A4 isoenzyme inducers and inhibitors as well as to determine the induction and inhibition potential of etonogestrel and ethinyl estradiol to cytochrome P450 3A4 isoenzyme and conjugation enzymes for better characterization of NuvaRing®'s drug interaction potential.
- The proposed etonogestrel and ethinyl estradiol in vitro/in vivo correlations are not acceptable at this time. Sponsor should address the first five comments listed at the end of Question 21 in this review (pages 28 to 29).

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

A Required Inter-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 21-187 was conducted on August 31, 2000; participants included S. Huang, M. Mehta, A. Selen, D. Lin, G. Willett, D. Davis, J. Hunt, A. Parekh, and J. Lau. Sponsor accepted the recommended in vitro release specifications for NuvaRing®. NuvaRing® Clinical Pharmacology labeling comments have been communicated to the sponsor.

FT signed by Ameeta Parekh, Ph.D., Team Leader 12/ /2000
cc: NDA 21-187, HFD-870 (H. Malinowski, A. Parekh, J. Lau), HFD-580 (D. Davis, D. Lin, J. Mercier), CDR (B. Murphy for Drugs)

The following questions, based on the content of NDA 21-187, guided this review.

1. What is NuvaRing®?

NuvaRing® is a non-degradable, flexible, transparent, 1-compartment combination contraceptive vaginal ring (CCVR) that contains 11.7 mg ENG and 2.7 mg EE. NuvaRing®'s core is made of ethylene vinylacetate (EVA) copolymer with 28% vinyl acetate. NuvaRing®'s skin is made of EVA copolymer with 9% vinyl acetate. Its outer diameter is 54 mm and cross-sectional diameter is 4 mm.

2. What is the proposed indication for NuvaRing®?

Prevention of pregnancy while providing menstrual cycle control.

3. What is ENG used for?

ENG is the 3-keto biologically active metabolite of DSG, which is a progestin. ENG is available in Europe as a 3-year implant of 68 mg ENG for contraception [redacted].

4. What is EE used for?

EE is a synthetic estradiol (E_2) analog. EE is used alone to treat moderate to severe vasomotor symptoms associated with menopause (Estinyl/Schering oral tablets). EE is used with progestins as oral contraceptives (Ortho-Novum®/Ortho-McNeil, Tri-Levlen®/Berlex, etc. tablets). EE with norethindrone (5 µg/1 mg) is indicated to treat moderate to severe vasomotor symptoms associated with menopause and for the prevention of osteoporosis (femhrt®/Parke-Davis). EE is also used to treat female hypogonadism and palliatively treat malignant prostate neoplasms.

5. What is the rationale of combining ENG and EE? How does NuvaRing® work?

Progestin only contraceptive results in irregular bleeding. Continuous estrogen use may lead to endometrial hyperplasia. Therefore, combining ENG and EE may minimize their adverse effects and maximize their therapeutic effects.

Estrogen and progestin contraceptives primarily act via suppression of ovulation (Hatcher and Guillebaud *The Pill: Combined Oral Contraceptives* in *Contraceptive Technology* 1998 ed., page 406). Individual effects follow:

Estrogenic:

- Suppression of gonadotropins release, namely follicle stimulating hormone (FSH) and luteinizing hormone (LH) and thereby inhibits ovulation.
- Alteration of secretion and cellular structure of endometrium, which leads to areas of edema alternating with areas of dense cellularity.

Progestational:

- Ovulation is inhibited via suppression of LH.
- Cervical mucus is thickened, hampering sperm transport.
- Capacitation of sperm may be inhibited.
- Implantation is hampered via production of a decidualized endometrial bed with exhausted and atrophied glands.

6. What are the adverse effects of ENG and EE (not from NuvaRing®)?

Use of combined oral contraceptive increases the risk of venous thromboembolism, ischemic heart disease, and stroke. Prolonged and particularly continuous use of EE without cyclical progestins may lead to endometrial hyperplasia, and rarely, to endometrial carcinoma.

7. What studies results are submitted to support the Human Pharmacokinetics (PK) and Bioavailability (BA) section of NDA 21-187?

CCVR	Study	Review Question
Dose finding	85012 and 86016	10
In vitro plasma protein binding	SDG RR 2601	12
In vitro metabolism	Gentile et al's 1999 manuscript	12
[redacted]		
Single dose PK	34218	14
Multiple dose PK	34226	19
Relative BA to intravenous administration	34218	14
Relative BA to oral contraceptive	34218	14
Interaction with vaginal spermicide	34255	15
Interaction with vaginal anti-mycotic	34255	15
PK/pharmacodynamics (PD)	34226 and 34218	18
In vitro/in vivo correlation (IVIVC)	34218	21
In vitro release	-	22
Proposed labeling	numerous	23

8. What are the clinical safety and efficacy studies results that support the approval of NDA 21-187?

Sponsor conducted 2 pivotal, adequate, and well-controlled studies (068003 and 34219) to support the safety and efficacy claim for NDA 21-187. Study 068003 is an U.S. study and study 34219 is a non-U.S. study.

9. What is the proposed dose for NuvaRing®?

A NuvaRing® is inserted into the vagina and remain there for 3 continuous weeks. The ring is then removed for 1 week, during which menstrual bleeding usually occurs, and then a new ring is inserted. NuvaRing® contains 11.7 mg ENG and 2.7 mg EE and nominally releases 120 μg ENG and 15 μg EE daily for 21 days.

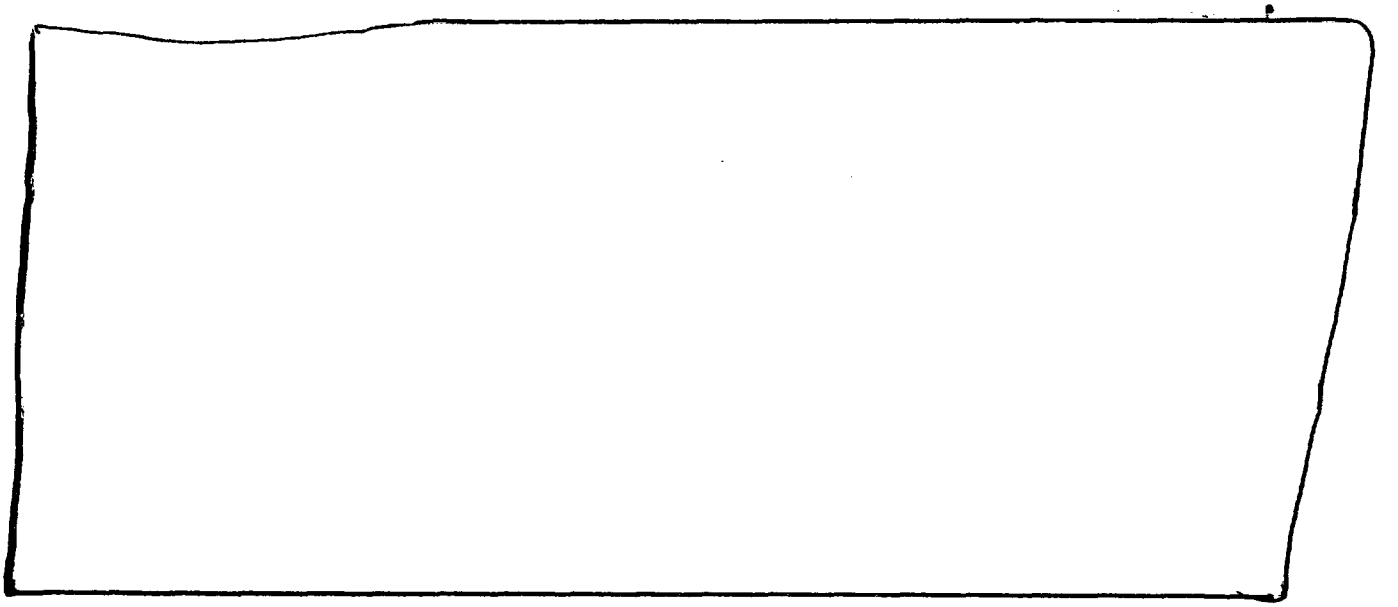
10. How is the NuvaRing® dose determined?

EE dose selection:

Clinical experience with oral 150 μg DSG and 20 μg EE tablet daily showed that 20 μg EE daily appeared to be acceptable for both bleeding patterns and estrogen replacement. Vaginal EE BA is 0.74 ± 0.16 upon intravenous and vaginal administration of 250 μg levonorgestrel (LNG) with 50 μg EE (Back et al. *Contraception* 36:471 1987). Therefore, 15 μg EE daily dose was selected for the early development of CCVR.

ENG dose selection:
Dose finding studies for ENG were conducted with 15 μg EE daily dose to establish optimal ENG release rate with respect to ovulation inhibition and bleeding pattern. Three Silastic® prototype vaginal rings (daily dose of 75 μg ENG/15 μg EE, 100 μg ENG/15 μg EE, and 150 μg ENG/15 μg EE) were tested in Studies 85012 and 86016, which results were directly compared with that upon daily oral administration of 150 μg DSG/30 μg EE tablet. Daily vaginal dose of 75 μg ENG/15 μg EE is insufficient for adequate ovulation inhibition. Daily vaginal doses of 100 or 150 μg ENG with 15 μg EE demonstrated not only ovulation inhibition but also acceptable bleeding patterns. However, daily release rate of 100 μg ENG showed pronounced ovarian activity (Study 86016). Moreover, this kind of vaginal controlled-release system showed 10 - 20% larger variation in the release of hormones than that for tablets.. Therefore, 120 μg ENG daily dose was selected for the CCVR.

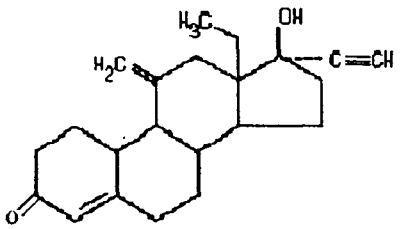
11. What are the bioanalytical methods for ENG and EE used in NDA 21-187?
Both bioanalytical methods for ENG and EE in Studies 34218, 34225, and 34226 (3 major studies to support the Human Pharmacokinetics and Biopharmaceutics section of NDA 21-187) involved the extraction of ENG, EE, and an internal standard from human serum. The extracted sample was separated via high pressure liquid chromatography and quantified via radioimmunoassay.



Sponsor did not provide the intra-assay accuracy validation for ENG and EE. Sponsor did not measure any metabolites for ENG and EE in Studies 34218, 34225, and 34226.

12. What are the clinical PK of ENG and EE (not from formulation related to NuvaRing®)?

ENG



$C_{22}H_{28}O_2$

Absorption

Absolute BA of ENG upon vaginal administration of 3-compartment Silastic® vaginal rings for the daily dose of 75 µg ENG/15 µg EE, 100 µg ENG/15 µg EE, and 150 µg ENG/15 µg EE are 97, 102, and 100%, respectively (C.J. Timmer et al. *Contraception* 42:629 1990). The intravenous (IV) dose was 150 µg ENG and 30 µg EE in Timmer et al.'s study.

Distribution

ENG is 31.6% bound to sex hormone binding globulin (SHBG) and 65.9% bound to albumin in blood (Kuhnz et al. *J. Steroid Biochem.* 35:313 1990). The dissociation constant (K_d) for ENG to SHBG is 4.7 nM via centrifugal ultrafiltration at 37°C (Hammond et al. *Contraception* 50:301 1994). The K_d for ENG to albumin is unknown. Progestin suppresses plasma SHBG concentrations (G. Cullberg *Pharmacology of the Contraceptive Steroids* 1994 ed., page 358). The ENG volume of distribution is 88 ± 39 L (mean ± s.d.; C.J. Timmer et al. *Contraception* 42:629 1990).

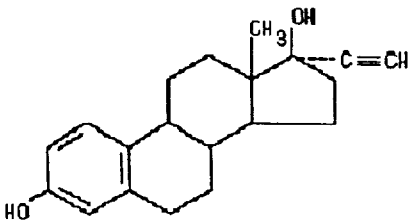
Study SDG RR2601 assesses the in vitro ENG protein binding in healthy female plasma via equilibrium dialysis at 37°C. The studied ENG concentration range was 500 - 5000 pg/mL and EE was added in a concentration ratio of 1:10 and 1:5 (EE:ENG by weight). In this study, ENG was 98.38 ± 0.11% plasma protein bound without information on the specific proteins that ENG was bound. ENG binding was not concentration-dependent. Addition of EE did not influence ENG plasma protein binding.

Metabolism

Cytochrome P450 3A4 (CYP3A4) mediates the metabolism of ENG to 6β-hydroxy ENG and 6β,13 ethyl-dihydroxy ENG as major metabolites in in vitro human liver microsomes (Gentile et al. *submitted manuscript for publication 1999*). The biological activity of these ENG metabolites is unknown (confirmed with Dr. Krishan Raheja, Pharmacology/Toxicology reviewer). No evidence of ENG metabolism via other studied enzymes (CYP 1A1, 1A2, 2C8, 2C9, and 2C19) was observed (Gentile et al. *manuscript 1999*).

The ENG elimination half-life is 15.0 ± 1.9 (mean ± s.d.) hours upon intravenous administration of 150 µg ENG/30 µg EE (C.J. Timmer et al. *Contraception* 42:629 1990). The ENG clearance is 5.0 ± 1.9 L/h (mean ± s.d.; C.J. Timmer et al. *Contraception* 42:629 1990).

EE



$C_{20}H_{24}O_2$

Absorption

Absolute BA of EE upon vaginal administration of 3-compartment Silastic® vaginal rings for the daily dose of 75 µg ENG/15 µg EE, 100 µg ENG/15 µg EE, and 150 µg ENG/15 µg EE are 58, 83, and 82%, respectively (C.J. Timmer et al. *Contraception* 42:629 1990). The IV dose was 150 µg ENG and 30 µg EE in Timmer et al.'s study. The oral BA of EE ranges from 38 - 48% (J.W. Goldzieher and S.A. Brody *Am. J. Obstet. Gynecol.* 163:2114 1990).

Distribution

EE is 95% bound in plasma, virtually all bound to albumin, with an equilibrium-association constant similar to that of estrone (J.W. Goldzieher *Pharmacology of the Contraceptive Steroids* 1994 ed., page 137). The K_d for EE to albumin is 12 - 18 µM via equilibrium dialysis at 4°C (N. Jenkins et al. *J. Endocrinol.* 87:12P 1980). EE does not bind to SHBG (M.L'E. Orme et al. *Clin Pharmacokinet.* 8:95 1983). EE stimulates the hepatic synthesis of plasma SHBG, cortisol binding globulin, ceruloplasmin, and other proteins; EE may reduce plasma haptoglobulin, orosomucoid, and albumin concentrations (Dollery et al. *Therapeutic Drugs* Supplement 1, 1992 ed, page E65, Churchill Livingstone). Almost all the EE sulfate (an EE metabolite) is albumin bound (Dollery et al. *Therapeutic Drugs* Supplement 1, 1992 ed, page E66, Churchill Livingstone). The EE volume of distribution is 167 ± 46 L (mean ± s.d.; C.J. Timmer et al. *Contraception* 42:629 1990).

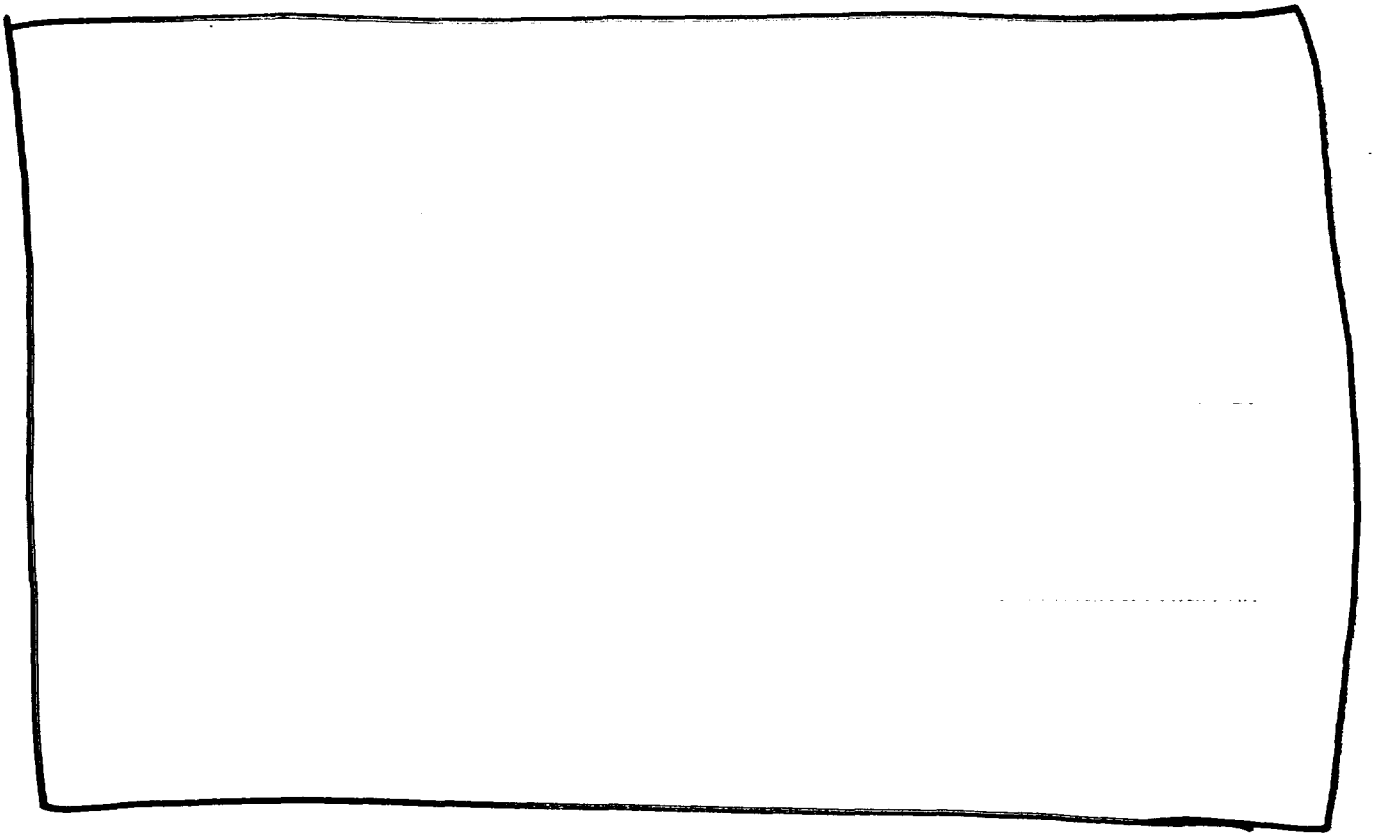
Metabolism

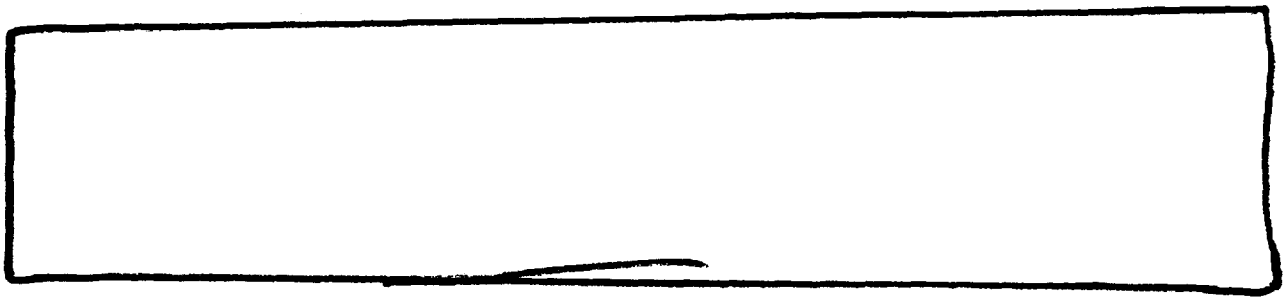
CYP3A4 mediates the metabolism of EE to 2-hydroxy EE as the major metabolite in in vitro human liver microsomes (H.S. Purba et al. *Br. J. Clin. Pharmacol.* 23:447 1987; F.P. Guengerich *Mol. Pharmacol.* 33:500 1988; F.P. Guengerich *Life Sci.* 47:1981 1990). Hydroxylation at the 16β- and 6α- positions of EE were reported as minor metabolic pathways (H.S. Purba et al. *Br. J. Clin. Pharmacol.* 23:447 1987; F.P. Guengerich *Life Sci.* 47:1981 1990). The extent of each EE metabolic pathway is unknown. 2-Hydroxylation was reported to account for about 29% of the ingested dose but in some individuals this figure may be as high as 64% (M.L'E. Orme et al. *Clin Pharmacokinet.* 8:95 1983). 2-Hydroxylation of EE may also be mediated via other CYPs (M.L'E. Orme et al. *Pharmac. Ther.* 43:251 1989). CYP2C and CYP2E enzymes also mediate the 2-hydroxylation of EE, although the relative contribution of CYP3A and CYP2C enzymes to 2-

hydroxylation of EE are still unknown (S.E. Ball et al. *Biochem. J.* 267:221 1990). Recent vaccinia virus cDNA expressed human CYPs data show that CYP3A3, CYP3A4, and CYP3A5 are involved in the oxidation of EE, but the major oxidation product may not be 2-hydroxy EE (A.K. Olsen et al. *ISSX Proceedings, 4th International ISSX Meeting, Seattle WA* 8:90 1995). Hydroxylated EE metabolites have little estrogenic activity (Dollery et al. *Therapeutic Drugs* Supplement 1, 1992 ed, page E66, Churchill Livingstone). EE undergoes conjugation with glucuronic acid and sulfate (F.P. Guengerich *Life Sci.* 47:1981 1990). EE sulfation occurs primarily in the small intestinal mucosa, whereas EE glucuronic acid conjugation is mainly a hepatic affair (M.L. Orme and D.J. Back *Am. J. Obstet. Gynecol.* 163:2146 1990). In vitro studies with jejunal biopsy samples or larger pieces of jejunum or terminal ileum mounted in Ussing chambers have indicated that > 30% of added EE is sulfated (D.J. Back et al. *Am. J. Obstet. Gynecol.* 163:2138 1990). EE conjugation occurs primarily at the 3 position but can occur at the 17 position (M.L. Orme and D.J. Back *Am. J. Obstet. Gynecol.* 163:2146 1990). Plasma 3-sulfate EE concentrations are an order of magnitude higher than unconjugated plasma EE concentrations (F.P. Guengerich *Life Sci.* 47:1981 1990). EE conjugates are excreted in the bile to the colon (M.L. Orme and D.J. Back *Am. J. Obstet. Gynecol.* 163:2146 1990). Bacteria in the colon can hydrolyze these conjugates and liberate unconjugated EE, which can be reabsorbed into the body and complete the enterohepatic recirculation cycle.

Elimination

The EE elimination half-life is 19.0 ± 3.3 (mean ± s.d.) hours upon intravenous administration of 150 µg ENG/30 µg EE (Timmer et al. *Contraception* 42:629 1990). The EE terminal half-life ranges from 13.1 - 27.0 hours (Goldzieher and Brody *Am. J. Obstet. Gynecol.* 163:2114 1990). The EE clearance is 8.2 ± 3.3 L/h (mean ± s.d.; C.J. Timmer et al. *Contraception* 42:629 1990).

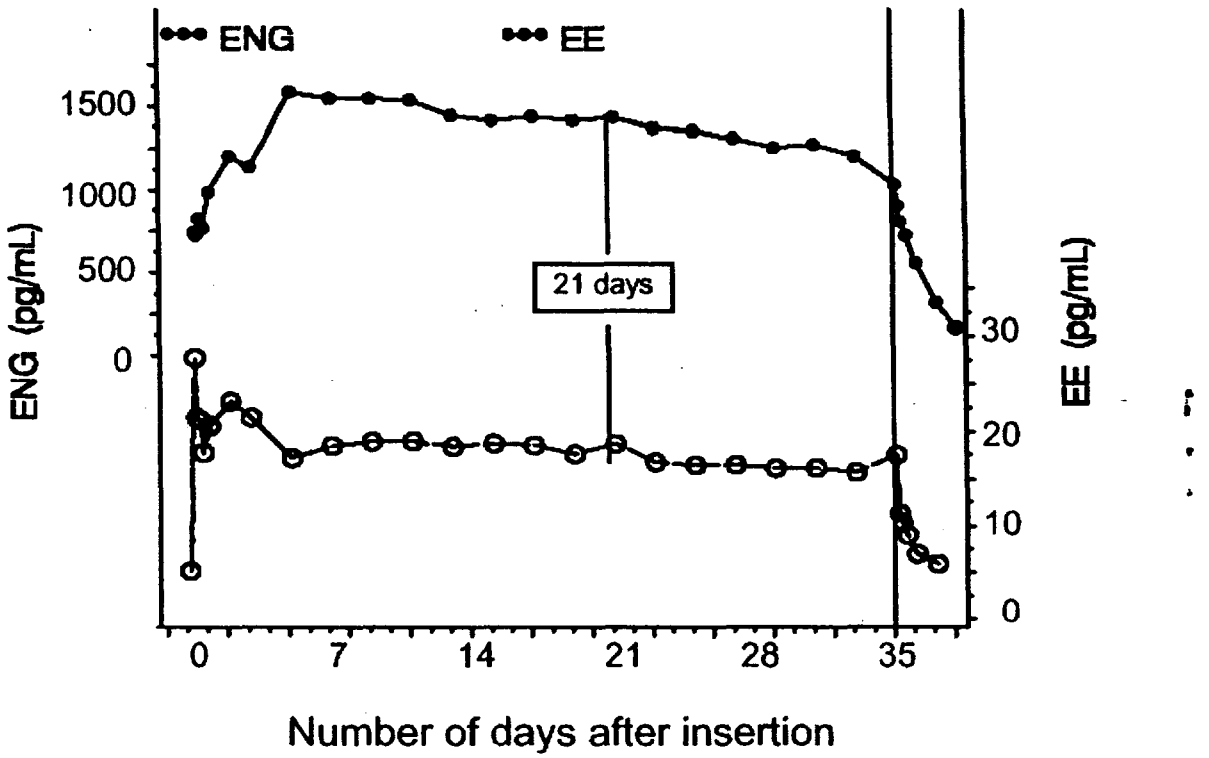




14. What is the absolute BA of NuvaRing® and relative BA of NuvaRing® to Marvelon®?
Study 34218 was a Phase IIIa, open-label, randomized, cross-over, PK/PD trial of the 1-compartment EVA CCVR versus Marvelon® in healthy female subjects. This study primarily assesses the: 1) PK of ENG and EE as released from the CCVR; 2) absorption rate and absolute BA of ENG and EE as released from the CCVR; 3) comparative PK of ENG and EE as released from the CCVR with that of Marvelon®; 4) effects of ENG and EE as released from the CCVR on ovarian function (PD). After screening, subjects were randomly allocated to either 1 of 2 groups. Group 1 subjects' treatment schedule consisted of 21 days of oral Marvelon® (150 µg DSG/30 µg EE), a 7-day tablet-free period, 35 days of CCVR use, a 3-day ring-free period and an 150 µg ENG/30 µg EE IV injection. Group 2 subjects received the same treatments except they started with the CCVR, then have their Marvelon® treatment period followed by the ENG/EE IV injection. To assess the PD of the CCVR, the trial assessments of Group 2 subjects started in the tablet-free period preceding the start of the CCVR treatment period. ENG and EE PK were assessed on the last day of Marvelon® intake, during the whole CCVR treatment period, and following the ENG/EE IV injection. PD of the CCVR was assessed before, during and after the CCVR treatment period via monitoring of ovarian function (vaginal ultrasound and analysis of serum hormone concentrations). The schematic of Study 34218 is in Attachment 1.

Sponsor's justifications for the 35-day CCVR use in Study 34218 instead of 21-day use were to: 1) assess the PK of ENG and EE as released from the CCVR, if a woman forgot to remove the ring after a 21 day period. 2) justify the lower release specification (Day 21) of 80 µg ENG and 10 µg EE (see Question 22 below). Since the release profile showed a slowly decreasing in vitro release rate for ENG to about 11 µg/day and EE to 80 µg/day at Day 35, the lower release specifications was studied by extending the ring use period to 35 days. 3) establish a quantitative correlation between the in vitro release rate and the in vivo absorption.

Figure 7 Serum ENG and EE Concentrations During NuvaRing® Treatment



The top curve indicates ENG and the lower curve indicates EE. The left ordinate indicates ENG and the right ordinate indicates EE.

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Table 18 Means and Standard Deviations (Mean±SD) of the ENG and EE Pharmacokinetic Parameters

Treatment	Parameter	ENG			EE		
CCVR	t_{max} (h)	200.30	±	69.58	59.26	±	67.53
	C_{max} (pg/mL)	1716	±	445	34.68	±	17.47
	Slope (pg/mL/day)	-14.57	±	11.20	-0.11	±	0.14
	$t_{½}$ (h)	29.28	±	6.09	44.72	±	28.78
	Apparent CL (L/h)	3.35	±	0.80	34.76	±	11.62
	In-vivo RR (µg/day) (35 days)*	107.43	±	2.57	14.55	±	0.73
	Absolute Bioavailability (%)**	102.86	±	12.82	55.60	±	12.88
Marvelon®	t_{max} (h)	1.30	±	0.76	1.18	±	0.39
	C_{max} (pg/mL)	4273	±	830	124.88	±	46.32
	$t_{½}$ (h)	30.17	±	5.15	29.50	±	16.73
	AUC_{0-24} (ng*h/mL; pg*h/mL)	38.81	±	11.77	827.23	±	258.38
	Average SS-concentr. (pg/mL)	1617	±	491	34.47	±	10.77
	Minimum SS-concentr. (pg/mL)	1004	±	405	17.20	±	7.03
	Apparent CL (L/h)	4.37	±	1.21	39.60	±	12.19
	Absolute Bioavailability (%)**	79.24	±	7.70	53.77	±	17.60
IV***	t_{max} (h)	0.08	±	0.00	0.08	±	0.00
	C_{max} (pg/mL)	10298	±	2585	598	±	191
	$t_{½}$ (h)	28.43	±	3.39	37.18	±	19.97
	$AUC_{0-\infty}$ (ng*h/mL; pg*h/mL)**	50.82	±	15.65	1939	±	824
	CL (L/h)	3.65	±	0.90	19.02	±	4.93
	V (L)	148.64	±	37.62	980.04	±	540.83

app = apparent; RR = release rate; SS = steady state

* based on remnant content

** corrected for pre-dose concentration

*** Subjects 0001, 0004, 0005, 0006, 0007, 0009, and 0010 were excluded from the pharmacokinetic calculations for the IV data for both ENG and EE due to contamination of the samples.

Serum ENG concentrations for the CCVR showed a continuous increase during the 1st week, followed by a decrease of the concentrations of approximately 100 pg/mL per week during the next 4 weeks of CCVR use. The mean serum ENG concentration after 1 week of CCVR use was similar to the mean steady state serum ENG concentration upon Marvelon® administration. The mean ± s.d. absolute BA of ENG for the CCVR was higher than that for Marvelon®: 102.86 ± 12.82% versus 79.24 ± 7.70%, respectively. The ENG absorption rate showed a downward trend of approximately 24% during the last 4 weeks of CCVR use: 122.30 mg/day after 1 week of CCVR use to 93.47 mg/day after 5 weeks of CCVR use (see Table 4 in Question 21 below for details). ENG t½ were 29.28 ± 6.09, 30.17 ± 5.15, and 28.43 ± 3.39 hours for vaginal, oral, and IV administration, respectively. For the 3 3-compartment Silastic® ring (75 µg ENG/15 µg EE, 100 µg ENG/15 µg EE, and 150 µg ENG/15 µg EE), Marvelon® oral tablet (150 µg DSG/30 µg EE), and IV injection (150 µg ENG/15 µg EE), the resulted corresponding ENG t½ are 22.0 ± 10.5, 22.0 ± 9.4, and 23.9 ± 11.5 (vaginal), 24.1 ± 6.2 (oral), and 15.0 ± 1.9 (IV) hours, respectively (Timmer et al. *Contraception* 42:629 1990). The ENG t½ observed in Study 34218 were longer than those observed by Timmer et al.

Serum EE concentrations for the CCVR showed an initial increase to reach a maximum 2 - 3 days after insertion. After that, serum EE concentrations gradually decreased at approximately 0.77

pg/mL per week during Weeks 2, 3, 4, and 5 of CCVR use. The mean ± s.d. absolute BA of EE for the CCVR and Marvelon® were 55.60 ± 12.88% and 53.77 ± 17.60%, respectively. It is unknown why the mean vaginal absolute BA for EE was low (55.60%). The EE absorption rate showed a downward trend of approximately 8% during the last 4 weeks of CCVR use: 8.55 µg/day after 1 week of CCVR use to 7.86 µg/day after 5 weeks of CCVR use (see Table 5 in Question 21 below for details). EE t½ were 44.72 ± 28.78, 29.50 ± 16.73, and 37.18 ± 19.97 hours for vaginal, oral, and IV administration, respectively. For the 3 3-compartment Silastic® ring, Marvelon® oral tablet, and IV injection, the corresponding EE t½ are 21.7 ± 13.0, 18.4 ± 12.0, and 18.8 ± 11.2 (vaginal), 20.8 ± 10.9 (oral), and 19.0 ± 3.3 (IV) hours, respectively (C.J. Timmer et al. *Contraception* 42:629 1990). The EE t½ observed in Study 34218 were also longer (consistent with the observation for ENG t½ above) and more variable than those observed by C.J. Timmer et al.

See Question 18 below for the PD results of Study 34218.

On average, the SHBG concentrations during CCVR treatment were found to be slightly higher for Group 1 (about 210 nmol/L on Days 50-64) than that for Group 2 (about 180 nmol/L on Days 22-36). This difference in SHBG concentrations may be attributed to the exposure difference to ENG/EE between Group 1 (Marvelon® and then CCVR) and Group 2 (CCVR). At the moment of IV bolus administration, a similar mean SHBG concentration for both groups was found: about 192 nmol/L.

Sponsor has published Study 34218's results in September 2000 (C.J. Timmer and T.M.T. Mulders *Clin. Pharmacokinet.* 39:233 2000).

15. What is the drug interaction potential for ENG and EE upon intravaginal NuvaRing® administration?

SHBG concentrations were assessed during and after 6 cycles of NuvaRing® use and compared to those during and after 6 cycles of daily oral 150 µg LNG/30 µg EE administration (1 cycle is 21 days of active drug use [redacted] and 7 days of tablet-free period; Study 34220). Blood samples for measurement of SHBG were obtained at screening and at the end of Cycles 3 and 6 for each treatment. Six cycles of NuvaRing® use resulted in a statistically significant higher increase in SHBG compared to those with LNG/EE oral contraceptive treatment. This reviewer discussed with Medical reviewer, Dr. Daniel Davis, and no unusual safety or efficacy issues upon 6 cycles of NuvaRing® use.

Both ENG and EE are primarily metabolized via CYP3A4. EE is a mechanism-based inactivator of CYP3A4 in in vitro human liver microsomes and the partition ratio (number of times that an enzyme turns over a substrate before it is inactivated) is about 120 (F.P. Guengerich *Mol. Pharmacol.* 33:500 1988). EE (100 µmol/L or 29.64 µg/mL) can inhibit CYP3A4 in vitro (F.P. Guengerich *Am. J. Obstet. Gynecol.* 163:2159 1990). ENG is also a mechanism-based inactivator of CYP3A4 and can inhibit (ENG: 100 µmol/L or 32.65 µg/mL) CYP3A4 metabolism in in vitro human liver microsomes (F.P. Guengerich *Am. J. Obstet. Gynecol.* 163:2159 1990). In in vitro human liver microsomes, EE inhibits the metabolism of cyclosporin (A. Lampen et al. *Pharmacol.* 52:159 1996), mifepristone (G.R. Jang and L.Z. Benet *ISSX Proceedings, 4th International ISSX Meeting, Seattle WA* 8:92 1995; G.R. Jang et al. *Biochem. Pharmacol.* 52:753 1996), tacrolimus (U. Christians et al. *Br. J. Clin. Pharmacol.* 41:187 1996), and E_2 (V. Kerlan et al. *Biochem.*

Pharmacol. 44:1745 1992). The K_i for EE to inhibit the metabolism of cyclosporin to AM1 is 185 ± 15 μM (mean ± sd). The K_i for EE to inhibit the tacrolimus metabolism is 117 ± 11 μM (mean ± sd); however, authors reported that this is a competitive inhibition. Since both EE and ENG are CYP3A4 mechanism-based inactivators and the K_i for EE and ENG on CYP3A4 are unknown, the potential for both ENG and EE to interact with other CYP3A4 substrates via CYP3A4 inhibition cannot be assessed.

The inducing effects of both ENG and EE on CYP isoenzymes and conjugation enzymes are unknown (confirmed with Dr. Krishan Raheja, Pharmacology/Toxicology reviewer). CYP3A4 inducers and inhibitors may induce and inhibit, respectively, the metabolism of both ENG and EE. Coadministration of systemic CYP3A4 inducers may decrease the efficacy of NuvaRing® and cause unexpected pregnancy. In in vitro human liver microsomes, mean ketoconazole IC_{50} (concentration producing 50% inhibition) for EE 2-hydroxylase is 1.9 μM and 50 μM terbinafine inhibits 35% of EE 2-hydroxylase activity (D.J. Back et al. *Br. J. Clin. Pharmacol.* 28:166 1989).

Felbamate, [redacted] and topiramate (2nd-generation anticonvulsants) have demonstrated enzyme-inducing activity leading to reduced plasma steroid concentrations and resulted in menstrual irregularity or bleeding disturbances (K. Wilbur and M.H.H. Ensom *Clin. Pharmacokinet.* 38:355 2000; A. Sabers and L. Gram *Drugs* 60:23 2000). Felbamate and [redacted] induces CYP3A4 (K. Wilbur and M.H.H. Ensom *Clin. Pharmacokinet.* 38:355 2000). Topiramate weakly induces cytochrome P-450 (W.E. Rosenfeld et al. *Epilepsia* 38:317 1997). Drug interactions between 1st-generation anticonvulsants and oral contraceptives have long been recognized. Coadministration with phenytoin, phenobarbital, carbamazepine, and primodone may cause oral contraceptive failure.

The effectiveness of oral contraceptives may be impaired via concomitant treatment with antimicrobials (E. Weisberg. *Clin. Pharmacokinet.* 36:309 1999). This may occur because of reduction in plasma EE concentrations via induction of hepatic metabolism with rifampin and possibly with griseofulvin, or in a small percentage of women because of interference with enterohepatic recirculation via antibiotics.

23 healthy female volunteers received 2 single doses of oral contraceptive of 50 μg EE on Day 1 (alone) and on Day 29 during concomitant ritonavir (human immunodeficiency virus protease inhibitor) administration. Ritonavir decreases EE C_{max} and AUC by 32% and 41%, respectively, and a significant increase in the mean terminal elimination rate constant (D. Ouellet et al. *Br. J. Clin. Pharmacol.* 46:111 1998). Despite the inhibitory effect of ritonavir on CYP3A enzymes, administration of ritonavir resulted in an overall increase in EE clearance. This effect may be attributed to both induction of glucuronidation and other CYP enzymes. Authors suggested that alternate contraceptive measures should be considered when ritonavir is coadministered with oral contraceptive. Coadministration of anti-HIV protease inhibitors and oral steroidal contraceptives: 1. ritonavir decreases EE AUC, 2. nelfinavir decreases plasma EE and norethindrone concentrations, 3. indinavir increases EE and norethindrone AUCs, 4. amprenavir may interact with estrogens, progestogens, and some glucocorticoids, and 5. saquinavir label did not mention interaction with oral steroidal contraceptives (individual anti-HIV protease inhibitor package insert *PDR®* 54 ed 2000).

Troglitazone, a thiazolidinedione, reduces about 30% of both plasma EE and norethindrone concentrations upon oral co-administration with Ortho-Novum® (Loi et al. *J. Clin. Pharmacol.* 39:410 1999). This decrease in plasma steroid concentrations may be resulted from troglitazone's CYP3A4 inducing ability. Authors suggested that a higher dose of oral contraceptive or an alternate method of contraception should be considered for patients treated with troglitazone.

Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively (atorvastin/LIPITOR® label *PDR®* 54 ed 2000 and norethindrone acetate and ethinyl estradiol/ESTROSTEP® per June 1999 revised label).

The PK of EE was studied in an open, randomized, cross-over study. 13 healthy female volunteers received 2 x 25 µg EE oral tablets with herbal tea or grapefruit juice (naringin 887 mg/mL; washout of a menstrual cycle ranging from 20 - 36 days) (A. Weber et al. *Contraception* 53:41 1996). In contrast to herbal tea, grapefruit juice increased the plasma EE C_{max} significantly to 137% (mean; range [redacted] $p = 0.0088$) and increased the EE $AUC_{0\text{-}8h}$ to 128% (mean; range [redacted] $p = 0.0186$). These observations are consistent with the inhibitory effect of grapefruit juice on CYP3A4, which primarily metabolizes EE. The clinical significance of this EE/grapefruit juice interaction remains to be determined.

Study 34255:
Study 34255 assesses the interaction of 1-compartment EVA CCVR and vaginally administered spermicide and anti-mycotic in healthy female subjects. This was an open-label, single-center, crossover study. At the screening visit, each subject received 150 µg DSG/30 µg EE daily oral contraceptive for 1 cycle (21 days of tablet usage and a 7-day tablet free period) before the start of the treatment period. Subjects were randomized to 1 of 2 treatment arms. The treatment period of all subjects consisted of 2 CCVR cycles. Treatment Arm A subjects received the spermicide (4% nonoxynol-9/Ortho-Options Conceptrol®; water-based formulation) and Treatment Arm B subjects received the anti-mycotic (1200 mg miconazole nitrate/Gyno-Daktarin-1®; oil-based formulation). Within each treatment arm, subjects were randomized to either Group 1 or Group 2. Group 1 subjects started with a control cycle followed by the interaction cycle, whereas Group 2 subjects received the reverse order of cycles. A cycle was 21 days of ring usage and a 7-day ring free period. Single dose of spermicide or anti-mycotic was administered on Day 8 of the interaction cycle.

The PK of ENG and EE was assessed during both CCVR treatment cycles. Serum SHBG concentrations was also assessed during these 2 cycles. ENG and EE $AUC_{8\text{-}9}$, $AUC_{8\text{-}10}$ and $AUC_{8\text{-}21}$ are measures as short-, intermediate- and long-term PK drug interaction, respectively.

Based on the ENG and EE $AUC_{8\text{-}9}$, $AUC_{8\text{-}10}$ and $AUC_{8\text{-}21}$, there was no PK drug interaction between ENG and EE as released from the CCVR and vaginally administered spermicide.

Based on the ENG and EE $AUC_{8\text{-}9}$ and $AUC_{8\text{-}10}$, there was neither a short-term (1 day after drug administration) nor an intermediate-term (2 days after drug administration) PK drug interaction between ENG and EE as released from the CCVR and vaginally administered anti-mycotic. Based on the $AUC_{8\text{-}21}$, a long-term (13 days after drug administration) PK interaction between ENG and

vaginally administered anti-mycotic was observed. The ENG AUC_{8-21} was 17% higher in the interaction cycle than that in the control cycle. The interaction between EE and vaginally administered anti-mycotic was found to be indeterminant due to large variation, although the EE AUC_{8-21} was 16% higher in the interaction cycle than that in the control cycle. The clinical relevance for the increase of serum ENG and EE concentrations upon coadministration of oil-based miconazole nitrate formulation with CCVR is unknown.

Table 16 Comparison of Interaction (Test) Cycle vs. Control (Reference) Cycle (Trial Arm A)

Parameter	ENG			EE		
	Point Estimate	90 % C.I.	Conclusion	Point Estimate	90 % C.I.	Conclusion
AUC_{8-9}	0.98	0.89-1.08	Effect absent	0.95	0.84-1.09	Effect absent
AUC_{8-10}	1.01	0.91-1.11	Effect absent	1.00	0.88-1.14	Effect absent
AUC_{8-21}_OC	0.98	0.90-1.07	Effect absent	1.04	0.99-1.08	Effect absent
AUC_{8-21}_LF	0.99	0.93-1.06	Effect absent	1.04	0.99-1.08	Effect absent

Point Estimate: Point estimate of parameter ratio (test/reference)
90 % C.I.: 90 % confidence interval for ratio
OC = Observed-Case Analysis, LF = Last-Observation-Carried-Forward Analysis
Spermicide (water-based formulation) was administered on Cycle Day 8
Data were taken from Listings 6.1-1 and 6.2-1 in Appendix B

Table 17 Comparison of Interaction (Test) Cycle vs. Control (Reference) Cycle (Trial Arm B)

Parameter	ENG			EE		
	Point Estimate	90 % C.I.	Conclusion	Point Estimate	90 % C.I.	Conclusion
AUC_{8-9}	1.03	0.95-1.11	Effect absent	1.06	0.96-1.18	Effect absent
AUC_{8-10}	1.07	0.97-1.17	Effect absent	1.09	0.97-1.21	Effect absent
AUC_{8-21}	1.17	1.09-1.25	Effect present	1.16	1.02-1.31	Indeterminant

Point Estimate: Point estimate of parameter ratio (test/reference)
90 % C.I.: 90 % confidence interval for ratio
Anti-mycotic (oil-based formulation) was administered on Cycle Day 8
Data were taken from Listings 6.1-1 and 6.2-1 in Appendix B

The nonoxynol-9 dose used in the spermicide interaction study is not stated in the final study report. Upon request, sponsor responded that 100 mg of nonoxynol-9 was used in Study 34255 (Attachment 2).

1200 mg miconazole nitrate is a high vaginal dose, though for single use. The highest approved miconazole nitrate dose was 200 mg in vaginal suppository for 7 days use. Miconazole is a strong CYP3A inhibitor (M. Maurice et al. *FASEB J.* 6:752 1992). Both ENG and EE are metabolized via CYP3A4 (Question 12 above). However, miconazole inhibition of CYP3A mediated ENG and EE metabolism during their 1st pass via the vagina and results in higher AUC_{8-21} values is unlikely because: 1) the mean vaginal absolute BA for ENG was 102.86% despite the mean vaginal absolutely BA for EE was 55.60% for the CCVR (Question 14 above). 2) low amount of CYP3A4 should be present in the vagina (J-G. Forsberg *Acta Obstet. Gynecol. Scand.* Supplement 163 75:3 1996; D.R. Krishna and U. Klotz *Clin. Pharmacokinet.* 26:144 1994). The possibility of the systemically absorbed vaginal miconazole inhibiting he metabolism of ENG and EE is unknown.

The ex-vivo data suggest that these higher AUC_{8-21} values in the interaction cycle may result from the higher ENG and EE in-vivo release rates from CCVRs when coadministered with oil-based 1200 mg miconazole vaginal formulation.

Table 18 Ex-Vivo Data for Trial Arm A: Spermicide (Water-Based Formulation)

	ENG			EE		
	Mean in-vivo release rate (ug/day)		Ratio (interaction versus control)	Mean in-vivo release rate (ug/day)		Ratio (interaction versus control)
Subject number	Control Cycle	Interaction Cycle		Control Cycle	Interaction Cycle	
3	135	134	0.99	18.3	17.3	0.95
4	140	130	0.93	15.9	15.3	0.97
12	136	126	0.93	15.7	15.8	1.00
14	137	134	0.98	18.3	15.8	0.86
18	130	133	1.02	16.2	15.0	0.92
21	135	140	1.04	16.4	15.0	0.91

Data were taken from Appendix B

Table 19 Ex-Vivo Data for Trial Arm B: Anti-Mycotic (Oil-Based Formulation)

	ENG			EE		
	Mean in-vivo release rate (ug/day)		Ratio (interaction versus control)	Mean in-vivo release rate (ug/day)		Ratio (interaction versus control)
Subject number	Control Cycle	Interaction Cycle		Control Cycle	Interaction Cycle	
1	131	145	1.10	16.3	17.3	1.06
6	146	154	1.06	19.5	20.3	1.04
13	141	141	1.00	18.6	19.1	1.03
15	129	144	1.11	15.8	16.9	1.07
23	139	158	1.13	16.4	19.0	1.16
24	133	135	1.01	16.1	15.9	0.98

Data were taken from Appendix B

Per Study 34225 report page 0072 volume 63 of 149, the analyses for the amounts of ENG and EE remaining in the used CCVRs were specified in Appendix B. This reviewer cannot find the data for the ex vivo analyses of used CCVRs in Appendix B, which spans from volumes 64 - 66. Appendix B contained the bioanalytical results for ENG and EE in human serum instead. However, the actual time of exposure to CCVRs for each subject was reported in Appendix F, page 0053 - 0055 volume 67 of 149. Therefore, this reviewer cannot verify sponsor's calculation of the ENG and EE in vivo-release rates from CCVRs. Sponsor should provide the ex vivo analyses data for the amounts of ENG and EE remaining in the CCVR used in Study 34225. During the Clinical Pharmacology and Biopharmaceutics Briefing on August 31, 2000, medical officer suggested that sponsor should conduct in vitro dissolution tests to characterize the dissolution of NuvaRing® in the presence and absence of the oil-based different doses of miconazole nitrate vaginal capsule and other oil-based vaginal products. Sponsor agreed to conduct in vivo drug interaction studies of oil-based vaginal anti-mycotic preparation with NuvaRing® as postapproval Phase IV commitment, per telephone conference on December 11, 2000. Hence, the in vitro dissolution tests become unnecessary.

For Study 34225, mean SHBG concentrations during CCVR treatment were similar between treatment cycles within each group (A-1, A-2, B-1, and B-2).

Sponsor is strongly encouraged to conduct in vivo and in vitro drug interaction studies for NuvaRing® coadministered with systemic CYP3A4 inducers and inhibitors as well as to determine the induction and inhibition potential of ENG and EE to CYP3A4 and conjugation enzymes to better characterize NuvaRing®'s drug interaction potential. CYP3A4 mediates the biotransformation of over 50% of commonly used drugs. (L.Z. Benet et al. in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* 1995 ed., page 14).

16. What are the formulations used in the clinical studies for NDA 21-187?
The clinically-tested drug formulation is identical to the to-be-marketed drug formulation.

17. Are NuvaRing®dose proportional kinetically?
Only 1 dose strength of NuvaRing® is being sought for approval. Sponsor did not provide PK study results with different NuvaRing® doses per route of administration.

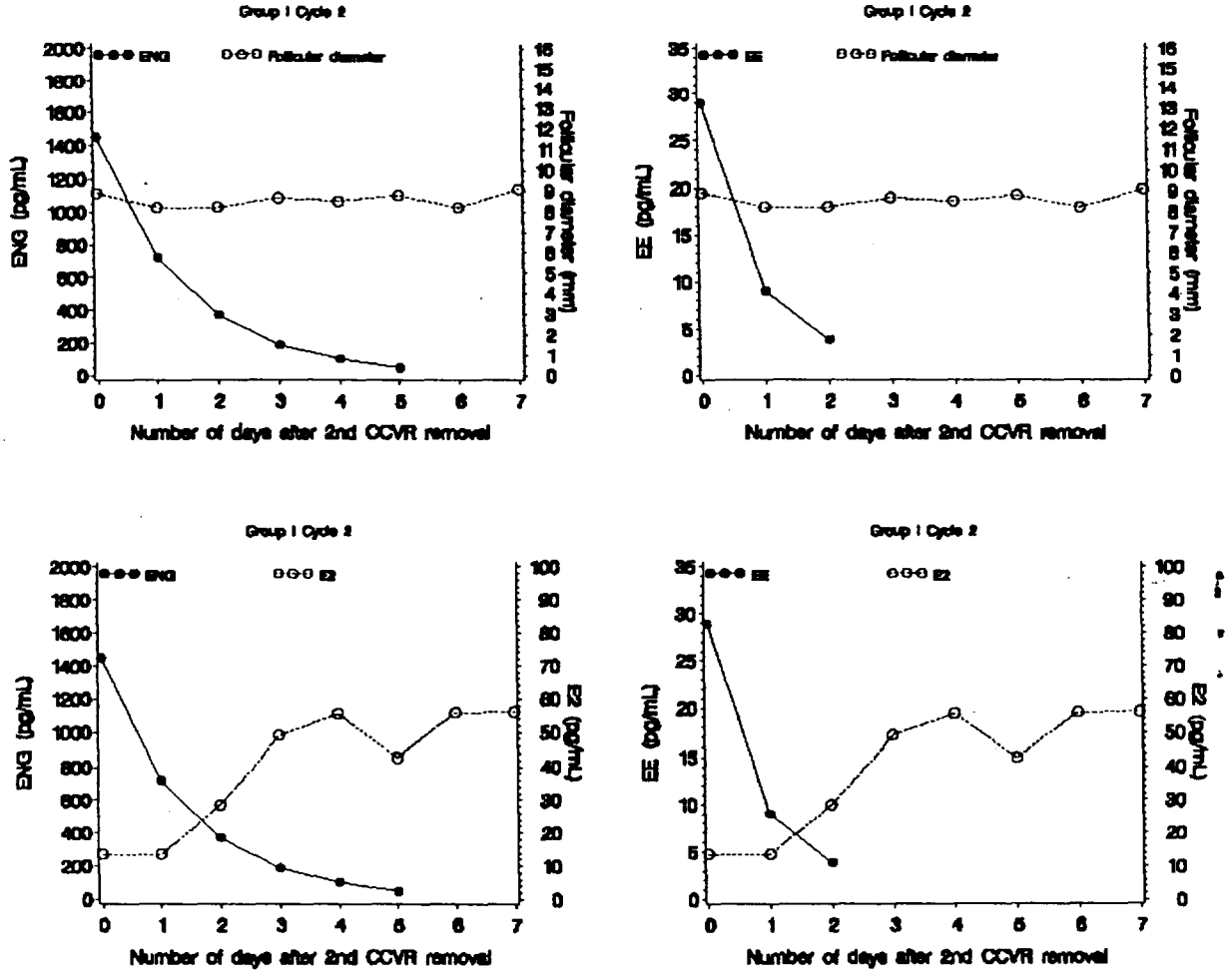
18. What are some PD effects of NuvaRing®?
Study 34226 was an open-label, randomized, single center, PD and PK trial with the 1-compartment EVA CCVR in healthy female subjects. The study primarily assesses 1) a window for removal of the CCVR within the ring-period of 21 days, 2) the time to ovulation after removal of the CCVR, and 3) whether further development of follicles with a diameter of at least 13 mm can be blocked by CCVR treatment. After screening, randomized subjects were allocated to 1 of 3 treatment groups. The treatment of all subjects consisted of 1 "control CCVR cycle" (21 days of CCVR treatment followed by a 7-day ring-free period) and 1 "intervention cycle." The length of the "intervention cycle" was different between the 3 treatment groups. The 2nd cycle of Group 1 subjects consisted of 3 days of CCVR treatment. After removal of the ring on Day 4 of this cycle, subjects were followed up until ovulation. The 2nd cycle of Group 2 subjects consisted of a 21-day CCVR treatment after which these subjects were also to be followed up until ovulation. Group 3 subjects inserted a 2nd CCVR only after follicles with diameter of at least 13 mm were present. After insertion of this 2nd ring, these subjects were followed up for a total period of 21 days of CCVR use. PD and PK assessments were to be performed in the 1st (Group 3 only) and 2nd (all groups) treatment cycles. Ovarian function was monitored via vaginal ultrasound, blood was collected for assessment of serum hormone and SHBG concentrations and for assessment of serum ENG and EE concentrations. The schematic of Study 34266 is in Attachment 3.

Group 2 subjects, who removed the ring after the "normal" 21 days of ring-use ovulated 19 days (median, range: 12 - >28 days) after the day of ring removal. Group 1 subjects, who removed the ring after a period of only 3 days of use, ovulated 17 days (median, range: 13 - >28 days) after the day of ring removal. The size of the largest follicle at the time of removal of the 2nd CCVR was larger in subjects of Group 1 than Group 2. In total, 3 subjects did not ovulate within 29 days after the removal of the ring: the latter concerned a Group 1 subject and 2 Group 2 subjects. The serum FSH, E_2, LH and progesterone (P) concentrations as observed in subjects of Group 1 and 2 corresponded with the pattern of follicular development and ovulation in these subjects. The 90% prediction interval indicates that ovulations will occur within a range of 12-22 days after removal of the CCVR following 3 days of use (Group 1). Following a 21-day of use (Group II), this range for

ovulations was established to be 13-26 days. Irrespective of CCVR use duration (3 versus 21 days of CCVR use), ovulations are unlikely to occur before 12 days after CCVR removal. The median length of the ring-free period after a 21-day period of ring use needed for follicles to grow until they reached a diameter of 13 mm was 11 days (Group 3, range: 8 – 21 days). In the 1st week after insertion of the 2nd CCVR, an equal number of subjects showed an increase, decrease, or no change in follicular diameter of the largest follicle. All except 4 subjects reached their maximum serum E_2 concentrations within the "extended" ring-free period: these 4 subjects reached their maximum E_2 concentrations within 9 days after insertion of the 2nd CCVR. For all subjects, follicular activity - as evidenced by the decrease of follicular size and serum E_2 concentrations - was not present anymore within 2 weeks after insertion of the 2nd CCVR. None of the Group 3 subjects ovulated. In addition to serum E_2 concentrations, serum FSH, LH, and P concentrations also corresponded with the pattern of follicular development.

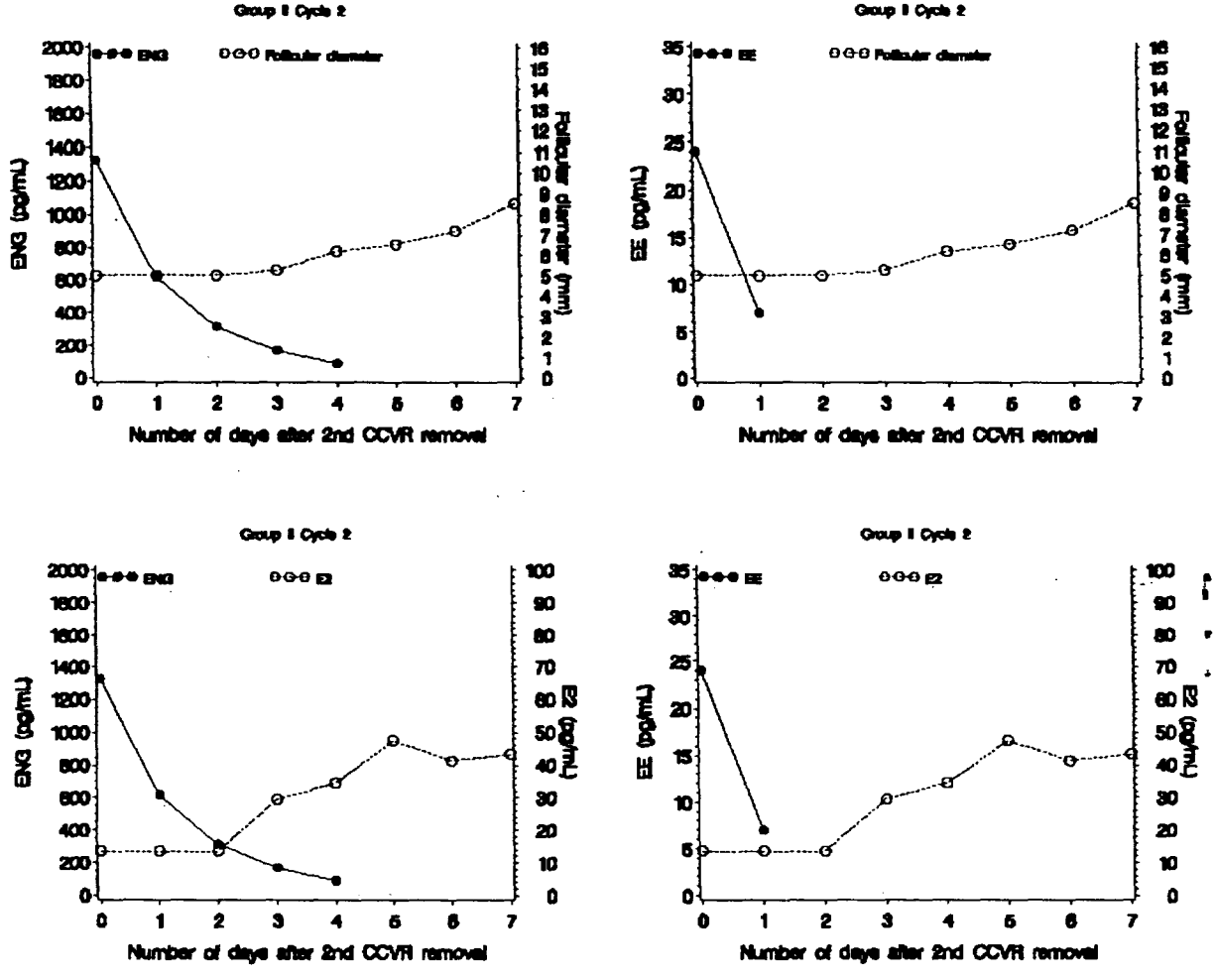
Pharmacokinetics/Pharmacodynamics: The mean half-lives were 30.1 h (ENG) and 34.0 h (EE) for Group 1, 25.8 h (ENG) and 32.7 h (EE) for Group 2, and 32.1 h (ENG) and 20.6 h (EE) for Group 3. The ENG/EE versus follicular diameter/E_2 plots against time for each of the 3 treatment groups showed that a decrease in serum ENG and EE concentrations (following removal of the CCVR) was associated with an increase in E_2 concentrations, irrespective of CCVR use duration (21 versus 3 days of CCVR use). This observation was less pronounced for follicular diameters, since they hardly showed any change for Group 1 subjects and only a small increase for Group 2 subjects (Cycle 2) and Group 3 (Cycle 1): Reinsertion of the ring at the time of follicles with a diameter of at least 13 mm (Group 3) showed the opposite effect as observed after removal of the CCVR, i.e., the increase of ENG and EE concentrations was associated with a decrease in E_2 concentrations and hardly any change in the size of the follicles during the 1st week of CCVR use. A correlation between the follicular diameters or serum E_2 concentrations and the mean serum ENG and EE concentrations per group could not be established.

Figure 10 PK/PD Plots for Group I, Cycle 2



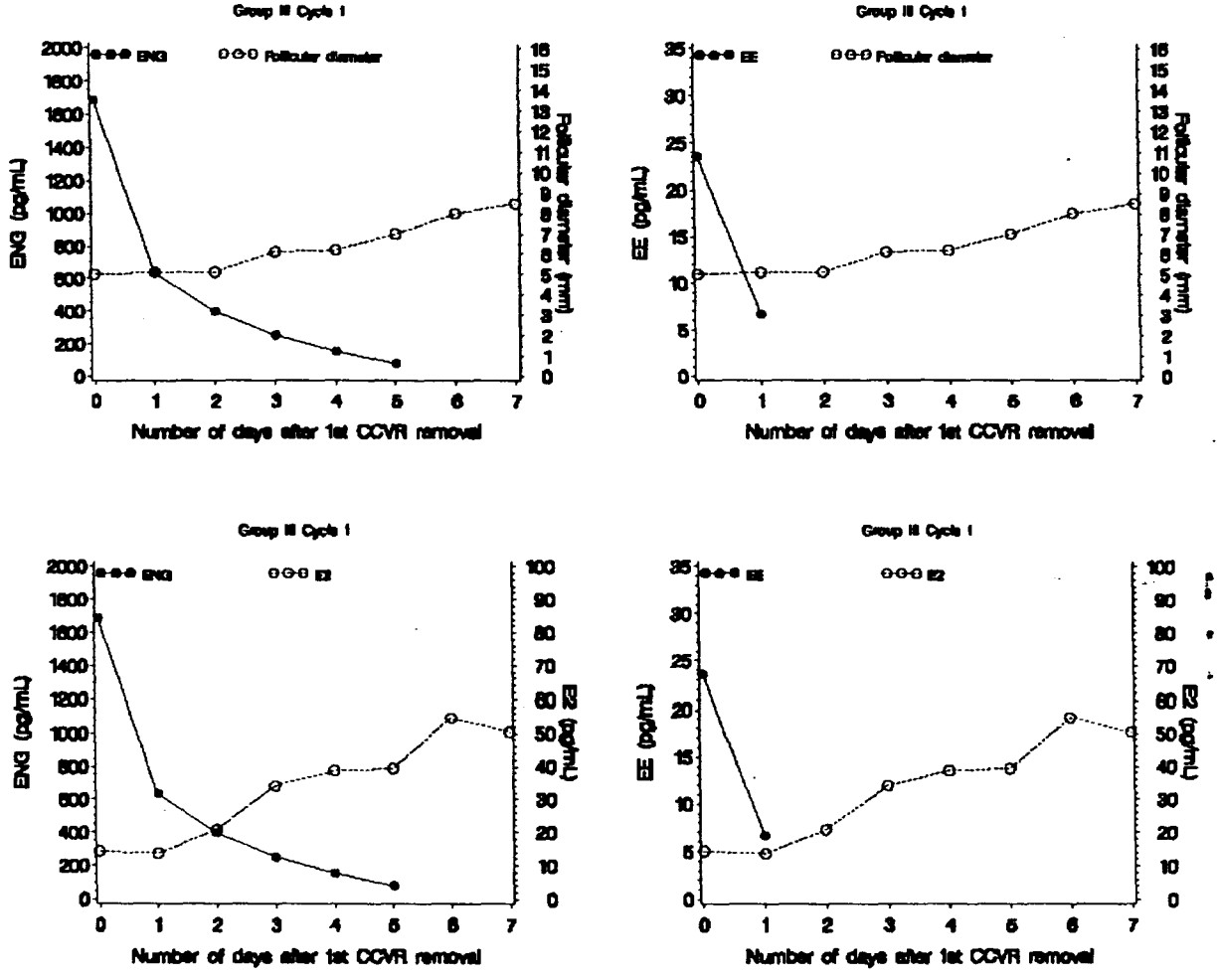
Upper left: Mean ENG and median max. follicular diameter versus time
Upper right: Mean EE and median max. follicular diameter versus time
Lower left: Mean ENG and median E_2 versus time
Lower right: Mean EE and median E_2 versus time
Data were taken from Figures 9-1 and 9-2 in Appendix B.

Figure 11 PK/PD Plots for Group II, Cycle 2



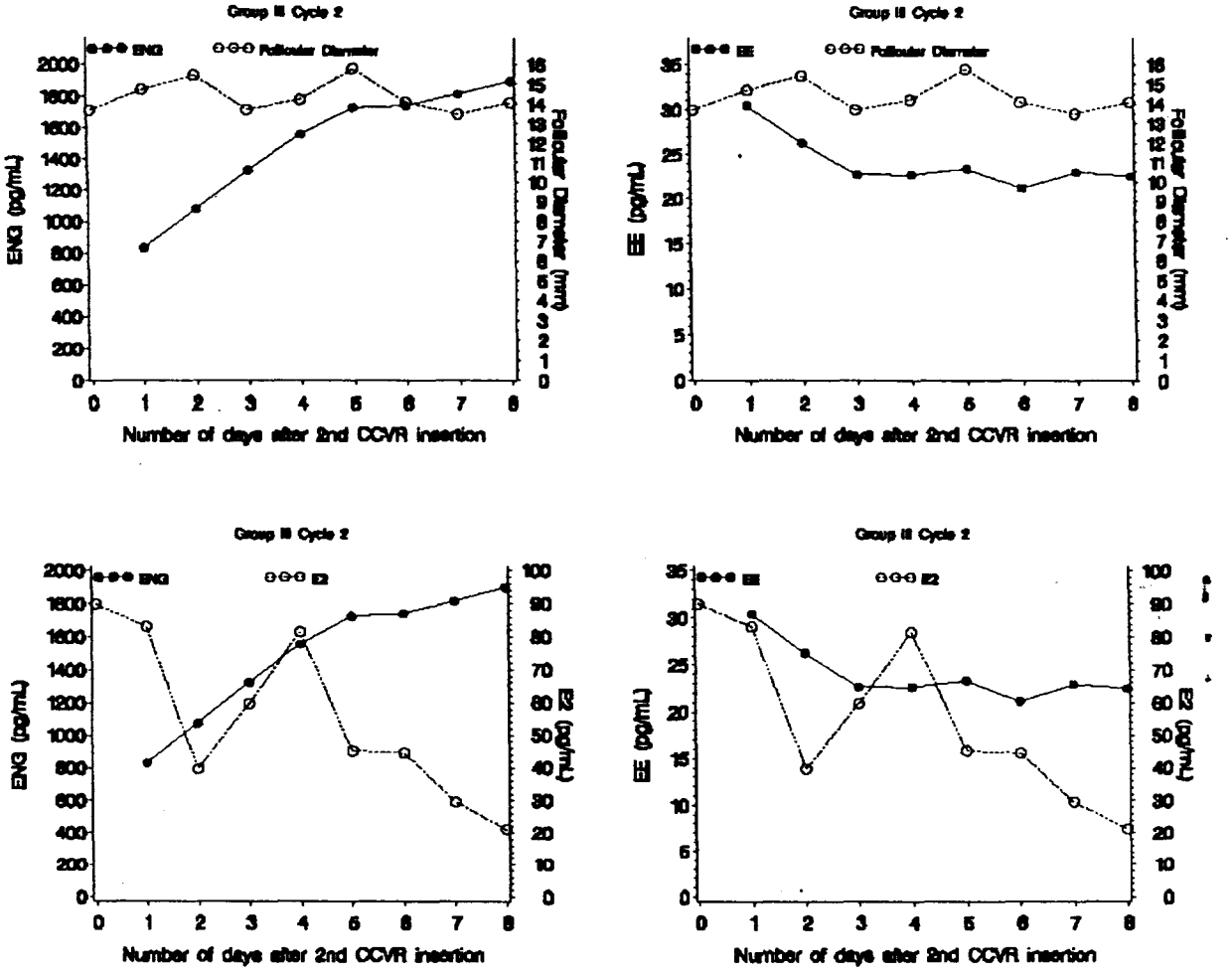
Upper left: Mean ENG and median max. follicular diameter versus time
Upper right: Mean EE and median max. follicular diameter versus time
Lower left: Mean ENG and median E_2 versus time
Lower right: Mean EE and median E_2 versus time
Data were taken from Figures 9-3 and 9-4 in Appendix B.

Figure 12 PK/PD Plots for Group III, Cycle 1



Upper left: Mean ENG and median max. follicular diameter versus time
Upper right: Mean EE and median max. follicular diameter versus time
Lower left: Mean ENG and median E_2 versus time
Lower right: Mean EE and median E_2 versus time
Data were taken from Figures 9-5 and 9-6 in Appendix B.

Figure 13 PK/PD Plots for Group III, Cycle 2



Upper left: Mean ENG and median max. follicular diameter versus time
Upper right: Mean EE and median max. follicular diameter versus time
Lower left: Mean ENG and median E_2 versus time
Lower right: Mean EE and median E_2 versus time
Data were taken from Figures 9-7 and 9-8 in Appendix B.

In Study 34218 (see Question 14 for study details), 35 days of CCVR use resulted in ovarian suppression and inhibited ovulation in all subjects for both the 21-day period of use and for the extended period of use between Days 22 - 35. Ovarian activity was assessed via vaginal ultrasonography and serum E_2, FSH, LH, and P concentrations. The diameter of the largest follicles as observed in all subjects ranged between 6.2 and 15.7 mm. These large follicles were mainly observed in the 1st week of CCVR use, which was preceded by a 7-day tablet-free period for the oral contraceptive Marvelon®. Consistent with the observed follicular development in each subject, the highest serum E_2 concentrations were also observed in the first week of CCVR use. Ovulations, as assessed by vaginal ultrasound, were not observed in any of the subjects. The latter was confirmed by the absence of high serum LH and P concentrations. Although assessment of ovarian activity in the Marvelon® treatment cycle of each subject was minimal, the ovarian suppression in a CCVR and Marvelon® cycle of 21 days seemed to be similar.

19. Does NuvaRing® accumulate upon multiple dose administration?

In Study 34226 (see Question 18 for study details), generally, serum ENG concentrations were not quantifiable (LOQ = [redacted] 5 - 6 days post CCVR removal and serum EE concentrations were not quantifiable (LOQ = [redacted] 2 - 3 days post CCVR removal. Per cross group comparison (Group 3 vs. Group 2), the mean serum ENG and EE concentrations between cycle 1 and cycle 2 were similar (see figures below).

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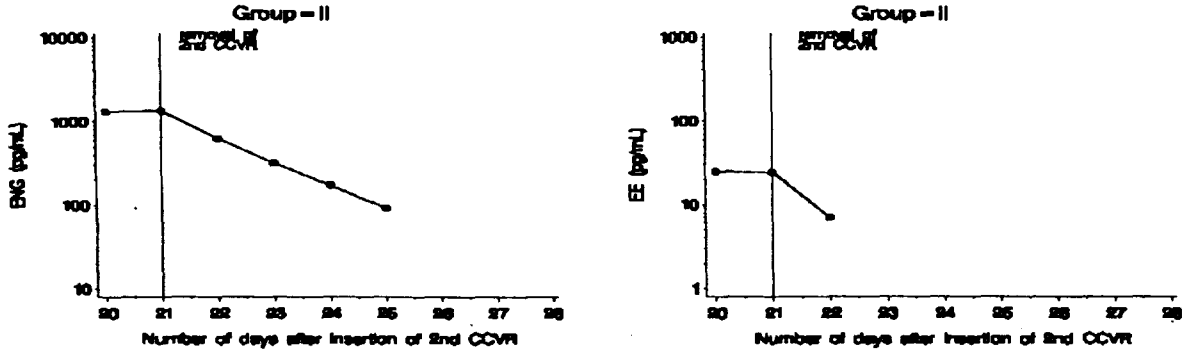
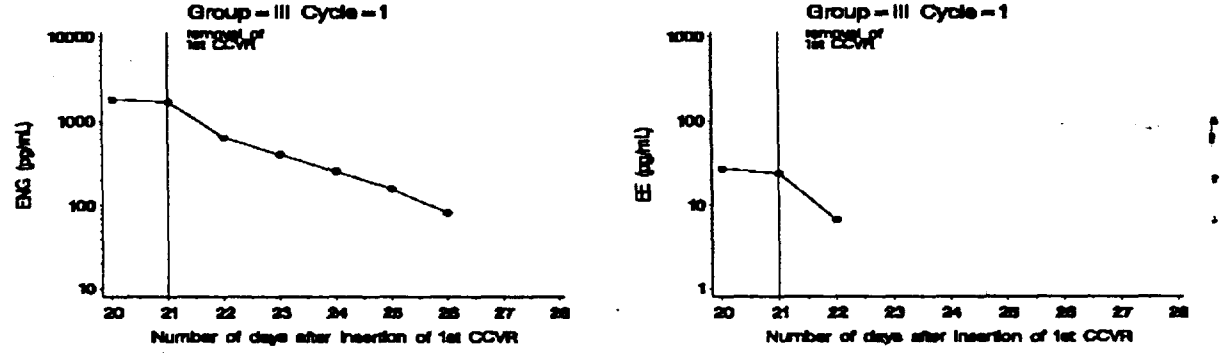
Figure 7 Mean ENG and EE Concentrations for Group II, Cycle 2



Data were taken from Table 2-1 in Appendix B

Figure 8 Mean ENG and EE Concentrations for Group III, Cycle 1



Data were taken from Table 2-1 in Appendix B

In Study 34218 (see Question 14 for study details), subjects wore CCVR for 35 days instead of 21 days. About 5 days post CCVR removal, the serum ENG concentrations were generally not quantifiable. About 72 hours post CCVR removal, the serum EE concentrations were generally not quantifiable. These observations are consistent with those in Study 34226 and suggest that ENG and EE did not accumulate upon repeated cycles of CCVR administration (1 cycle = 21 days of ring use and then 7-day of ring free period).

20. How does the PK of NuvaRing® differ in special populations?

Sponsor did not study NuvaRing® in any special populations such as obese, ethnic, pulmonary disease, heart disease, renally and hepatically impaired patients. Sponsor did not submit any population PK data for NDA 21-187.

21. What was sponsor's proposed IVIVC for NuvaRing®?

During different stages of NuvaRing® development, PK studies were performed with the Silastic® vaginal ring prototypes, with different ENG loading and release rates, to assess the relationship between the in vitro ENG release rates and in vivo ENG absorption rates. For these prototype rings, a linear 1-point in-vivo/in-vitro correlation (adjusted $R^2 = 0.998$) was found, indicating a linear

relation between the mean steady-state serum ENG concentration and the mean steady-state in-vitro ENG release rate. The changes from Silastic® prototypes to NuvaRing® are:

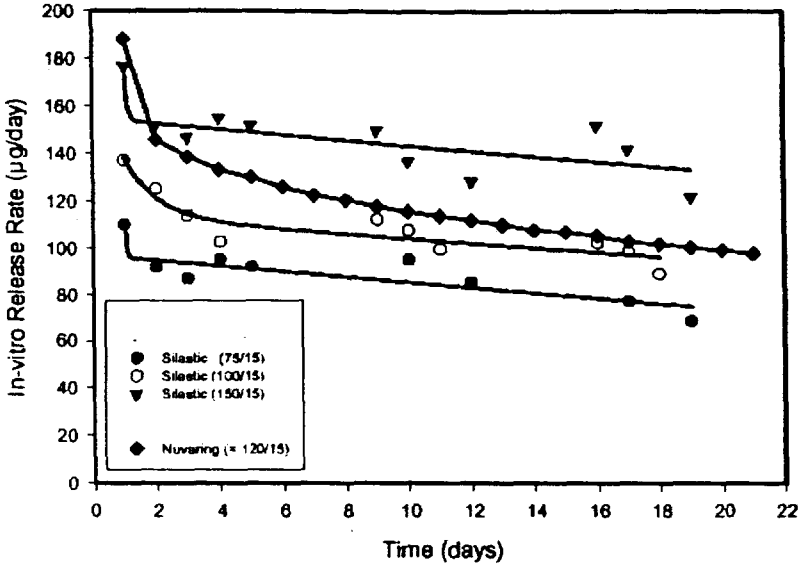
[redacted]

To characterize the PK profile of NuvaRing®, Study 34218 was conducted. Comparing in vitro ENG release data and PK results from Study 34218 with those of the prototype ring, sponsor proposed the following:

- In-vitro ENG release profile for NuvaRing® fits within the 3 variants of the Silastic® ring, i.e., between that of "100/15" and "150/15" Silastic® rings (Figure 3).
- The mean steady-state serum ENG concentrations (reached after 5 days of NuvaRing® treatment) are between that of "100/15" and "150/15" Silastic® rings (Figure 4). Sponsor proposed that a large interstudy variation existed for the ENG assay between the earlier studies with Silastic® rings and those values with Study 34218. To compensate for the variability, sponsor used the serum ENG concentrations upon oral administration of 150 µg DSG/30 µg EE as an internal standard in the prototype ring studies. In Study 34218, the mean steady-state serum ENG concentration upon oral preparation administration of 150 µg DSG/30 µg EE was 1617 pg/mL, versus that of 1100 pg/mL for the Silastic® PK studies. Therefore, serum ENG concentrations for the prototype ring studies were multiplied with a factor of 1.47.

After correction for interstudy assay variation, a 1-point linear IVIVC between the average in-vitro ENG release rates and the average steady-state serum ENG concentrations is observed for the 3 variants of the Silastic® prototype ring and NuvaRing® (Fig. 5). Direct point-for-point comparison at different time points of the ENG and EE in-vivo absorption rate versus the corresponding in-vitro release rate appeared linear (Fig. 6).

Figure 3 ENG In-Vitro Release profiles of Silastic Prototype Ring and NuvaRing®



Serum ENG concentrations from the Silastic® prototype rings were corrected in the following figure:

Figure 4 ENG Serum Concentrations of Silastic Prototype Ring and NuvaRing®

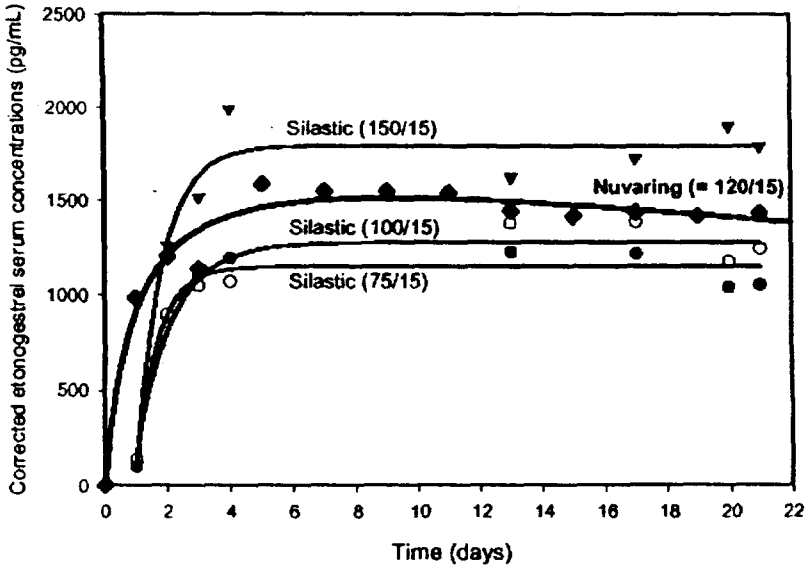
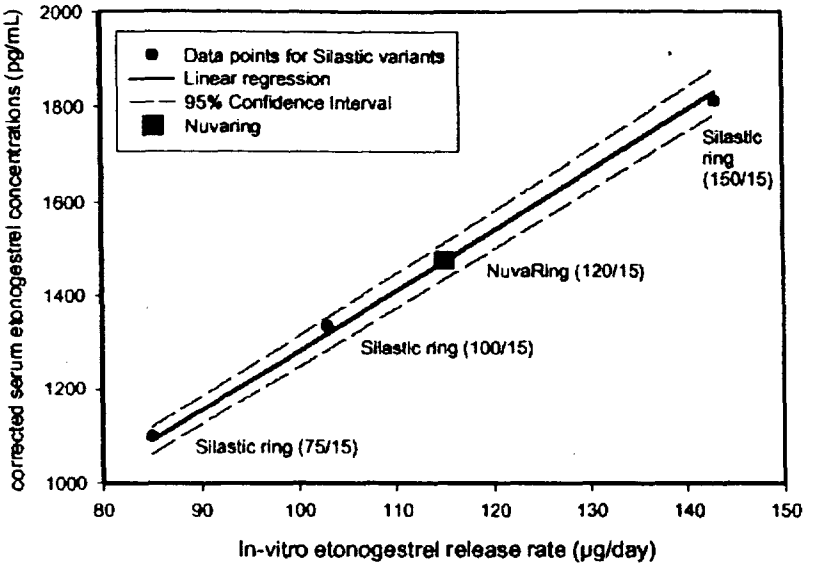
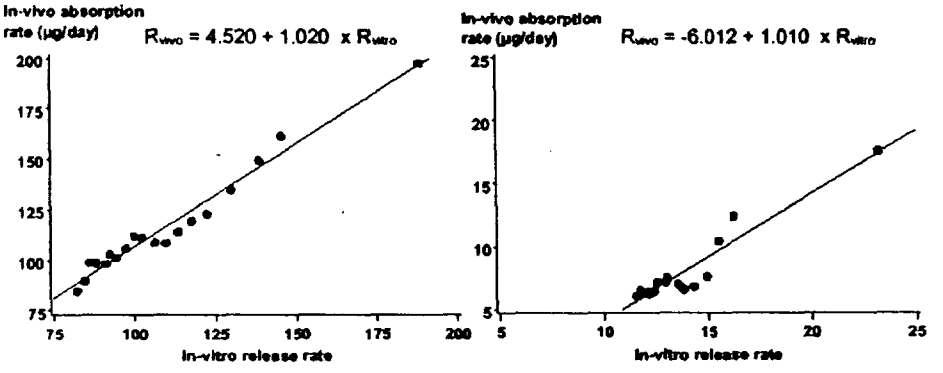


Figure 5 In-Vivo/In-Vitro Correlation for NuvaRing® and Prototype Silastic Ring



Note: The serum ENG concentrations for the Silastic variants were corrected for interassay variation.

Figure 6 Point-to-point In-Vivo/In-Vitro Correlation for ENG and EE from NuvaRing® Study 34218



The correlation in the left is for ENG whereas the correlation on the right is for EE.
In Study 34218, the release characteristics of ENG from NuvaRing® are in Table 4. The in-vitro ENG release rate as well as the absorption rate showed a downward trend in time: a decrease of

approximately 33% for the in-vitro release rate and 24% for the absorption rate from Week 1 up to and including Week 5 of NuvaRing® use.

Table 4 Release Characteristics of ENG from NuvaRing® (Mean±SD)

	1 week	2 weeks	3 weeks	4 weeks	5 weeks
Concentration (pg/mL)	1578 ± 408	1476 ± 362	1374 ± 328	1272 ± 311	1170 ± 313
In-vitro RR (µg/day)	122.4	107.6	97.6	89.4	82.3
Absorption rate (µg/day)	122.30 ± 19.04	115.09 ± 16.20	107.88 ± 13.78	100.67 ± 12.03	93.47 ± 11.25

RR = release rate

The absorption rate (mg/day) after 1, 2, 3, 4 and 5 weeks of CCVR use was calculated as Cv,y week(s) × CLi. It represents the daily amount absorbed into the general circulation at a certain time point.

The release characteristics of EE from NuvaRing® are in Table 5. The in-vitro EE release rate as well as the absorption rate showed a downward trend: a decrease of approximately 17% for the in-vitro release rate and 8% for the absorption rate from Week 1 up to and including Week 5 of NuvaRing® use.

Table 5 Release Characteristics of EE from NuvaRing® (Mean±SD)

	1 week	2 weeks	3 weeks	4 weeks	5 weeks
Concentration (pg/mL)	19.09 ± 4.45	18.34 ± 4.29	17.58 ± 4.34	16.83 ± 4.62	16.07 ± 5.08
In-vitro RR (µg/day)	14.3	13.3	12.6	11.9	11.8
Absorption rate (µg/day)	8.55 ± 2.50	8.38 ± 2.38	8.21 ± 2.29	8.03 ± 2.22	7.86 ± 2.19

RR = release rate

Reviewer's comments follow:

1. Sponsor did not provide either internal or external validation for the ENG and EE IVIVC. See "Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In vitro Dissolution Testing and In Vivo Bioequivalence Documentation, USHHS, FDA, CDER, September 1997, CMC 8" for reference; though for oral MR products, principles may apply to NuvaRing®. Sponsor indicated intention to use Studies 34255 (interaction) and 34226 (pharmacodynamic) to validate their IVIVC during the proposed postapproval changes meeting on November 16, 2000.
2. Sponsor did not describe the details of deconvoluting the serum ENG or EE concentrations via intravaginal administration with the corresponding serum ENG or EE concentrations via intravenous administration to estimate the in vivo ENG or EE absorption rate from CCVR. Only a reference page 077 of volume 55 of 149 volumes was cited. Thus, the validity of the ENG or EE in vivo absorption rate cannot be assessed.
3. Sponsor should provide data to demonstrate that the in vitro release method is independent of conditions such as release media and agitation during development.

4. For the 1-point linear IVIVC, serum ENG concentrations for the Silastic® prototype ring had to be multiplied with 1.47 in order to fit those with NuvaRing®. Sponsor justified this multiplication factor as variability difference for the assay used between the Silastic® prototypes and CCVR. However, sponsor should provide substantiation for the difference (1.47 factor) in etonogestrel bioanalytical assays for the prototype and NuvaRing®.
5. Sponsor should provide the ex vivo analyses data for the amounts of ENG and EE remaining in the combined contraceptive vaginal rings used in Study 34225, which were missing from Appendix B of Study report 34225 (see response to Question 15 above; page 16 for details).
6. Sponsor provided the 1-point linear IVIVC for ENG from Silastic® prototype and NuvaRing® data. In order to consider bioequivalence study waiver via 1-point linear IVIVC for future formulation or manufacturing changes, sponsor should also provide the 1-point linear IVIVC for EE from Silastic® prototype and CCVR data. Sponsor explained in the proposed postapproval changes meeting on November 16, 2000 that since all nominal prototype EE delivery rate was 15 µg/day, theoretically the correlation for EE will just have 1 point. Sponsor's explanation is acceptable.
7. Sponsor should provide explanation to Study 34218's observations that the ENG in vitro release rate is lower than the ENG estimated in vivo absorption rate and the EE in vitro release rate is higher than the EE estimated in vivo absorption rate. Sponsor explained in the proposed postapproval changes meeting on November 16, 2000 that the vaginal absolutely bioavailability for ENG is about 100% whereas the vaginal absolutely bioavailability for EE is about 55%. This may account for these observations. Sponsor's explanation is acceptable.
8. During the proposed postapproval changes meeting on November 16, 2000, sponsor was reminded that if the IVIVC could not be validated, human bioequivalence study might be required to document future proposed postapproval changes; sponsor expressed awareness of this fact.
9. Hence, the proposed ENG and EE IVIVCs are not acceptable at this time. Sponsor should address the 1st 5 comments above for the proposed ENG and EE IVIVCs.

22. What are the proposed in vitro dissolution method and specifications for NuvaRing®?
No standard USP or regulatory in vitro dissolution method is available to test vaginal ring dosage form.

The in-vitro release conditions are:

Apparatus	
In-vitro release medium	
Volume of in-vitro release medium	
Temperature	
Stirring speed	
Sampling times	
Sampling volume	

Note- Full details of the in-vitro release test method may be found in the NDA Vol:1.8 (pages 0043-0047).

The proposed in vitro release specifications for NuvaRing are:

Note- The specifications in the above table are taken from the drug product regulatory specifications (NDA Vol:1.8, page 0012).

mr = mean result rs = result single u = unit d = determination

The proposed NuvaRing® in vitro release specifications were based on the proposed IVIVC. Since the proposed IVIVC is unacceptable, the recommended NuvaRing® in vitro release specifications should be based on the CCVR in vitro release results for the lot that was used in the clinical safety and efficacy studies. The recommended NuvaRing® in vitro release specifications follow:

	ENG (µg/day/ring)	EE (µg/day/ring)
Day 1	≤ 360	≤ 30
Day 2 - 21	120 (mean) (96 - 144)	15 mean (10 - 20)
Day 21	≥ 80	≥ 10

Attachment 5 contains the individual in vitro release rate results for the CCVRs that were used in the clinical safety and efficacy studies 068003 and 34219; this paragraph pertains to these in vitro

release rates. Day 1 ENG in vitro release rate was 186 - 205 µg/day/ring per clinical lots. However, the highest ENG in vitro release rate for the stability lot was 359 µg/day/ring (per review chemist, David Lin). This initial burst of ENG released from CCVR was consistent among the lot tested for stability purpose. High initial burst of ENG from CCVR does not raise safety concern, especially ENG is a progestin (consent with medical officer, Daniel Davis). Therefore, the recommended specification for Day 1 ENG in vitro release rate is ≤ 360 µg/day/ring. Day 2 - Day 21 ENG in vitro release rates ranged from 98.2 to 153 µg/day/ring per clinical lots; sponsor's proposed ENG mean and range in vitro release rate from Day 2 - Day 21 were acceptable. Day 21 ENG in vitro release rate was 97 - 103 µg/day/ring per clinical lots; sponsor's proposed ENG in vitro release rate at Day 21 was acceptable. Day 1 EE in vitro release rate was 23 - 28 µg/day/ring per clinical lots. The highest EE in vitro release rate for the stability lot was 27.5 µg/day/ring (per review chemist, David Lin). Therefore, the recommended specification for Day 1 EE in vitro release rate is ≤ 30 µg/day/ring. Day 2 - Day 21 EE in vitro release rates were 12.5 - 17.4 µg/day/ring per clinical lots; sponsor's proposed EE mean and range in vitro release rate from Day 2 - Day 21 were acceptable. Day 21 EE in vitro release rate was 12 - 14 µg/day/ring per clinical lots; sponsor's proposed EE in vitro release rate at Day 21 was acceptable. Sponsor reproposed in their Chemistry Amendment November 14, 2000 that Day 1 EE in vitro release rate to be ≤ 35 µg/day/ring. For the 4 lots that were used for the clinical safety and efficacy studies, mean ± SD for Day 1 EE in vitro release was 24.8 ± 1.44 µg/day/ring. Mean + 3 SD for Day 1 EE in vitro release was 29.1 µg/day/ring (see the last page of Attachment 5). Hence, sponsor's reproposed Day 1 EE in vitro release rate to be ≤ 35 µg/day/ring was not acceptable. Based on the recommended Day 1 EE in vitro release (30 µg/day/ring) was larger than the mean + 3 SD for Day 1 EE in vitro release (29.1 µg/day/ring), sponsor finally accepted that Day 1 EE in vitro release rate should be ≤ 30 µg/day/ring instead of ≤ 35 µg/day/ring, per telephone conference on December 11, 2000.

The Office of Clinical Pharmacology and Biopharmaceutics concurs with the following recommended in vitro release acceptance criteria for NuvaRing® that were set by the reviewing chemist, David Lin (The exact wording for the acceptance criteria may be different from the review chemist's, but the acceptance criteria numbers are identical):

Day 1: The individual daily amounts of ENG or EE released for each of the 12 rings tested has to be less than or equal to the stated limit (sponsor's proposal).

Days 2 through 21:

Stage I: the mean should be within the specification range (96-144 µg ENG/day/ring and 10-20 µg EE/day/ring); not less than 11 samples should be within ± 10% of the specification mean (120 µg ENG/day/ring and 15 µg EE/day/ring) for the specification range that is 84-156 µg ENG/day/ring and 8.5-21.5 µg EE/day/ring; and no 1 sample will be outside ± 15% of the specification mean for the specification range that is 78-162 µg ENG/day/ring and 7.7-22.3 µg EE/day/ring.

Stage II: If more than 1 sample is outside the ± 10% of the specification mean for the specification range, the test must be repeated with another 12 rings, which must meet Stage I requirements.

Day 21: The individual daily ENG and EE amounts released for each of the 12 rings has to be greater than or equal to the stated limit (sponsor's proposal).

23. What are sponsor's proposed labeling for NuvaRing® Clinical Pharmacology section? What are the labeling comments?

Proposed Labeling:

CLINICAL PHARMACOLOGY

Combination hormonal contraceptives act by suppression of gonadotropins. Although the primary effect of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation). Receptor binding studies, as well as studies in animals, have shown that etonogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with low intrinsic androgenicity.

Pharmacokinetics

Absorption

Etonogestrel: Etonogestrel released by NuvaRing® (etonogestrel/ethinyl estradiol ring) is rapidly absorbed. Absolute bioavailability of etonogestrel is approximately 100%, which is higher than that with oral administration of desogestrel. The serum etonogestrel concentrations observed during 3 weeks of NuvaRing® use are summarized in Table I.

TABLE I: Mean (SD) Serum Etonogestrel Concentrations (n=16).

	1 week	2 weeks	3 weeks
Etonogestrel concentration (pg/mL)	1578 (408)	1476 (362)	1374 (328)

Ethinyl estradiol: Ethinyl estradiol released by NuvaRing® is rapidly absorbed. Absolute bioavailability is approximately 55.6%, which is comparable to that with oral administration of ethinyl estradiol. The serum ethinyl estradiol concentrations observed during 3 weeks of NuvaRing® use are summarized in Table II.

TABLE II: Mean (SD) Serum Etonogestrel Concentrations (n=16).

	1 week	2 weeks	3 weeks
Ethinyl estradiol concentration (pg/mL)	19.1 (4.5)	18.3 (4.3)	17.6 (4.3)

The pharmacokinetic parameters of etonogestrel and ethinyl estradiol were determined during one cycle of NuvaRing® use in 16 healthy female subjects and are summarized in Table III.

TABLE III: Mean (SD) Pharmacokinetic Parameters Of NuvaRing® (n=16).

Etonogestrel

C_{max} pg/mL	T_{max} hr	$t_{1/2}$ hr	CL L/hr
1716 (445)	200.3 (69.6)	29.3 (6.1)	3.4 (0.8)

Ethinyl Estradiol

C_{max} pg/mL	T_{max} hr	$t_{1/2}$ hr	CL L/hr
34.7 (17.5)	59.3 (67.5)	44.7 (28.8)	34.8 (11.6)

C_{max} - maximum serum drug concentration
T_{max} - time at which maximum serum drug concentration occurs
$t_{1/2}$ - elimination half-life, calculated by $0.693/K_{elim}$
CL - apparent clearance

Distribution
Etonogestrel: Etonogestrel is bound to serum albumin and to sex hormone-binding globulin (SHBG).
Ethinyl estradiol: Ethinyl estradiol is highly but not specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG.

Metabolism
Etonogestrel: Etonogestrel is completely metabolized by known pathways of steroid metabolism.

Ethinyl estradiol: Ethinyl estradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as sulfate and glucuronide conjugates.

Excretion
Etonogestrel and ethinyl estradiol are primarily eliminated in urine, bile and feces. The elimination half-life is 29.3±6.1 hours for etonogestrel and 44.7± 28.8 hours for ethinyl estradiol.

Special Populations
Race
No formal studies were conducted to evaluate the effect of race on the pharmacokinetics of NuvaRing® (etonogestrel/ethinyl estradiol ring).
Hepatic Insufficiency
No formal studies were conducted to evaluate the effect of hepatic disease on the disposition of NuvaRing®. However, steroid hormones may be poorly metabolized in patients with impaired liver function (see PRECAUTIONS).

Renal Insufficiency
No formal studies were conducted to evaluate the effect of renal disease on the disposition of NuvaRing®.
Drug-Drug Interactions
Interactions between contraceptive steroids and other drugs have been reported in the literature (see PRECAUTIONS). The pharmacokinetics of NuvaRing® were evaluated after the vaginal administration of spermicides or antimycotics in 24 healthy female subjects in one cycle. In this study, it was determined that vaginally-administered, oil-based antimycotics increased the serum concentrations of etonogestrel and ethinyl estradiol by approximately 17% and 16%, respectively. There is no indication that the safety or efficacy of NuvaRing® is affected. It was determined that vaginally-administered, water-based spermicides did not affect the serum concentrations of etonogestrel or ethinyl estradiol.

PRECAUTION
8. DRUG INTERACTIONS
Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of combination hormonal contraceptives and rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium; carbamazepine and possibly with griseofulvin, ampicillin, and tetracyclines.

2 page(s) of revised draft labeling has been redacted from this portion of the review.

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Attachment 1

Table 2 Time Table for Blood Sampling and Ultrasonography - Group I (n=8)

Day	Treatment	Time ** (hours)	Sample code	ENG, EE	SHBG	Hormones (FSH, LH, E2, P)	Blood ** volume (ml)	USS
1-20	Marvelon®							
21		- 5 min.	A1	●	●	●	6.0	●
		0.25	A2	●			4.5	
		0.5	A3	●			4.5	
		1	A4	●			4.5	
		1.5	A5	●			4.5	
		2	A6	●			4.5	
		3	A7	●			4.5	
		4	A8	●			4.5	
		6	A9	●			4.5	
		8	A10	●			4.5	
		12	A11	●			4.5	
		16	A12	●			4.5	
22	Pill-free period	24	A13	●	●		6.0	
23		48	A14	●	●		6.0	
24		72	A15	●	●	●	6.0	●
25								
26								
27								
28								
29	1 CCVR	- 5 min.	A16	●	●	●	6.0	●
		6	A17	●			4.5	
		8	A18	●			4.5	
		12	A19	●			4.5	
		16	A20	●			4.5	
30	2	24	A21	●	●	●	6.0	●
31	3	48	A22	●			4.5	
32	4	72	A23	●	●	●	6.0	●
33	5							
34	6		A24	●	●	●	6.0	●
35	7							
36	8		A25	●	●	●	6.0	●
37	9							
38	10		A26	●	●	●	6.0	●
39	11							
40	12		A27	●	●	●	6.0	●
41	13							
42	14		A28	●	●	●	6.0	●
43	15							
44	16		A29	●	●	●	6.0	●
45	17							
46	18		A30	●	●	●	6.0	●
47	19							
48	20		A31	●	●	●	6.0	●
49	21							
50	22		A32	●	●	●	6.0	●
51	23		A33			●	1.5	●
52	24		A34	●	●	●	6.0	●
53	25		A35			●	1.5	●
54	26		A36	●	●	●	6.0	●
55	27		A37			●	1.5	●
56	28		A38	●	●	●	6.0	●
57	29		A39			●	1.5	●
58	30		A40	●	●	●	6.0	●
59	31		A41			●	1.5	●
60	32		A42	●	●	●	6.0	●
61	33		A43			●	1.5	●

Day	Treatment	Time ** (hours)	Sample code	ENG, EE	SHBG	Hormones (FSH, LH, E2, P)	Blood ** volume (ml)	USS
62	34		A44	●	●	●	6.0	●
63	35		A45			●	1.5	●
64	Ring-free period	- 5 min.	A46	●	●	●	6.0	●
		3	A47	●			4.5	
		6	A48	●			4.5	
		12	A49	●			4.5	
65		24	A50	●	●		6.0	
66		48	A51	●	●	●	6.0	●
67	ENG/EE IV	- 5 min.	B01	●	●		6.0	
		5 min.	B02	●			4.5	
		10 min.	B03	●			4.5	
		15 min.	B04	●			4.5	
		30 min.	B05	●			4.5	
		45 min.	B06	●			4.5	
		1	B07	●			4.5	
		1.5	B08	●			4.5	
		2	B09	●			4.5	
		4	B10	●			4.5	
		6	B11	●			4.5	
		8	B12	●			4.5	
		12	B13	●			4.5	
		16	B14	●			4.5	
68		24	B15	●	●		6.0	
		36	B16	●			4.5	
69		48	B17	●	●		6.0	
70		72	B18	●	●		6.0	
71		96	B19	●	●		6.0	
72		120	B20	●	●		6.0	

** Relative time to last pill intake (Marvelon®), first ring insertion (Day 29 (Group I) and Day 1 (Group II)), removal of last ring (Day 64 (Group I) and Day 36 (Group II)), or IV injection of ENG/EE .

++ ENG and EE: 4.5 ml blood; Hormones (FSH, LH, E2 and P) and SHBG: 1.5 ml blood. The total amount of blood to be collected for Group I was 345 ml. The total amount of blood to be collected for Group II was 354 ml.

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Table 3 Time Table for Blood Sampling and Ultrasonography - Group II (n=8)

Day	Treatment	Time ** (hours)	Sample code	ENG, EE	SHBG	Hormones (FSH, LH, E2, P)	Blood ** volume (ml)	USS
-7	Pill-free period		A01			●	1.5	●
-6								
-5								
-4			A02			●	1.5	●
-3								
-2								
-1								
1	CCVR	- 5 min.	A03	●	●	●	6.0	●
		6	A04	●			4.5	
		8	A05	●			4.5	
		12	A06	●			4.5	
		16	A07	●			4.5	
2		24	A08	●	●	●	6.0	●
3		48	A09	●			4.5	
4		72	A10	●	●	●	6.0	●
5								
6			A11	●	●	●	6.0	●
7								
8			A12	●	●	●	6.0	●
9								
10			A13	●	●	●	6.0	●
11								
12			A14	●	●	●	6.0	●
13								
14			A15	●	●	●	6.0	●
15								
16			A16	●	●	●	6.0	●
17								
18			A17	●	●	●	6.0	●
19								
20			A18	●	●	●	6.0	●
21								
22			A19	●	●	●	6.0	●
23			A20			●	1.5	●
24			A21	●	●	●	6.0	●
25			A22			●	1.5	●
26			A23	●	●	●	6.0	●
27			A24			●	1.5	●
28			A25	●	●	●	6.0	●
29			A26			●	1.5	●
30			A27	●	●	●	6.0	●
31			A28			●	1.5	●
32			A29	●	●	●	6.0	●
33			A30			●	1.5	●
34			A31	●	●	●	6.0	●
35			A32			●	1.5	●
36	Ring-free period	-5 min.	A33	●	●	●	6.0	●
		3	A34	●			4.5	
		6	A35	●			4.5	
		12	A36	●			4.5	
37		24	A37	●	●		6.0	
38		48	A38	●	●	●	6.0	●
39		72	A39	●	●		6.0	
40								
41								
42								

Day	Treatment	Time ** (hours)	Sample code	ENG, EE	SHBG	Hormones (FSH, LH, E2, P)	Blood ** volume (ml)	USS
43-62	1-20 Marvelon®							
63	21	- 5 min.	A40	●	●	●	6.0	●
		0.25	A41	●			4.5	
		0.5	A42	●			4.5	
		1	A43	●			4.5	
		1.5	A44	●			4.5	
		2	A45	●			4.5	
		3	A46	●			4.5	
		4	A47	●			4.5	
		6	A48	●			4.5	
		8	A49	●			4.5	
		12	A50	●			4.5	
		16	A51	●			4.5	
64	Pill-free period	24	A52	●	●		6.0	
65		48	A53	●	●		6.0	
66		72	A54	●	●	●	6.0	●
67	ENG/EE IV	- 5 min.	B01	●	●		6.0	
		5 min.	B02	●			4.5	
		10 min.	B03	●			4.5	
		15 min.	B04	●			4.5	
		30 min.	B05	●			4.5	
		45 min.	B06	●			4.5	
		1	B07	●			4.5	
		1.5	B08	●			4.5	
		2	B09	●			4.5	
		4	B10	●			4.5	
		6	B11	●			4.5	
		8	B12	●			4.5	
		12	B13	●			4.5	
		16	B14	●			4.5	
68		24	B15	●	●		6.0	
		36	B16	●			4.5	
69		48	B17	●	●		6.0	
70		72	B18	●	●		6.0	
71		96	B19	●	●		6.0	
72		120	B20	●	●		6.0	

** Relative time to last pill intake (Marvelon®), first ring insertion (Day 29 (Group I) and Day 1 (Group II)), removal of last ring (Day 64 (Group I) and Day 36 (Group II)), or IV injection of ENG/EE .

++ ENG and EE: 4.5 ml blood; Hormones (FSH, LH, E2 and P) and SHBG: 1.5 ml blood. The total amount of blood to be collected for Group I was 345 ml. The total amount of blood to be collected for Group II was 354 ml.

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Attachment 2

4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Attachment 4

3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Attachment 5

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Org 3236 and EE in-vitro release of the all-EVA CCVR

Sample code: CP097055 (ENG)

Org 3236 release (µg/200ml)

Date	time (days)	1 1.1	2 1.2	3 1.3	4 1.4	5 1.5	6 1.6	7 2.1	8 2.2	9 2.3	10 2.4	11 2.5	12 2.6	Mean n= 12	RSD (%)
29/8/97	1	185.8	189.4	190.6	189	186.9	188	187.1	189.9	186.6	188.4	190.7	188.8	*188.4*	*0.85*
30/8/97	2	143.8	146.4	147.6	146.3	145	144.9	144.8	146.5	144.4	144.9	147.2	145.8	*145.6*	*0.81*
31/8/97	3	137.1	139.4	140.4	139.1	138.3	138.3	137.7	139.5	137.4	137.6	140.1	138.7	*138.6*	*0.78*
1/9/97	4	129.8	132.1	135.7	130.9	130.4	133.7	133.3	134.9	133	133.2	135.5	134.2	*133.1*	*1.46*
2/9/97	5	128.4	130.9	131.6	130.8	129.7	129.6	129.4	130.7	129.1	129.3	131.4	130.2	*130.1*	*0.76*
3/9/97	6	124.6	126.5	127.3	126.1	125.4	125.2	125	126.3	124.8	125.1	127	125.8	*125.8*	*0.70*
4/9/97	7	121.2	123.1	124	122.8	122.1	121.9	121.8	123	121.5	121.8	123.7	122.3	*122.4*	*0.72*
5/9/97	8	119.1	121.1	121.8	120.7	120.1	119.8	119.5	120.9	119.6	119.6	121.4	120.2	*120.3*	*0.71*
6/9/97	9	116.6	118.6	119.3	118.1	117.5	117.2	117.1	118.3	117	117	118.8	117.6	*117.8*	*0.72*
7/9/97	10	114.4	116.3	117.3	115.7	115.3	115	115	116	115	115	116.7	115.4	*115.6*	*0.73*
8/9/97	11	112.6	114.5	115.1	113.9	113.4	113	113	114.1	112.9	113	114.7	113.6	*113.7*	*0.71*
9/9/97	12	110.8	112.5	113.5	112.3	111.6	111.4	111.2	112.3	111.3	111.3	112.8	111.7	*111.9*	*0.71*
10/9/97	13	108.5	109.9	111	110	109.4	109.2	109.3	110.4	109.4	109.7	111.1	110.6	*109.9*	*0.71*
11/9/97	14	105.9	107.5	108.4	107.6	107	106.8	107.2	108.3	107.4	107.8	109.2	108.2	*107.6*	*0.80*
12/9/97	15	105.8	107.4	108.1	107	106.4	106	106.2	107.1	106.1	106	107.5	106.3	*106.7*	*0.69*
13/9/97	16	104.3	105.9	106.6	105.6	104.9	104.5	104.7	105.5	104.6	104.5	105.9	104.7	*105.1*	*0.70*
14/9/97	17	100.6	102.3	103.4	102.6	102	101.9	102.2	103.3	102.4	102.7	104.2	103.2	*102.6*	*0.89*
15/9/97	18	101	102.3	102.8	101.9	101.4	100.9	101.2	102	100.8	101.2	102.4	101.2	*101.6*	*0.65*
16/9/97	19	99.5	100.6	101.1	100.5	99.9	99.4	99.8	100.5	99.2	99.6	100.9	99.8	*100.1*	*0.63*
17/9/97	20	98.2	99.4	100.1	99.3	98.6	98.4	98.6	99.2	98.2	98.7	99.7	98.7	*98.9*	*0.61*
18/9/97	21	96.8	98.2	98.6	98.1	97.2	97.1	97.2	97.9	96.8	97.2	98.3	97.4	*97.6*	*0.64*
Mean		114.0	115.7	116.7	115.5	114.8	114.7	114.7	115.8	114.5	114.8	116.4	115.3		

98.2 - 147.6

Summary Org 3236 release (µg/CCVR)

	Mean n= 12	Sd (n-1)	RSD (%)
day 1	188.4	1.60	0.85
day 2-21	115.2	0.81	0.71
day 21	97.6	0.62	0.64

Org 3236 and EE in-vitro release of the all-EVA CCVR

Sample code: CP097056 ENG

Org 3236 release (µg/200ml)

Date	time (days)	1	2	3	4	5	6	7	8	9	10	11	12	Mean	RSD (%)
		15.1	15.2	15.3	15.4	15.5	15.6	16.1	16.2	16.3	16.4	16.5	16.6	n= 12	
19/9/97	1	196.4	198.1	197	198.6	197.4	196.5	198.2	197.1	196.6	196	199	198.8	*197.5*	*0.52*
20/9/97	2	149.9	151	149.5	152.1	151.2	150.4	150.4	149.8	148.8	150	153	152.3	*150.7*	*0.83*
21/9/97	3	142.1	143.1	141.6	144	143.3	142.4	142.3	142	141.2	142.5	145.2	144.2	*142.8*	*0.82*
22/9/97	4	136.9	137.9	136.5	139	138	137.4	137.3	136.9	136.2	137.2	140	138.9	*137.7*	*0.82*
23/9/97	5	133.9	133.9	132.6	134.7	134.9	133.3	133	132.6	132.1	132.9	135.6	134.6	*133.7*	*0.82*
24/9/97	6	130.3	131	129.9	132.1	131.5	130.8	130.8	130.4	129.9	130.6	133.3	132.2	*131.1*	*0.79*
25/9/97	7	126.3	126.9	126.1	128.1	127.3	126.7	126.8	126.6	125.9	126.6	129.1	128.1	*127.0*	*0.75*
26/9/97	8	123.4	124.3	123.3	125.2	124.5	123.8	123.9	123.8	123.3	123.7	126.3	125.4	*124.2*	*0.76*
27/9/97	9	120.9	121.4	120.5	122.5	121.6	121.1	121.4	121.1	120.5	121	123.4	122.7	*121.5*	*0.74*
28/9/97	10	118.3	119.1	118.2	120.1	118.9	118.8	119	118.7	118.3	118.7	120.8	120.1	*119.1*	*0.69*
29/9/97	11	116.5	117.3	116.4	118.1	117.3	117.1	117.1	116.8	116.5	116.9	118.9	118.4	*117.3*	*0.68*
30/9/97	12	115.8	115.7	114.7	116.5	116.6	115.5	115.2	115	114.5	115.1	117.2	116.3	*115.7*	*0.72*
1/10/97	13	112.6	113.3	112.5	114	113.2	113.1	113.2	112.6	112.4	112.7	114.8	114	*113.2*	*0.65*
2/10/97	14	110.4	111.2	110.4	111.8	110.7	111.3	111.1	110.7	110.6	110.7	112.7	112.5	*111.2*	*0.70*
3/10/97	15	108.6	109.3	108.6	109.9	109.1	109.7	109.2	109	108.7	108.8	110.8	110.9	*109.4*	*0.73*
4/10/97	16	107.5	108	107.4	108.7	108.2	108.6	107.9	107.9	107.5	107.6	109.7	109.9	*108.2*	*0.77*
5/10/97	17	105.7	106.4	105.6	106.8	106.4	107	106.5	106.2	105.8	105.9	107.9	108.1	*106.5*	*0.76*
6/10/97	18	104.4	105	104.3	105.5	105.3	105.7	105.1	105	104.5	104.6	106.6	106.8	*105.2*	*0.77*
7/10/97	19	104.9	105.6	104.4	106.2	105.7	106.4	105.6	105.4	104.8	105.3	107.2	107.4	*105.7*	*0.87*
8/10/97	20	103	102.9	101.8	103.3	103.6	103.4	102.5	102.2	101.8	102	104	104	*102.9*	*0.79*
9/10/97	21	99.9	100.4	99.2	101	100.6	101	100.4	100.2	99.5	100.1	102	102.1	*100.5*	*0.88*
Mean		118.6	119.2	118.2	120.0	119.4	119.2	118.9	118.6	118.1	118.6	120.9	120.4		

101.8 - 153

Summary Org 3236 release (µg/CCVR)

	Mean n= 12	Sd (n-1)	RSD (%)
day 1	197.5	1.03	0.52
day 2-21	119.2	0.88	0.73
day 21	100.5	0.89	0.88

0033

Org 3236 and EE in-vitro release of the all-EVA CCVR

Sample code: CP097057

EVA

Org 3236 release (µg/20ml)

Date	time (days)	1 3.1	2 3.2	3 3.3	4 3.4	5 3.5	6 3.6	7 4.1	8 4.2	9 4.3	10 4.4	11 4.5	12 4.6	Mean n= 12	RSD (%)
9/10/97	1	192.8	194	194.4	205.2	199.6	200	199.4	195.9	197.7	202.3	200.6	198.3	*198.4*	*1.83*
10/10/97	2	144	144.9	145.6	144.6	150.4	150.3	149.6	146.8	146.6	146.2	151.3	150.1	*147.5*	*1.78*
11/10/97	3	136.4	137.2	138.1	136	142.2	142.2	141.4	138.8	138.8	137.8	143.4	141.8	*139.5*	*1.83*
12/10/97	4	131.3	132.3	133	131.2	136.6	136.7	135.9	133.9	133.5	132.7	137.9	136.4	*134.3*	*1.72*
13/10/97	5	123.9	126.2	128.3	127.8	133.5	133.6	133	130.9	130.6	129.5	134.9	133.4	*130.5*	*2.61*
14/10/97	6	122.1	124.4	129.6	126.5	130.6	132.1	129.5	127.5	129.1	127.9	133.4	131.8	*128.7*	*2.54*
15/10/97	7	119.6	121.9	122.6	121.1	125.8	125.7	125.3	123.4	123.1	122.3	126.9	125.5	*123.6*	*1.81*
16/10/97	8	119.4	120.4	120.7	119.3	123.9	124	123.5	121.6	121.3	120.4	125	123.6	*121.9*	*1.62*
17/10/97	9	116.6	117.6	118	116.4	121.1	121	120.6	118.7	118.5	117.7	122	120.7	*119.1*	*1.61*
18/10/97	10	114.7	115.6	116	114.5	119	118.9	118.4	116.7	116.5	115.7	120	118.6	*117.1*	*1.58*
19/10/97	11	112.6	113.4	113.7	112.2	116.7	116.7	116.3	114.6	114.2	113.6	117.7	116.5	*114.9*	*1.60*
20/10/97	12	111.1	112.1	112.3	111	115.1	115.3	114.6	113.1	113	112.1	116.1	114.9	*113.4*	*1.54*
21/10/97	13	108.5	109.6	109.9	108.5	112.6	112.6	112.1	110.7	110.4	109.7	113.5	112.3	*110.9*	*1.54*
22/10/97	14	105.6	106.8	107.5	106.1	109.5	110.1	109.8	108.2	108.2	107.4	111.1	110	*108.4*	*1.61*
23/10/97	15	104.6	105.4	107	105	108.8	109.1	108.4	106.6	106.7	106.3	109.5	108.7	*107.2*	*1.58*
24/10/97	16	106.2	105.4	105.8	104.8	109.3	108.2	107.5	105.7	105.8	105	108.4	107.5	*106.6*	*1.39*
25/10/97	17	103.4	103.3	103.7	102.5	106.7	106	105.8	103.9	103.9	103.3	106.5	105.7	*104.6*	*1.40*
26/10/97	18	101.9	101.8	102.2	101.1	105.1	104.4	104.2	102.5	102.4	101.8	104.9	104	*103.0*	*1.35*
27/10/97	19	100	100	100.4	99.3	103.3	102.6	102.2	100.7	100.4	100	103.2	102.1	*101.2*	*1.39*
28/10/97	20	99	98.8	99.5	98.3	102.2	101.5	101.3	99.5	99.4	98.9	101.9	101	*100.1*	*1.37*
29/10/97	21	97.6	97.6	98.2	97.1	100.9	100.2	99.9	98.3	98.1	97.8	100.7	99.7	*98.8*	*1.36*
Mean		1139	114.7	115.6	114.2	118.7	118.6	118.0	116.1	116.0	115.3	119.4	118.2		

98.9 - 150.4

Summary Org 3236 release (µg/CCVR)

	Mean n= 12	Sd (n-1)	RSD (%)
day 1	198.4	3.63	1.83
day 2-21	116.6	1.91	1.64
day 21	98.8	1.34	1.36

Org 3236 and EE in-vitro release of the all-EVA CCVR

Sample code: CP097171

Org 3236 release (µg/200ml) EKG

Date	time (days)	1 20.1	2 20.2	3 20.3	4 20.4	5 20.5	6 20.6	7 21.1	8 21.2	9 21.3	10 21.4	11 21.5	12 21.6	Mean n= 12	RSD (%)
23/6/98	1	196.5	199.6	200.8	201.2	198.7	198.2	199.4	199.4	201.2	200.6	202	199.9	*199.8*	*0.76*
24/6/98	2	149.1	150.9	151.4	153	150.3	149.8	150.8	151.2	152.6	151.9	152.3	151.3	*151.2*	*0.76*
25/6/98	3	140.2	142.4	142.4	143.8	141.4	140.8	142.3	142.1	144.1	142.9	143	142.4	*142.3*	*0.79*
26/6/98	4	136.2	137.8	138.1	138.8	137	136.4	137.7	137.8	139.4	138.8	138.8	137.6	*137.9*	*0.72*
27/6/98	5	132.9	134.5	134.6	135.6	133.7	133.4	134.4	134.4	135.7	135.4	135.2	134.6	*134.5*	*0.65*
28/6/98	6	128.8	130.5	130.7	131.7	129.8	129.4	130.5	130.2	132	131	131.3	130.4	*130.5*	*0.70*
29/6/98	7	125.8	127.3	127.3	128	126.7	126.1	127.1	127	128.4	128	128.1	126.8	*127.2*	*0.63*
30/6/98	8	123.3	124.8	124.5	125.5	123.9	123.4	124.6	124.3	126	125.4	125.4	124.6	*124.6*	*0.68*
1/7/98	9	120.8	122.4	122.3	123	121.4	120.9	122.3	122.2	123.4	122.9	122.9	121.8	*122.2*	*0.68*
2/7/98	10	118.7	120	120.1	120.5	119.4	118.8	119.7	119.8	121.2	120.7	120.7	119.8	*120.0*	*0.63*
3/7/98	11	116.6	117.5	117.8	118.2	116.9	116.7	117.7	117.1	118.8	118.2	118.3	117.7	*117.6*	*0.59*
4/7/98	12	114.4	115.1	115.5	115.7	114.4	114.2	115.7	114.8	116.3	115.5	115.7	115	*115.2*	*0.56*
5/7/98	13	112.9	113.6	113.8	114.1	113.1	112.6	114.2	113.1	114.7	113.9	114.2	113.6	*113.7*	*0.55*
6/7/98	14	111.2	112	112	112.3	111.3	110.7	112.2	111.6	113.1	112.3	112.6	111.6	*111.9*	*0.59*
7/7/98	15	109.3	110.4	110.1	110.4	109.2	108.8	110.6	110.2	110.7	110.6	110.3	109.5	*110.0*	*0.58*
8/7/98	16	107.8	109.1	108.8	109	107.8	107.3	109.1	108.7	109.6	109	109	108.3	*108.6*	*0.63*
9/7/98	17	106.6	107.7	107.4	107.8	106.7	106.3	107.7	107.4	108.2	107.8	107.8	107	*107.4*	*0.55*
10/7/98	18	105.8	106.4	106.4	106.4	105.5	105.5	106.8	106.5	107.2	106.6	106.7	106.2	*106.3*	*0.48*
11/7/98	19	103.9	104.8	104.8	104.6	104	103.6	104.9	104.7	105.4	104.4	104.9	104.4	*104.5*	*0.48*
12/7/98	20	102.9	103.8	103.5	103.3	103	102.6	103.9	103.5	104.1	103.2	104.1	103.5	*103.5*	*0.46*
13/7/98	21	101.4	102.4	102.2	102	101.6	101.1	102.5	102.1	102.9	101.9	102.6	102.1	*102.1*	*0.51*
Mean		118.4	119.7	119.7	120.2	118.9	118.4	119.7	119.4	120.7	120.0	120.2	119.4		

102.6 - 153

Summary Org 3236 release (µg/CCVR)

	Mean n= 12	Sd (n-1)	RSD (%)
day 1	199.8	1.52	0.76
day 2-21	119.6	0.70	0.59
day 21	102.1	0.52	0.51

Application No.: 97-261/-

Sample code: EE CP097055

EE release (µg/200ml)

Date	time (days)	1 1.1	2 1.2	3 1.3	4 1.4	5 1.5	6 1.6	7 2.1	8 2.2	9 2.3	10 2.4	11 2.5	12 2.6	Mean n= 12	RSD (%)
29/8/97	1	22.6	23.3	23.5	23.5	22.9	23.2	23.2	23.4	23.2	23.4	23.5	23.3	*23.3*	*1.15*
30/8/97	2	15.9	16.1	16.4	16.4	16	16.3	16.1	16.4	16.3	16.4	16.4	16.3	*16.3*	*1.10*
31/8/97	3	15.1	15.5	15.6	15.4	15.4	15.6	15.6	15.7	15.5	15.5	15.9	15.6	*15.5*	*1.24*
1/9/97	4	14.7	15.2	15.2	15.1	15	15.3	15.1	15.3	15.1	15.2	15.4	15.3	*15.2*	*1.21*
2/9/97	5	14.4	15.1	15.1	14.9	15	14.9	14.9	15.1	15.1	14.9	15.1	15	*15.0*	*1.32*
3/9/97	6	14	14.6	14.5	14.3	14.4	14.3	14.6	14.6	14.6	14.4	14.6	14.6	*14.5*	*1.30*
4/9/97	7	14.1	14.4	14.5	14.3	14.4	14.2	14.3	14.5	14.3	14.3	14.5	14.3	*14.3*	*0.86*
5/9/97	8	13.8	14.1	14.3	14.1	14	14.2	14.4	14.3	14.1	14.3	14.3	14.2	*14.2*	*1.17*
6/9/97	9	13.4	13.8	14	13.9	13.8	13.8	13.8	14.1	14	14	14	13.9	*13.9*	*1.31*
7/9/97	10	13.2	13.6	13.9	13.9	13.7	13.8	13.8	13.9	13.9	13.9	14.1	13.9	*13.8*	*1.64*
8/9/97	11	13.4	13.7	13.9	13.7	13.6	13.7	13.6	13.8	13.8	13.6	13.7	13.7	*13.7*	*0.93*
9/9/97	12	13.2	13.6	13.8	13.6	13.6	13.6	13.6	13.7	13.6	13.5	13.7	13.7	*13.6*	*1.09*
10/9/97	13	13.2	13.5	13.6	13.7	13.5	13.6	13.6	13.8	13.6	13.5	13.6	13.7	*13.6*	*1.09*
11/9/97	14	13	13.3	13.4	13.3	13.2	13.3	13.3	13.5	13.4	13.3	13.6	13.5	*13.3*	*1.17*
12/9/97	15	12.9	13	13.3	13	12.9	13	13.1	13.3	13	13	13	13	*13.0*	*1.01*
13/9/97	16	12.9	13.3	13.2	13.4	13.1	13	13.1	13.3	13.1	13.1	13.5	13.2	*13.2*	*1.29*
14/9/97	17	12.7	13	13.1	12.9	12.9	13.1	13.1	13.1	13	13	13.1	12.8	*13.0*	*1.03*
15/9/97	18	12.6	12.9	12.9	12.9	12.7	12.9	12.9	12.9	12.7	12.8	12.9	12.6	*12.8*	*0.97*
16/9/97	19	12.3	12.5	12.7	12.6	12.5	12.3	12.6	12.7	12.5	12.6	12.7	12.4	*12.5*	*1.15*
17/9/97	20	12.5	12.6	12.8	12.7	12.6	12.5	12.6	12.6	12.6	12.6	12.8	12.7	*12.6*	*0.78*
18/9/97	21	12.3	12.6	12.6	12.6	12.5	12.6	12.7	12.6	12.5	12.6	12.9	12.6	*12.6*	*1.10*
Mean		13.5	13.8	13.9	13.8	13.7	13.8	13.8	14.0	13.8	13.8	14.0	13.9		

12.5 – 16.4

Summary EE release (µg/CCVR)

	Mean n= 12	Sd (n-1)	RSD (%)
day 1	23.3	0.27	1.15
day 2-21	13.8	0.13	0.94
day 21	12.6	0.14	1.10

Analist: Wa
Date: 21.10.1997

0036

Org 3236 and EE in-vitro release of the all-EVA CCVR

Sample code: **CP097056**

EE 7

EE release (µg/200ml)

Date	time (days)	1 15.1	2 15.2	3 15.3	4 15.4	5 15.5	6 15.6	7 16.1	8 16.2	9 16.3	10 16.4	11 16.5	12 16.6	Mean n= 12	RSD
	1	24.6	25	25	25.1	24.6	24.7	25.5	25.2	25.1	24.9	25.3	25.1	*25.0*	*1.10*
19/9/97	2	16.8	17.2	17	17.3	17.1	17.2	17.1	17.1	17.1	17.1	17.4	17.3	*17.1*	*0.91*
20/9/97	3	16	16.2	16.2	16.6	16.3	16.4	16.5	16.4	16.2	16.3	16.7	16.8	*16.4*	*1.42*
21/9/97	4	15.3	15.5	15.5	15.9	15.4	15.8	15.8	15.6	15.5	15.7	16	16.1	*15.7*	*1.59*
22/9/97	5	15.8	16	15.7	16	16	15.8	15.8	16	15.6	15.8	16	15.7	*15.9*	*0.91*
23/9/97	6	15	15.5	15.4	15.8	15.4	15.6	15.6	15.6	15.7	15.6	15.9	15.8	*15.6*	*1.53*
24/9/97	7	14.9	15	14.8	15.2	14.9	15.1	15	15.1	15.1	14.9	15.2	15.3	*15.0*	*1.00*
25/9/97	8	14.5	14.9	14.8	15.2	14.9	14.8	15.2	15	14.7	14.9	15.2	15.3	*15.0*	*1.60*
26/9/97	9	14.3	14.4	14.4	14.6	14.2	14.4	14.3	14.3	14	14.1	14.2	14.3	*14.3*	*1.09*
27/9/97	10	14	14.4	14.1	14.5	14.2	14.3	14.6	14.4	14.4	14.4	14.5	14.6	*14.4*	*1.31*
28/9/97	11	13.9	14.2	14.1	14.3	13.8	14.1	14.3	14.3	14.1	14.1	14.3	14.5	*14.2*	*1.36*
29/9/97	12	14.8	14.4	14.6	14.7	14.4	14.4	14.4	14.5	14.4	14.4	14.5	14.5	*14.5*	*0.93*
30/9/97	13	13.9	14.3	14.1	14.4	14.2	14.1	14.3	13.8	14	14.1	14.3	14.5	*14.2*	*1.45*
1/10/97	14	13.7	14	13.9	14.2	13.8	14.5	14.2	14.4	14	14.2	14.4	14.4	*14.1*	*1.85*
2/10/97	15	13.7	14.1	13.9	14.1	13.6	13.8	13.9	14.1	13.8	13.9	14.3	14.4	*14.0*	*1.71*
3/10/97	16	13.8	14.6	14.1	14.2	14	14.4	14.3	14.6	14.4	14.3	14.4	14.7	*14.3*	*1.83*
4/10/97	17	13.4	13.8	13.7	13.8	13.4	13.8	14.1	13.8	13.8	13.9	14.1	14.3	*13.8*	*1.90*
5/10/97	18	13	13	13.1	13.2	13.3	13.5	13.3	13.2	13.2	13.2	13.5	13.6	*13.3*	*1.45*
6/10/97	19	13	13	12.9	13	13.1	13.1	13	12.9	12.9	12.9	13.1	13.2	*13.0*	*0.77*
7/10/97	20	13	12.9	12.8	12.9	12.9	12.9	12.8	12.8	12.7	12.7	12.8	13	*12.9*	*0.78*
8/10/97	21	13.2	13.4	13.3	13.6	13.3	13.5	13.5	13.4	13.4	13.5	13.6	13.8	*13.5*	*1.20*
9/10/97	22	13.1	13.3	13.3	13.4	13	13.4	13.4	13.4	13.3	13.3	13.5	13.6	*13.3*	*1.21*
Mean		14.3	14.5	14.4	14.7	14.4	14.6	14.6	14.6	14.5	14.5	14.7	14.8		

12.7 - 17.4

Date: 31.10.1997

Analist: Wa

Summary EE release (µg/CCVR)

	Mean n= 12	Sd (n-1)	RSD (%)
day 1	25.0	0.27	1.10
day 2-21	14.5	0.14	0.98
day 21	13.5	0.16	1.20

0037

Org 3236 and EE in-vitro release of the all-EVA CCVR

Sample code: CP097057

EE

Org 224 release (µg/200ml)

Date	time (days)	1 3.1	2 3.2	3 3.3	4 3.4	5 3.5	6 3.6	7 4.1	8 4.2	9 4.3	10 4.4	11 4.5	12 4.6	Mean n= 12	RSD (%)
9/10/97	1	26.3	26.7	26.8	26.5	26.9	27.1	27.4	26.9	26.9	26.8	27.5	27.3	*26.9*	*1.32*
10/10/97	2	16.5	16.6	16.8	16.8	17.1	17.4	17.4	17	17	16.9	17.3	17.4	*17.0*	*1.84*
11/10/97	3	15.8	15.8	15.9	15.7	16.3	16.4	16.4	16	16	15.9	16.5	16.4	*16.1*	*1.79*
12/10/97	4	15.2	15.3	15.4	15.3	15.8	15.9	15.9	15.6	15.6	15.4	15.9	15.9	*15.6*	*1.75*
13/10/97	5	15.2	15.2	15.2	15.1	15.5	15.6	15.7	15.3	15.3	15.2	15.6	15.6	*15.4*	*1.36*
14/10/97	6	14.7	15.1	15.2	15	15.4	15.6	15.8	15.4	15.3	15.1	15.8	15.8	*15.4*	*2.30*
15/10/97	7	14.7	14.9	14.9	14.7	15.2	15.2	15.3	14.9	14.9	14.7	15.2	15.1	*15.0*	*1.46*
16/10/97	8	14.4	14.5	14.4	14.3	14.8	15	15	14.6	14.6	14.4	15	15	*14.7*	*1.89*
17/10/97	9	14.2	14.3	14.4	14.2	14.6	14.8	14.8	14.5	14.4	14.4	14.7	14.8	*14.5*	*1.57*
18/10/97	10	14.1	14.1	14.2	14	14.5	14.5	14.6	14.4	14.2	14.1	14.5	14.5	*14.3*	*1.47*
19/10/97	11	13.8	14	13.9	13.8	14.1	14.3	14.3	14	14	13.8	14.5	14.3	*14.1*	*1.67*
20/10/97	12	13.6	13.8	13.7	13.5	14.1	14.2	14.1	13.9	13.8	13.7	14.2	14.2	*13.9*	*1.81*
21/10/97	13	13.5	13.7	13.7	13.6	14	14	14.1	13.8	13.8	13.6	14.1	14	*13.8*	*1.51*
22/10/97	14	13.1	13.3	13.5	13.3	13.4	13.9	14	13.8	13.5	13.5	14	14	*13.6*	*2.33*
23/10/97	15	13.2	13.5	13.5	13.4	13.9	14	13.9	13.6	13.7	13.6	14	13.9	*13.7*	*1.89*
24/10/97	16	14	13.7	13.6	13.4	14	13.9	13.9	13.5	13.5	13.5	13.9	13.8	*13.7*	*1.59*
25/10/97	17	13.4	13.4	13.4	13.2	13.8	13.7	13.7	13.5	13.4	13.4	13.7	13.7	*13.5*	*1.38*
26/10/97	18	13.4	13.2	13.1	13	13.4	13.6	13.6	13.3	13.2	13.1	13.6	13.6	*13.3*	*1.67*
27/10/97	19	13.1	13.1	13.1	13	13.5	13.4	13.5	13.1	13	13.1	13.3	13.3	*13.2*	*1.39*
28/10/97	20	13.1	12.9	12.9	12.9	13.4	13.4	13.4	13.2	13.1	13	13.4	13.4	*13.2*	*1.65*
29/10/97	21	13.2	12.9	13.1	12.8	13.4	13.4	13.3	13.1	13.1	12.9	13.2	13.2	*13.1*	*1.46*
Mean		14.1	14.2	14.2	14.1	14.5	14.6	14.6	14.3	14.3	14.2	14.6	14.6		

12.9 - 17.4

Date: 20.11.1997

Analist: Wa

Summary EE release (µg/CCVR)

	Mean n= 12	Sd (n-1)	RSD (%)
day 1	26.9	0.35	1.32
day 2-21	14.4	0.22	1.56
day 21	13.1	0.19	1.46

0038

Org 3236 and EE in-vitro release of the all-EVA CCVR

Sample code: CP097171

Org 224 release (µg/200ml) EE

		1	2	3	4	5	6	7	8	9	10	11	12	Mean	RSD (%)
Date	time (days)	20.1	20.2	20.3	20.4	20.5	20.6	21.1	21.2	21.3	21.4	21.5	21.6	n= 12	
23/6/98	1	23.2	23.8	23.8	23.9	23.6	23.7	23.9	23.9	24.1	24.1	24.1	24.3	*23.9*	*1.20*
24/6/98	2	16.3	16.5	16.6	16.8	16.4	16.5	16.5	16.2	16.5	16.6	16.5	16.5	*16.5*	*0.91*
25/6/98	3	16.5	16.7	16.3	16.6	16	16.2	16.4	16.5	16.6	16.6	16.6	16.5	*16.5*	*1.23*
26/6/98	4	15.2	15.6	15.6	15.4	15.2	15.2	15.4	15.5	15.4	15.4	15.4	15.2	*15.4*	*0.97*
27/6/98	5	14.9	15	14.7	15.1	14.9	14.9	15	15	15.1	15.1	15.1	15	*15.0*	*0.80*
28/6/98	6	14.5	14.8	14.7	14.7	14.6	14.5	14.8	14.6	14.9	14.9	14.8	14.5	*14.7*	*1.02*
29/6/98	7	14.4	14.6	14.3	14.5	14.2	14.3	14.6	14.5	14.6	14.6	14.5	14.5	*14.5*	*0.95*
30/6/98	8	13.8	13.9	13.9	14.2	14.4	13.6	14.1	14.1	14.3	14.2	14.1	13.9	*14.0*	*1.62*
1/7/98	9	14.4	14.6	14.3	14.5	14.3	14.1	14.5	14.3	14.5	14.3	14.5	14.3	*14.4*	*0.98*
2/7/98	10	14.1	14.1	14.2	14.2	14.1	14	14.2	14.1	14.3	14.2	14.2	14	*14.1*	*0.64*
3/7/98	11	13.5	13.5	13.6	13.4	13.4	13.4	13.6	13.5	13.7	13.7	13.6	13.4	*13.5*	*0.84*
4/7/98	12	13.5	13.7	13.6	13.5	13.4	13.3	13.7	13.5	13.7	13.6	13.6	13.5	*13.6*	*0.92*
5/7/98	13	13.8	13.9	14.1	13.9	13.9	13.7	14	13.9	14	14.1	13.9	13.8	*13.9*	*0.86*
6/7/98	14	13.3	13.3	13.4	13.4	13.3	13.1	13.6	13.3	13.5	13.3	13.3	13.5	*13.4*	*0.98*
7/7/98	15	13.4	13.4	13.4	13.4	13.3	13.2	13.5	13.4	13.5	13.4	13.4	13.3	*13.4*	*0.62*
8/7/98	16	13.1	13.3	13.3	13.2	13	13	13.4	13.2	13.3	13.3	13.3	13.1	*13.2*	*0.99*
9/7/98	17	13.2	13.4	13.4	13.2	13.1	13.1	13.5	13.1	13.3	13.1	13.2	13.2	*13.2*	*1.04*
10/7/98	18	13.1	13.4	13.2	13.2	13	13.1	13.3	13.1	13.3	13.3	13.3	13.2	*13.2*	*0.88*
11/7/98	19	13.2	13.4	13.3	13.2	13.1	12.9	13.4	13.3	13.4	13.1	13.3	13.1	*13.2*	*1.17*
12/7/98	20	12.7	12.9	12.9	12.8	12.5	12.5	12.8	12.7	12.9	12.6	12.8	12.7	*12.7*	*1.13*
13/7/98	21	12.4	12.8	12.7	12.6	12.6	12.6	12.7	12.6	12.8	12.7	12.7	12.7	*12.7*	*0.86*
Mean		14.0	14.1	14.1	14.1	13.9	13.9	14.2	14.0	14.2	14.1	14.1	14.0		

12.5 — 16.8

Analist:

Date:

Summary Org 224 release (µg/CCVR)

	Mean	Sd (n-1)	RSD (%)
	n= 12		
day 1	23.9	0.29	1.20
day 2-21	14.1	0.10	0.69
day 21	12.7	0.11	0.86

Verifier:

0039

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.