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RESEARCH**

APPLICATION NUMBER:

21-529

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ADDENDUM TO CLINICAL PHARMACOLOGY REVIEW

NDA: 21-529
Submission Date: January 16, 2006
Generic Name: Etonogestrel implant
Brand Name: Implanon™
Sponsor: Organon USA Inc.
Date: June 16, 2006
Reviewer: Myong-Jin Kim, PharmD
Team Leader: Ameeta Parekh, PhD

Background:

Implanon™ (etonogestrel implant, NDA 21-529) is a progestin-only contraceptive for subdermal use. On October 29, 2004, the application received an approvable action based on three deficiencies. The deficiencies were 1) concerns about the quality of the clinical data from Study 34507, 2) labeling was not finalized, and 3) incomplete inspection of the sterilization facility. The overall Human Pharmacokinetic Section of this NDA was acceptable to the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (see the Clinical Pharmacology and Biopharmaceutics Original NDA review, October 26, 2004).

b(4)

The application received its second approvable action on June 14, 2005 (see Addendum to Clinical Pharmacology and Biopharmaceutics Review, June 8, 2005). To address the issue of the adequacy of the clinical data to support approval of Implanon, the sponsor was advised to submit new clinical trial data from a clinical trial(s) that has been conducted in accordance with Good Clinical Practices. In addition, the sponsor was advised to submit an acceptable plan for a post-marketing monitoring program for Implanon-related insertion and removal adverse events in U.S. patients.

In response to the June 14, 2005 Approvable Letter, the sponsor submitted their complete response on January 16, 2006. In this new submission, no new clinical pharmacology studies were submitted for Clinical Pharmacology review.

Recommendation:

The overall Human Pharmacokinetic Section of NDA 21-529 submitted on September 30, 2003 is *acceptable* to the Office of Clinical Pharmacology/Division of Clinical Pharmacology III. Labeling comments outlined in this addendum should be conveyed to the sponsor as appropriate.

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6/16/2006 03:49:46 PM
BIOPHARMACEUTICS

**ADDENDUM TO CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW**

NDA: 21-529
Submission Date: December 14, 2004
Generic Name: Etonogestrel implant
Brand Name: Implanon™
Sponsor: Organon USA Inc.
Date: June 6, 2005
Reviewer: Myong-Jin Kim, PharmD, HFD-870
Team Leader: Ameeta Parekh, PhD, HFD-870
Pharmacometrics: He Sun, PhD, HFD-870

Background:

Implanon™ (etonogestrel implant, NDA 21-529) is a progestin-only contraceptive for subdermal use. On October 29, 2004, the application received an approvable action based on three deficiencies. The deficiencies were 1) concerns about the quality of the clinical data from Study 34507, 2) labeling was not finalized, and 3) incomplete inspection of the sterilization facility. The overall Human Pharmacokinetic Section of this NDA was acceptable to the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II).

b(4)

In response to the October 29, 2004 Approvable Letter, the sponsor submitted a class 2, complete response on December 14, 2004. This submission consists of the following sections:

1. Sponsor's response to Good Clinical Practice Issues
2. Revised Labeling
3. Status of Facility Inspection
4. Safety Update Report
5. Foreign Registration History

b(4)

The revised Clinical Pharmacology section of the product label is attached to this addendum (Appendix A). The Absorption section was revised based on the following data from 3 studies:

Study		n	Etonogestrel (ENG) concentration (pg/mL) Mean (SD)
34502	Year 1 (Week 48-53)	15	260.5 (94.3)
	Year 2 (Week 98-104)	15	190.6 (64)
	Year 3 (Week 150-155)	11	177.2 (68.8)
34508	Year 1 (Day 366)	10	196
	Year 2 (Day 731)	8	194
	Year 3 (Day 1096)	6	156
069001	Year 1	16	192.1 (47.2)
	Year 2 (23 month)	12	153.6 (32.3)

The effect of body mass index on ENG concentrations was evaluated using a population PK model approach. The pharmacometrics review by Dr. He Sun is attached here (Appendix B).

Recommendation:

The overall Human Pharmacokinetic Section of NDA 21-529 is *acceptable* to the OCPB/DPE-II. Labeling comments outlined in this addendum to Clinical Pharmacology and Biopharmaceutics Review should be conveyed to the sponsor as appropriate.

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Appendix B:

PHARMACOMETRICS REVIEW

NDA:	21-529
Product:	Implanon
Sponsor:	Organon USA Inc.
Type of Submission:	Original NDA
Indication:	Prevention of pregnancy
Primary Reviewer:	Myong-Jin Kim, Pharm.D.
Team Leader	Ameeta Parekh, Ph.D.
Pharmacometrics:	He Sun, Ph.D.

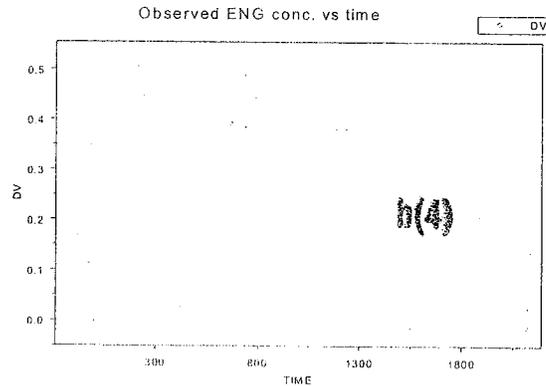
OBJECTIVES:

(1) To estimate % of subjects with serum etonogestrel (ENG) concentrations > 90-120 pg/mL at the end of 1, 2 and 3 years post implantation of Implanon, (2) to estimate the average number of days at which serum ENG concentrations are >90-120 pg/mL for subjects with a body mass index (BMI) between 17 and 30.

METHODS:

(1) To establish a population PK model for ENG implant including all possible covariates, (2) to simulate the ENG concentrations as a function of time for all included subjects, (3) to estimate % of subjects with serum ENG concentrations >90-120 pg/mL at the end of 1, 2, and 3 years post implantation, and the number of days at which mean serum ENG concentrations are >90-120 pg/mL for BMI 17 - 30.

There were a total of 845 subjects. Single ENG concentration was observed for each subject randomly distributed across ~ 150 to 1,800 days post implantation. The dataset provided by the reviewer was reformatted for NONMEM use. The raw observed ENG concentration vs. time plot is given below:



RESULTS:

PopPK Modeling:

Several user models were generated, compiled and tested. The models tested include a model that has two release rates from the depot compartment to mimic the drug release characteristics from an implant. Flip-flop mechanism was observed. The final population PK model included BMI as covariate for volume of distribution (Vd). The drug elimination rate constant (Ke) was not well estimable due to a lack of observation at early times of post-implantation. Therefore, search of covariates for Ke was also not successful. The final population PK parameters are as follows:

$$K_r (\text{day}^{-1}) = 0.000219$$

$$V_d (\text{L}) = 159 + 6.83 * \text{BMI} \quad (\text{Mean } V_d = 317 \pm 55)$$

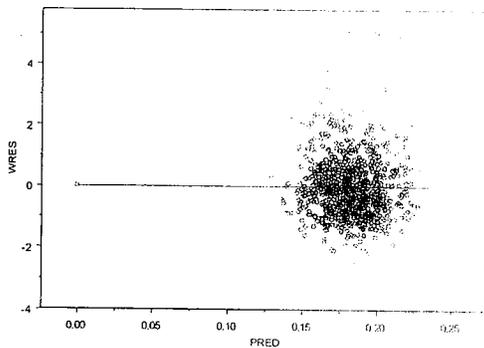
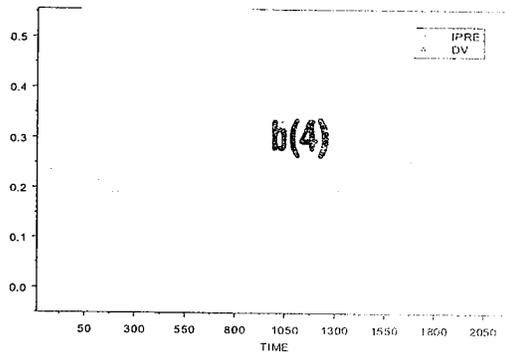
$$K_e (\text{day}^{-1}) = 29.6 \quad (\text{no real physiological meanings. The } t_{1/2} \text{ of ENG is about 1 day from other studies.})$$

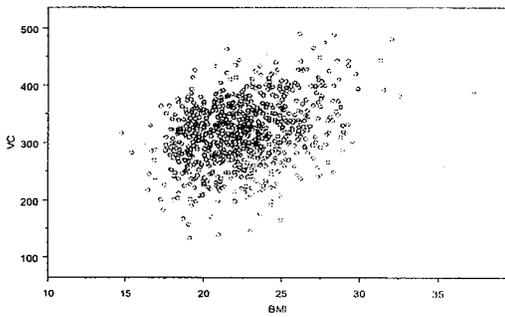
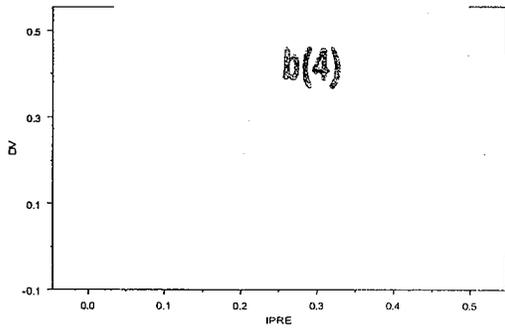
Inter-subject variability for Ke = 45%

Inter-subject variability for Kr = 22%

Residual variability = 14%

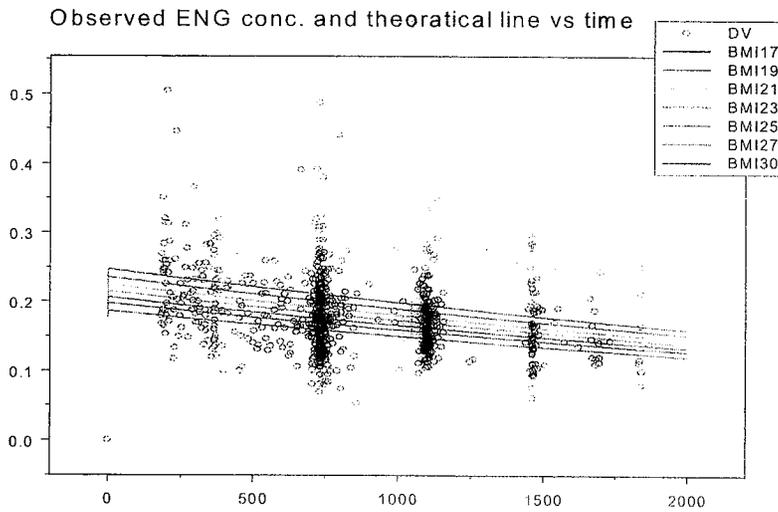
Some goodness-of-fit and observed-predicted correlation plots are provided below, where IPRE = individual model predicted values and DV = observed values.





Effect of BMI on ENG concentrations as a function of time:

The figure below is a superimposed plot of observed ENG concentrations vs. time, and the mean predicted ENG concentrations vs. time with a BMI between 17 and 30.



Estimations:

(1) The percentage of subjects with ENG concentrations > 90 – 120 pg/mL at the end of 1 – 3.5 years was calculated using the data derived from 100 replicated simulations with 845 subjects (without a BMI sub-grouping).

	% of subjects with ENG concentration > the cutoff value at the end of 1 – 3.5 yrs					
ENG (pg/mL)	Year 1	Year 1.5	Year 2	Year 2.5	Year 3	Year 3.5
> 120	98.22	97.96	94.12	88.0	82.78	79.55
> 110	99.46	98.98	96.59	95.18	93.88	89.77
> 100	100	100	100	97.44	97.96	92.05
> 90	100	100	100	100	100	93.18

(2) For subjects with BMI between 17 and 30, the mean duration at which serum ENG concentrations are > 90-120 pg/mL is about 3.5 years after insertion of Implanon. However, it appears that serum ENG concentrations decrease with an increase in BMI. Due to a nature of large variability in ENG exposure from Implanon, it should be noted that likelihood of subjects with BMI > 26 to have ENG concentrations < 90-120 pg/mL at the end of 3 years is greatly increased and should be a concern.

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/s/

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Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA: 21-529

Brand Name: Implanon

Generic Name: Etonogestrel Implant

Sponsor: Organon

Relevant IND(s): 42,877

Date of Submission: 09-30-2003
05-20-2004
07-14-2004

Type of Submission: Original NDA

Formulation: Implant
Strength: 68 mg

Indication: Prevention of Pregnancy

Reviewer: Myong-Jin Kim, Pharm.D.

Team Leader: Ameeta Parekh, Ph.D.

OCPB Division: DPE-II

OND Division: Reproductive & Urologic Drug Products

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1. Executive Summary

Implanon (etonogestrel implant) is a progestin-only contraceptive for subdermal use. The implant is a co-axial rod with a length of 4 cm and a diameter of 2 mm. The core contains 68 mg of etonogestrel (ENG) dispersed in a polymeric matrix (ethylenediacrylate/ethyl methacrylate copolymer with a vinylacetate content of 28%), surrounded by a 60 µm skin (ethylenediacrylate copolymer with a vinylacetate content of 14%). Using a ready-for-use disposable applicator, the non-biodegradable implant is designed to be inserted subdermally at the inner side of the upper arm. After insertion, ENG is slowly released through the rate-controlling skin over a period of 3 years.

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Implanon is approved in Europe, South America, South East Asia, and Australia. Currently, one ENG product is approved and marketed in the U.S. for the prevention of pregnancy. NuvaRing® (Organon USA) is a combination contraceptive vaginal ring containing ENG and ethinyl estradiol (EE) designed to release on average 0.120 mg/day of ENG and 0.015 mg/day of EE over a 3-week period.

The inspection of two Indonesian study sites in early March 2004 revealed several Good Clinical Practice (GCP) violations. Therefore, the sponsor withdrew 5 studies which were conducted from these sites. These studies include 2 clinical studies (34506, 34520), 1 clinical pharmacology study (34503), 1 lipid metabolism study (34510, Indonesia site only), and 1 endometrial histology study (34514). These 5 studies involved the data from 720 Indonesian women. In result of this major amendment, the user fee goal date was extended by 3 months for a full review of the submission.

The pharmacokinetic (PK) profile of ENG during 2 years of Implanon use was evaluated in a subset of the U.S. Study 069001. Four studies (34502, 34504, 34508, RM01) were conducted to evaluate the PK/PD of Implanon. Study 34507 was conducted to assess the absolute bioavailability of ENG from Implanon. Study 34523 was conducted to evaluate ENG concentrations in the maternal serum and breast milk of healthy lactating women. In addition, a single ENG serum concentration measurement was determined just prior to removal of Implanon in 9 studies (34505, 34509, 34510, 34511, 34512, 34515, 34522, RM02, RM04).

2.2 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-529 submitted on September 30th, 2003. The overall Human Pharmacokinetic Section is *acceptable*. Labeling comments outlined in the labeling section have been conveyed to the sponsor. An addendum will be added to this review when agreement on labeling is reached. The effect of body mass index will be addressed in the label.

1.2 Phase IV Commitments

None.

1.3 Summary of CPB Findings

The absorption and release profiles of ENG from Implanon were characterized by initial burst followed by relatively fast decrease during the first 6 weeks. The mean peak serum ENG

concentrations (Studies 34502, 34508, 069001, and RM01) were between 781 and 894 pg/mL and they were reached within the first few weeks after insertion. Serum ENG concentrations gradually declined to 192 – 261 pg/mL at the end of 1st year. The mean serum ENG concentrations were between 156 and 177 pg/mL at the end of 3rd year. The bioavailability of Implanon was about 100%. In the U.S. Study 069001, the C_{max} of ENG ranged from 323-1560 pg/mL (mean, 781 pg/mL) and occurred at 24-263 hrs (median, 144 hrs) after insertion. At 2 weeks following implantation, the mean ENG concentration was 441 pg/mL. The mean ENG concentrations slowly declined to 192 pg/mL at 1 year and to 160.3 pg/mL at 2 years. The in vivo release rate of ENG was approximately 60 µg/day at 3 months and slowly decreased to 30 µg/day after 2 years of use. After implant removal, serum ENG concentrations rapidly declined and within 1 week these concentrations were below the detection limit of the assay. The mean half-life of ENG was 34.6 hrs (range, 21-56 hrs). Following a slow IV bolus dose of 150 µg ENG, the total volume of distribution was 201.1 ± 149.2 L and the mean t_{1/2} was about 25 hours. The clearance was relatively constant over 2 years of treatment, ranging from 8.5 L/hr at 1 year and 7.0 L/hr after implant removal.

Effect of body weight/body mass index (BMI)

The effect of body weight/BMI on ENG concentrations was evaluated using a population PK model approach. The pharmacometrics review by Dr. He Sun will be added to this review as an addendum once the analysis has been completed. Appropriate recommendation related to the effect of body weight/BMI on ENG exposure will be incorporated in the label based on this analysis.

Body weight and BMI contributed to the observed differences in mean ENG serum concentrations. Serum ENG concentrations were inversely related to body weight and decreased with time after insertion. However, the absence of in-treatment pregnancies limits the ability to predict at what ENG serum concentration a woman would be at risk of pregnancy. It cannot be excluded that the contraceptive effect in obese women during the 3rd year of use may be lower.

The clinical experience with Implanon in obese women in the 3rd year of use is limited. In addition, the clinical studies included women with body weight between 80% and 130% of their ideal body weight. In the clinical and clinical pharmacology studies, 13 subjects with body weight ≥ 70 kg (n=12, 70-80 kg; n=1, >90 kg) were exposed to Implanon for ≥ 3 years while 131 subjects (n=109, 70-80kg; n=21, 80-90 kg; n=1, >90 kg) were exposed for 2 – 3 years.

ENG concentrations in breast milk

During the 4-month lactation period, the mean breast milk ENG concentrations were 178±82 pg/mL, 153±78 pg/mL and 131±78 pg/mL at 1, 2, and 4 months after Implanon insertion, respectively. The mean maternal serum and mean breast milk ENG concentrations decreased over time. The mean breast milk over mean maternal serum ENG concentration ratio did not change over time and remained between 0.44 and 0.50. The mean daily ingested infant ENG doses were about 20±9 ng/kg/day, 15±8 ng/kg/day and 10±6 ng/kg/day at 1, 2, and 4 months after insertion, respectively. The mean transfer of ENG to the infant was approximately 20 ng/kg/day at Month 1. This was about 1.7 % of the maternal daily dose/kg of 1200 ng/kg/day for a mean maternal body weight of 55.9 kg. The mean daily infant ENG dose calculated with the assumption that the infant had drunk 150 mL/kg/day showed a gradual decrease over time during the 4 treatment months. The calculated mean daily ingested infant ENG doses were about 27±12 ng/kg/day, 23±12 ng/kg/day and 20±11 ng/kg/day at 1, 2, and 4 months after implantation, respectively.

In Vitro In Vivo Correlation (IVIVC)

The sponsor has attempted to develop an IVIVC model (a Level A correlation) using a formulation with a single release rate. Although there was an association between the in vitro release and in vivo performance, the data did not support the validation of IVIVC.

The in vivo absorption rates were calculated by means of numerical deconvolution using the mean serum ENG concentrations during Implanon use and serum ENG concentrations after i.v. administration as reference formulation, followed by linear regression on in vitro release rates and corresponding in vivo absorption rates. Bioavailability studies for IVIVC development were performed in 8 healthy female subjects with the implant in situ for 2 years (Study 34507). The established IVIVC model was used to predict the ENG serum concentrations during the use of the implant in Study 34507. The mean (SD) absolute internal prediction error (PE) was $2.0 \pm 1.7\%$ (range, 0.4 – 4.8%). The IVIVC was used to predict the in vivo performance for a formulation with the similar release rate obtained from another batch with no changes in manufacturing. The mean (SD) absolute external PE was $19.7 \pm 16.7\%$ (range, 0.4 – 50.7%).

Sex hormone binding globulin (SHBG)

Mean SHBG concentrations decreased significantly after insertion of implant (from pre-implantation, 43.1 ± 20.9 nmol/L to Month 1, 25.3 ± 17.2 nmol/L), and remained at these levels until Month 9 (27 ± 19.3 nmol/L). A trend toward return to baseline was observed after Month 9.

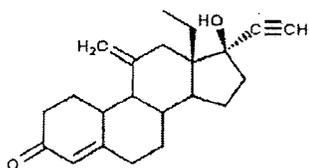
2. Question-Based Review

2.1 General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Physico-chemical properties

- Structural formula:

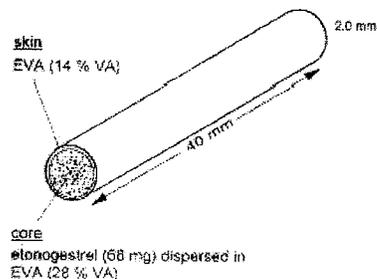


- IUPAC Name: 17 α -ethyl-17-hydroxy-18-methyl-11-methylene-4-estren-3-one
- Molecular Weight: 324.46
- Molecular Formula: C₂₂H₂₈O₂
- Chemical Name: (17 α)13-ethyl-17-hydroxy-11-methylene-18,19-dinorpregn-4-en-20-yn-3-one
- Appearance: White to practically white crystalline powder which may have a slight odor
- Solubility at 22°C: n-Hexane, 2 mg/mL; Ethanol (96%), 60 mg/mL; Ethyl Acetate, 60 mg/mL; Water, practically insoluble
- Melting Range: 196.5 – 199.5°C

Drug Formulation

Implanon is a coaxial rod consisting of an ethylene vinyl acetate (EVA) copolymer core (28% vinyl acetate) containing 68 mg ENG, surrounded by a 60 µm skin of EVA (14% vinyl acetate). The implant is 40 mm in length with a diameter of 2 mm.

Names of Ingredients	Quantity (mg/Implant)	Function
Active ingredient Etonogestrel (Org 3236) (micronized)	68	Drug substance
Other ingredients Ethylene vinylacetate copolymer (28% vinylacetate) Ethylene vinylacetate copolymer (14% vinylacetate)		Core polymer Skin polymer



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After insertion, ENG is slowly released through the rate-controlling skin. The in vitro release rate is approximately 60-70 µg/day during week 5-6, declining to about 35-45 µg/day at the end of the 1st year, to about 30-40 µg/day at the end of 2nd year and approximately 25-30 µg/day at the end of the 3rd year.

What is the proposed mechanism of action?

The contraceptive effect of Implanon is primarily achieved by suppression of ovulation. Secondary effects include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and changes in the endometrium (which reduce the likelihood of implantation).

What are the proposed indication, dosage and route of administration?

Implanon contains 68 mg of the synthetic progestin ENG. After the implant is inserted subdermally at the inner side of the upper arm with a disposable applicator, a continuous release of ENG occurs, proposed to provide contraceptive protection for up to 3 years.

General Clinical Pharmacology

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Ovulation suppression is a surrogate endpoint for prevention of pregnancy. Progesterone concentrations > 10 nmol/L were used as a threshold level for occurrence of ovulation. The assessment of clinical efficacy was based on the occurrence of pregnancies during the treatment period. Pregnancies were categorized as those that occurred pre-treatment (prior to implantation), in-treatment (with implant in place), and post-treatment (after removal of implant).

Four clinical studies (Studies 069001, 34505, 34507, and 34507 CDN) were evaluated for efficacy and safety. There were no pregnancies during the two-year treatment. Of 215 subjects

who entered into the 3rd year of treatment, 195 (90.7%) subjects completed the treatment. No pregnancies were reported in the third year.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Blood samples for determination of ENG, progesterone, estradiol, and SHBG were collected after implantation.

What are the characteristics of drug absorption?

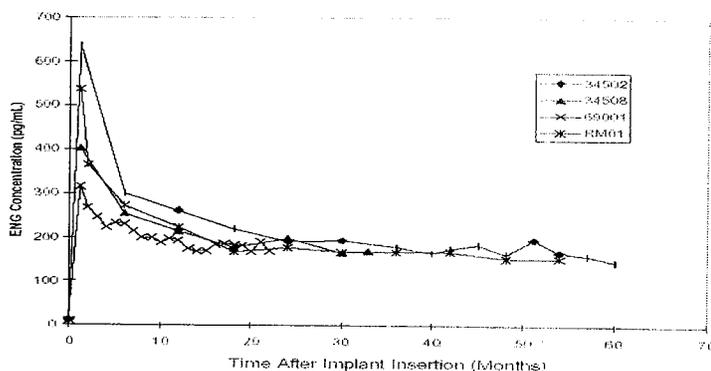
Four studies (069001, 34502, 34508, RM01) evaluated the mean serum concentrations of ENG during 2 – 5 years of treatment with Implanon.

After subdermal insertion of Implanon, ENG was rapidly released into the circulation and was about 100% bioavailable. The mean peak serum concentrations in PK studies ranged between 781 and 894 pg/mL and were reached within the 1st few weeks after insertion. The release rate of ENG decreased gradually over time with mean concentrations of ENG declining to between 192 and 261 pg/mL at the end of one year. Over the additional 2 years of treatment, mean serum ENG concentrations remained relatively stable reaching levels between 156 and 177 pg/mL.

In Study 069001, the absorption/release profile of ENG following implantation was characterized by an initial burst effect (mean C_{max} , 781 pg/mL, range, 323-1560 pg/mL, median T_{max} of 144 hrs, range, 24-263 hrs) followed by a slow decline in concentrations over time. At 2 weeks following implantation (visit Month 0, 336 hr), the mean ENG concentration was 441 pg/mL. The mean ENG concentrations slowly declined to 192 pg/mL at 12 months and to 160.3 pg/mL at 24 months.

In study 34508, C_{max} of 472-1270 pg/mL (mean, 813 pg/mL) was reached in T_{max} of 1-13 days (mean, 4 days). Serum concentrations of ENG after 1, 2, and 3 years were 150-261 pg/mL (mean, 196 pg/mL), 135-265 pg/mL (mean, 194 pg/mL), and 111-202 pg/mL (mean, 156 pg/mL), respectively.

Figure 1. Mean serum ENG concentrations over time (Studies 34502, 34508, 069001, RM01)



- The PK profile of Implanon is characterized by an initial increase in serum ENG concentrations, followed by a slow and gradual decrease over time.
- The initial burst is caused by the temporary higher release of ENG from the tips of the implant that are not covered by the rate-controlling EVA-skin.

The release rate is 60-70 µg/day in week 5-6 and decreases to approximately 35-45 µg/day at the end of the 1st year, to approximately 30-40 µg/day at the end of the 2nd year, and then to approximately 25-30 µg/day at the end of the 3rd year.

Table 1. Comparison of ENG exposures following NuvaRing[®] (Product Label) and Implanon (Study 069001)

Mean (SD) PK Parameters of ENG following NuvaRing[®] (source: Product Label)							
	1 st Week (pg/mL)	2 nd Week (pg/mL)	3 rd Week (pg/mL)	C _{max} (pg/mL)	T _{max} (hr)	t _{1/2} (hr)	CL (L/hr)
ENG	1578 (408)	1476 (362)	1374 (328)	1716 (445)	200.3 (69.6)	29.3 (6.1)	3.4 (0.8)
Mean (range) PK Parameters of ENG following Implanon (Study 069001)							
	1 st Year (pg/mL)	2 nd Year (pg/mL)	C _{max} (pg/mL)	T _{max} (hr)	t _{1/2} (hr)		
ENG	192	160.3	781 (323-1560)	median, 144 (24-263)	34.6 (21-56)		

-NuvaRing[®] (Organon USA, ENG/EE vaginal ring) designed to release on average 0.120 mg/day of ENG and 0.015 mg/day of EE over a 3-week period.

What are the characteristics of drug distribution?

ENG is 98.4% bound to serum proteins, predominantly albumin (66%) and to a lesser extent (32%) to SHBG. Following a slow IV bolus dose of 150 µg ENG, the total volume of distribution was 201.1 ± 149.2 L.

What are the characteristics of drug metabolism?

In vitro data show that ENG is metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme. CYP3A4 is involved in the oxidative metabolism of ENG with the formation of 6β-hydroxy-ENG and 6β, 13 ethyl-dihydroxylated metabolites being among the major metabolites observed.

What are the characteristics of drug elimination?

ENG is primarily eliminated in urine, bile and feces.

The parameters λ_z and t_{1/2} were estimated following removal of the implant at Visit Month 24 (Study 069001). Serum ENG decreased gradually, with a mean t_{1/2} of 34.6 hrs (range, 20.7 – 55.9 hrs). ENG serum concentrations were undetectable within one week after removal. Following a slow IV bolus dose of 150 µg ENG, the mean t_{1/2} was about 25 hours and the clearance was relatively constant over 2 years of treatment, ranging from 8.5 L/hr at 1 year and 7.0 L/hr after implant removal.

Lactation study

During the 1st month after Implanon insertion, about 100 ng of ENG may be ingested by the child per day based on an average daily milk ingestion of 658 mL. Based on daily milk ingestion of 150 mL/kg, the mean daily infant ENG dose calculated after one month of ENG release is approximately 27 ng/kg/day. This corresponds to approximately 2.2% of the weight-adjusted maternal daily dose and to approximately 0.2% of the estimated absolute maternal daily dose.

Table 2. Mean (SD) ENG concentrations, the ingested volume of breast milk/kg body weight infant/day (V_{milk}) and PK parameters for all subjects

Parameter (Units)	Month 1			Month 2			Month 4		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
ENG _{serum} (pg/mL)	41	399.0	130.7	38	347.8	77.2	38	278.1	80.7
ENG _{milk} (pg/mL)	41	177.7	81.9	38	153.1	77.6	38	131.4	78.1
Milk over Serum ratio	40	0.448	0.176	38	0.442	0.181	37	0.498	0.256
V_{milk} (mL/kg/day)	41	114.2	24.9	38	101.0	28.8	38	80.6	24.3
D_{infant}^1 (ng/kg/day)	41	19.86	9.19	38	15.08	7.88	37	10.45	6.27
Hypothetical D_{infant}^2 (ng/kg/day)	41	26.65	12.29	38	22.96	11.64	37	20.19	11.49

¹ daily ENG dose per kg ingested by the infant based on the actual amount of breast milk ingested

² daily ENG dose per kg based on a hypothetical breast milk volume of 150 mL/kg/day taken from the literature

- The mean transfer of ENG to the infant for up to 4 months was highest at Month 1 and amounted to 19.86 ng/kg/day. Concentrations decreased with time. In the comparison of the D_{infant}^1 an overall statistically significant difference was found with time.
- The initial release rate of Implanon is about 67 ug ENG per day after insertion. This results in a maternal daily ENG dose per kg of around 1200 ng/kg/d for a mean maternal weight of 55.9 kg. With a daily ingested infant ENG dose of 19.86 ng/kg/d at Month 1, it can be shown that 1.7 % of the maternal daily dose per kg was ingested by the infant via breast milk.
- With a daily infant ENG dose of 26.65 ng/kg/d at Month 1, calculated with a milk consumption of 150 mL/kg/d, it can be shown that 2.2% of the maternal daily dose per kg would be ingested by the infant via breast milk.
- The mean maternal serum ENG concentration decreased over time and this decrease was accompanied by a decrease in mean breast milk ENG concentration
- The milk over serum ENG concentration ratio did not show a statistically significant change over time

2.3 Intrinsic Factors

What intrinsic factors (race, body mass index, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

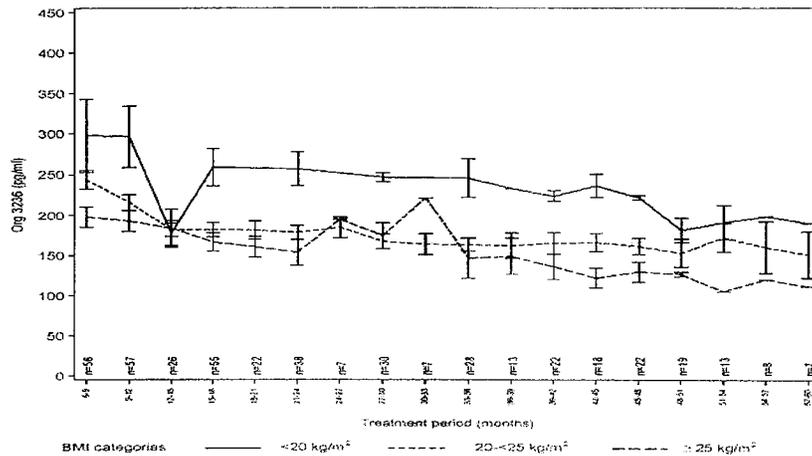
Race

No formal studies were conducted to evaluate the effect of race on the PK of Implanon.

Body Weight/Body Mass Index (BMI)

Body weight and BMI contributed to the observed differences in mean ENG serum concentrations. Serum ENG concentrations were inversely related to body weight and decreased with time after insertion. However, the absence of in-treatment pregnancies limits the ability to predict at what ENG serum concentration a woman would be at risk of pregnancy. It cannot be excluded that the contraceptive effect in obese women during the 3rd year of use may be lower.

Figure 2. Mean (SE) of time-integrated averaged ENG concentrations over consecutive 3-month intervals during treatment stratified for BMI categories



- ENG concentrations for subjects with BMI $< 20 \text{ kg/m}^2$ were about 47% and 29 % higher than subjects with BMI $\geq 25 \text{ kg/m}^2$ and $20 - 25 \text{ kg/m}^2$, respectively. ENG concentrations for subjects with BMI $20-25 \text{ kg/m}^2$ were about 13% higher than subjects with BMI $\geq 25 \text{ kg/m}^2$.

The clinical experience with Implanon in obese women in the 3rd year of use is limited. In the U.S. clinical trial (069001, a 2-year study), women enrolled were between 80% and 130% of their ideal body weight with weights ranging from 42 to 101 kg and 24% of women weighing $>70\text{kg}$.

Table 3. Baseline BMI of subjects (Clinical studies, 069001, 34505, 34507, 34507 CDN)

BMI (kg/m ²)	Study 069001 (n=330)	Study 34505 (n=100)	Study 34507 (n=635)	Study 34507 CDN (n=52)
	n (%)	n (%)	n (%)	n (%)
≤ 20	46 (13.9)	29 (29.0)	116 (18.3)	11 (21.2)
$>20-22$	84 (25.4)	27 (27.0)	153 (24.1)	14 (26.9)
$>22-24$	74 (22.4)	29 (29.0)	178 (28.0)	11 (21.2)
$>24-26$	46 (13.9)	10 (10.0)	100 (15.7)	5 (9.6)
>26	80 (24.2)	5 (5.0)	88 (13.9)	11 (21.2)
Mean (SD)	23.6 (3.6)	21.7 (2.8)	22.7 (2.8)	22.8 (3.3)

Table 4. Exposure to Implanon by body weight category and duration of use

Body weight category	Exposure in years (n)			
	≤ 1 year	1 -2 years	2 - 3 years	≥ 3 years
$< 50 \text{ kg}$	182	157	127	59
50 – 60 kg	539	423	292	96
60 – 70 kg	442	344	239	46
$\geq 70 \text{ kg}$	248	188	131	13
70 – 80 kg	201	151	109	12
80 – 90 kg	42	35	21	0
$> 90 \text{ kg}$	5	2	1	1
Total	1411	1112	789	214

Studies 069001, 34502, 34505, 34507, 34507 CDN, 34508, 34509, 34510 (excluding Indonesian center), 34511, 34512, 34514 (excluding Indonesian center), 34515, 34522, 34523)

Renal Impairment

No formal studies were conducted to evaluate the effect of renal disease on the PK of Implanon.

Hepatic Impairment

No formal studies were conducted to evaluate the effect of hepatic function on the PK of Implanon. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

2.4 Extrinsic Factors

Drug-Drug Interactions

No formal drug interaction studies were conducted.

2.5 General Biopharmaceutics

The drug substance, ENG is produced by Diosynth B.V., Oss, Netherlands.

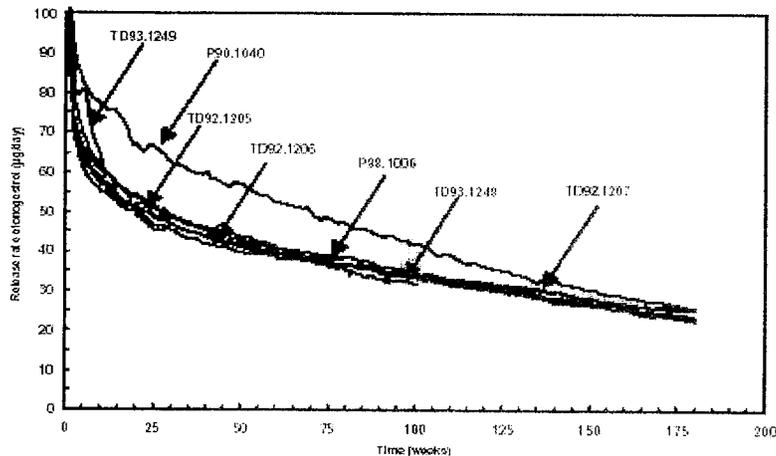
No pharmacopoeial methods are available to test the in vitro release rate over the lifetime of the implant. Therefore, the sponsor developed a method

to measure the in vitro release profile in water at 37°C over several years.

In the method, the release medium (100.0 mL water at 37 ± 0.2°C) is analyzed every 24 hours for ENG content, and substituted subsequently. The concentration of ENG is determined using an UV-spectrophotometer fitted with a flow-through cell.

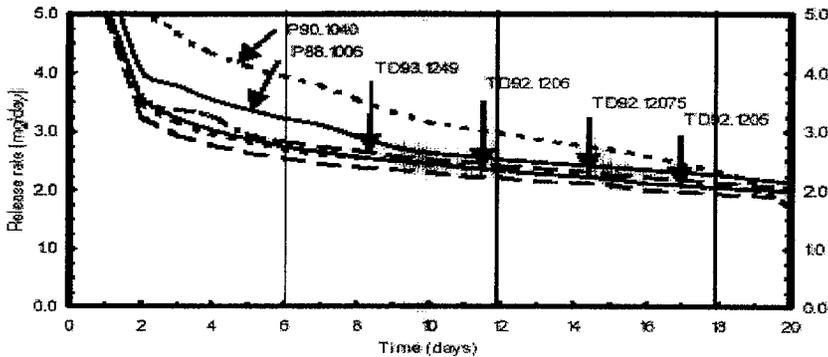
(4)

Figure 3. In vitro release rate in water of ENG from Implanon batches (mean values per week)



- In general, all Implanon batches showed similar in vitro profiles in water for at least 3 years. For batch P.90.1040 (clinical lot # CP 090032), the in vitro release profile was higher than the other batches. The sponsor considered this to be normal manufacturing variance.

Figure 4. Mean release rate profiles of batches in ethanol/water

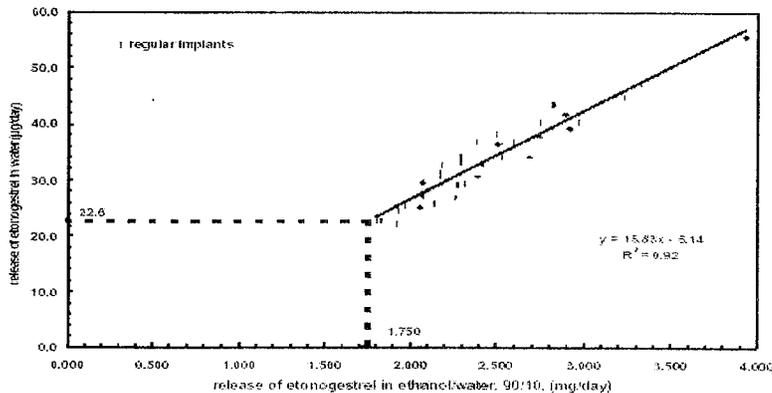


- The accelerated in-vitro release test was able to distinguish the batch P90.1040 profile from the other profiles.

Accelerated in vitro release rate

In the accelerated in vitro release rate method, the release medium (100.0 mL 90% ethanol, 10% water) at $45 \pm 0.2^\circ\text{C}$ was analyzed every 24 hrs for ENG content, and substituted subsequently. The concentration of ENG was determined using an UV-spectrophotometer fitted with a flow-through cell. To correlate the release rate of the water and 90% ethanol methods, several batches were tested in both media.

Figure 5. Correlation between release rates of ENG from Implanon in water (37°C) and in ethanol/water, 90/10 (45°C)



- A strong correlation was observed between the released quantities after 6, 12, and 18 days in 90% ethanol and after 1, 2, and 3 years in water.

What are the differences between the clinical and the to-be-marketed formulations?

All formulations used in the clinical trials are identical and the same as the to-be-marketed formulation, except for the lot used in one study (Study 34504). The implant used in Study 34504 was a leached implant prepared by extracting approximately 20 mg of ENG using ethanol-water mixtures. This resulted in a release rate of approximately 40 ug/day.

Formulation

Components	Clinical Batches		Market Formula
	Implanon™	Leached Implant used in study 34504	Implanon™
Etonogestrel (Active Ingredient) EVA Copolymer (28% Vinylacetate: Core Polymer) EVA Copolymer (14% Vinylacetate: Skin Polymer)	66 mg	50 mg	66 mg

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Table 5. List of batch numbers used in clinical trials

Fiber code	P. 88.1.006			P. 00.1.040	TD93.1249	TD94.1211	TD95.1223
Batch number	CP 088007	CP 088066	CP 088155	CP 080032	CP 092124	CP 094012	CP 095160
Study	34502 RMD1	34505 34508 RMD2 RMD4	34504	34505 34507 34509 34510 34511 34512	069001 34507CDN 34515	34522	34523

In Vivo/In Vitro Correlation

Bioavailability studies for IVIVC development were performed in 8 healthy female subjects with the implant in situ for 2 years and i.v. administrations of ENG before insertion, after 1 year in situ and after removal of Implanon (Study 34507). To develop a Level A IVIVC model, the sponsor used a formulation with a single release rate. Therefore, the consistency of this IVIVC relationship was not demonstrated with two or more formulations with different release rates.

The in vivo absorption rates were calculated by means of numerical deconvolution using the mean serum ENG concentrations during Implanon use and serum ENG concentrations after i.v. administration as reference formulation, followed by linear regression on in vitro release rates and corresponding in vivo absorption rates (data from Study 34507).

Evaluating the predictability of a Level A correlation:

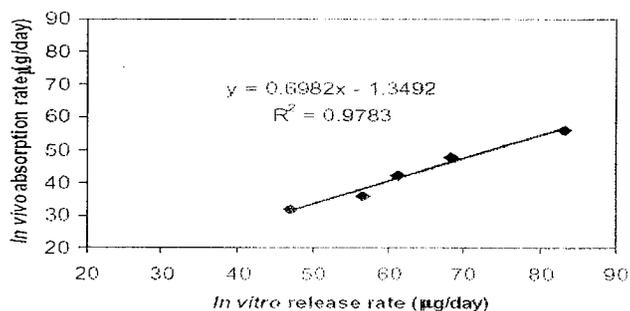
Internal predictability:

- Calculation by numerical convolution of ENG serum concentrations for Study 34507 from IVIVC model to predict in vivo absorption rates.

External predictability:

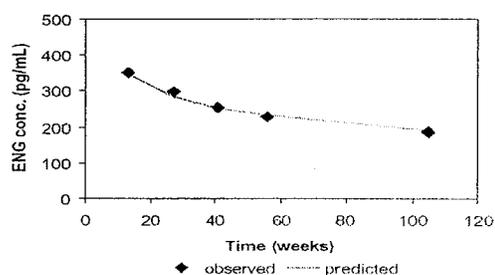
- Calculation by numerical convolution of ENG serum concentrations for Study 069001 from IVIVC model to predict in vivo absorption rates.

Figure 6. The in vitro release rates versus the in vivo absorption rates



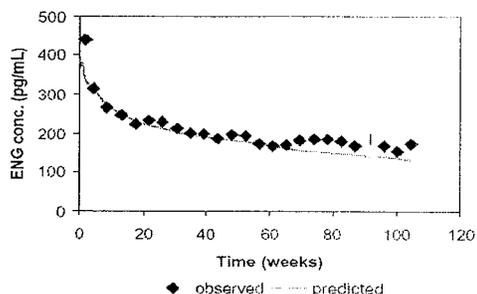
- A linear relationship between the *in vitro* release rate (R_{rel}) and *in vivo* absorption rate (R_{abs}) over the *in vitro* release range 47-83 $\mu\text{g}/\text{day}$ for Implanon was developed resulting in the IVIVC model $R_{abs} = -1.3492 + 0.6982 R_{rel}$.

Figure 7. Observed and predicted ENG serum concentrations in Study 34507 (internal predictability).



- The developed IVIVC model was used to predict the ENG serum concentrations during the use of the implant in Study 34507 (internal predictability). The mean (SD) absolute prediction error (PE) was $2.0 \pm 1.7\%$ (range, 0.4 – 4.8%).

Figure 8. Observed and predicted ENG serum concentrations in Study 069001 (external predictability)



- For external predictability, the developed IVIVC obtained from the data collected for batch CP090032 (Study 34507) was used to predict the *in vivo* ENG concentrations for batch CP092124 (Study 069001). The mean (SD) absolute PE was $19.7 \pm 16.7\%$ (range, 0.4 – 50.7%). Limiting the prediction to the *in vitro* release of range 47 – 83 $\mu\text{g}/\text{day}$ corresponding to Day 275 and Day 9 respectively, the mean \pm SD PE was $15.4 \pm 16.1\%$ (range, 0.8 – 46.5%).

2.6 Analytical

The pharmacokinetics of ENG were evaluated using two validated radioimmunoassay (RIA) methods. All serum samples collected in the clinical pharmacology studies were analyzed using an analytical method developed and validated by NV Organon, except for one study. The samples from Study 069001 were analyzed using a method developed and validated by

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Laboratory	Type of Method	Type of Biological Fluid	Sensitivity Range (pg/mL)	Specificity
NV Organon Oss. The Netherlands	RIA	Serum	20.0 – 1280 pg/mL	See SDGRR 4891
			As of April 2001: 40.0 – 1200 pg/mL	See SDGRR 4891 and R&DRR NL0027857
	RIA	Serum	17.73 – 598.55 pg/mL	Not reported

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Release Specification

The initial release rate of the product was determined in water for the 1st 3 days to assess the onset of release. A bath was used instead of for improved control of the temperature of the release medium. A 100 mL tube with a screw cap was used. The medium is stirred at 750 rpm

The release test and specification for Days 1-3:

Medium: Water,
Volume: 100 mL
Stirring Rate: 750 ± 20 rpm
Temperature: 37 ± 0.2°C
Detection: UV spectrophotometry absorbance
Sampling Frequency: every 24 hrs
Specification:

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An accelerated test was developed to obtain information about long-term release behavior. The in-vitro release rate was determined on Days 6, 12, and 18 in 90/10 ethanol/water at 45°C. The speed was controlled

The accelerated test and release specification:

Medium: 90% ethanol/10% water,
Volume: 100 mL
Stirring Rate: 750 ± 20 rpm
Temperature: 45 ± 0.2°C
Detection: UV spectrophotometry absorbance
Sampling Frequency: every 24 hrs (for 18 days)
Specification: Day 6:
Day 12
Day 18.

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The following release rate acceptance criteria were proposed based on the performance of the clinical and stability lots without an IVIVC:

Final accepted release specification
Sum of Days 1 – 3, in water
Day 6, (90/10 ethanol/water)
Day 12, (90/10 ethanol/water)
Day 18, (90/10 ethanol/water)

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 Trade Secret / Confidential

 b Draft Labeling

 Deliberative Process

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4. Appendices

4.1 Individual Study Reviews

Study 34507: An open, multi-center, efficacy and safety study of Implanon in healthy female volunteers (Austria)

An open, multi-center, non-comparative efficacy and safety study, with a PK subset in one center was conducted in healthy female subjects. The objectives of the PK sub-study were to assess the bioavailability of ENG, 3 months, 1 and 2 years after implant insertion and to evaluate ENG concentrations as function of time over a long period of time. Eight subjects aged 18-40 years, with body weights between 80 – 130 % of their ideal body weight participated in the PK study from the Vienna, Austria study center. A bolus injection (5 min infusion) of 150 ug ENG was

given one or two months before implant insertion, after one year with the implant in situ and during a spontaneous menses after implant removal (after approximately two years). By combining the ENG serum concentrations due to ENG release from the implant with the estimated clearance, the in-vivo release rate (ug/day) and bioavailability (%) of the implant were calculated. Blood samples were taken prior to each i.v. administration and at regular intervals thereafter up to 4 days (96 h). Additional blood samples were taken every 3 months after implant insertion and just prior to removal of the implant.

One or 2 months before implant insertion, each subject received a slow i.v. bolus dose of 150 ug ENG between days 1 and 7 of a menstrual cycle. Another i.v. bolus dose was given after 1 year with the implant in situ. After removal of the implant (2 yrs after implant insertion), a washout period was observed until the first spontaneous menstrual bleeding. Then, another i.v. bolus dose was given between days 1 and 7 of that first cycle.

Blood samples for serum concentration determinations were taken pre-dose, 1, 2, 5, 10, 15, 30, and 45 minutes and 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours after i.v. administration. Additional blood samples were taken 3, 6, 9, 15, 18, and 21 months after implant insertion and just prior to removal.

The in vivo absorption rate (R_{abs}) was calculated by multiplying the serum ENG concentration released from the implant (C_{imp}) by the estimated clearance determined after the i.v. bolus administration of ENG. The bioavailability of the implant was calculated using the following formula:

$$F(\%) = (R_{abs}/R_{in\ vivo}) \times 100, \text{ where } R_{in\ vivo} = 0.8 \times \text{in vitro release rate}$$

For the batch used (CP090032) the in vitro release rates were 75, 55, and 40 ug/day after 3 months, 1 year, and 2 years, respectively.

Table 6. Mean (SD) for the PK parameters of ENG due to ENG release from Implanon

Pharmacokinetic Parameters	Time after Implant insertion		
	3 Months	1 Year	2 Years
ENG serum concentration (pg/mL)	338.0 ± 76.7	223.6 ± 48.0	189.9 ± 42.9
In vivo absorption rate (ug/day)	59.95 ± 15.72	41.57 ± 8.82	30.27 ± 4.18
Bioavailability (%)	99.93 ± 26.20	94.46 ± 20.05	94.60 ± 13.06

- During the 2-year study period the mean ENG in-vivo release rate was found to decrease with time from approximately 60 ug/day after 3 months to 30 ug/day after 2 years with the implant in situ.
- The mean bioavailability was approximately 95 – 100%.
- The mean ENG serum concentration due to ENG release from the implant was found to decrease with time from approximately 340 pg/mL (range, 272 – 481 pg/mL) after 3 months to 190 pg/mL (range, 139 – 254 pg/mL) after 2 years with the implant in situ.
- The total ENG clearance was found to remain constant during the 2-year study period at approximately 7.5L/hr. The mean clearance before implant insertion, after one year with the implant, and after implant removal was observed to be 7.33, 8.46 and 6.93 L/h, respectively.

Table 7. Mean (SD) for the PK parameters calculated by means of fitting a 2-compartment PK model to the ENG serum concentrations following a slow i.v. bolus dose of 150 ug ENG

Pharmacokinetic Parameters	Timing of IV injection in relation to implant insertion		
	Before	1 Year	After Removal
n	6	6	6
Elimination $t_{1/2}$ (h)	25.03 ± 6.74	23.53 ± 12.59	28.35 ± 8.77
V_{total} (L)	201.1 ± 149.2	245.3 ± 233.2	203.1 ± 108.6
CL (L/h)	7.33 ± 2.78	8.46 ± 2.65	6.93 ± 1.58

- With a clearance that remained similar during the 2-year study period and a bioavailability that did not change, it can be concluded that the decrease in ENG serum concentration can solely be ascribed to a decrease in in-vivo release rate of the implant.

Study 34502 (Phase II, Thailand): A PD/PK study with a one-rod implant containing ENG in healthy female subjects

An open-label, single-center, PK/PD study was conducted in Thailand to investigate the PK of ENG, the effect of ENG on ovarian function, and the effects of ENG on bleeding pattern in 15 healthy female subjects (20-37 years old, BMI of 17-26 kg/m²). SHBG and ENG were measured once every 2 weeks in the 1st 3 years following the implant insertion (from weeks 1-6, 24-29, and 48-53). During the 4th and 5th year of treatment, ENG was measured once every week (from weeks 11-14, 24-27, 37-40, and 50-53) while SHBG was not measured. ENG was measured just prior to removal and 24, 48, and 96 hours after removal. No pregnancies occurred during treatment.

Table 8. Summary table of SHBG

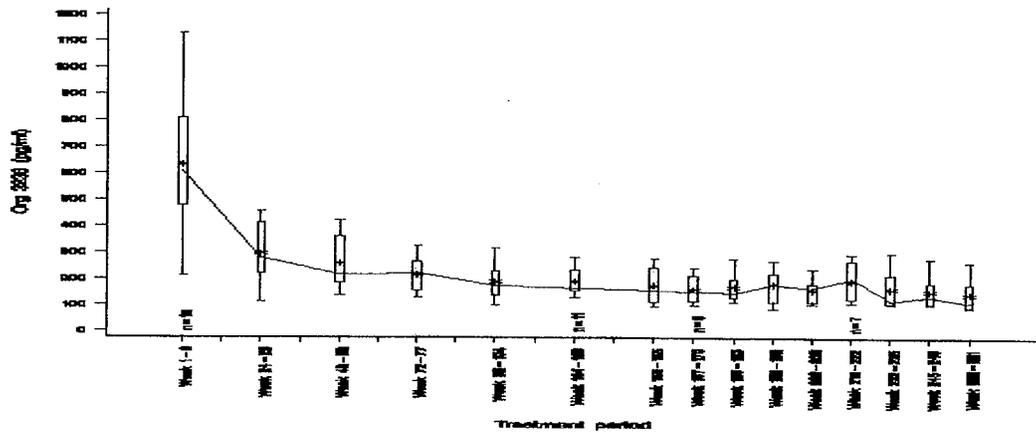
Assessment	N	Mean SHBG (nmol/l)			% change SHBG ^a		
		Mean	SD	Median	Mean	SD	Median
Screening	15	67.2	26.4	70			
Week 1-6	15	42.9	21.1	41	-36.4	12.0	-33
Week 24-29	15	52.6	26.1	50	-20.5	26.5	-26
Week 48-53	15	58.8	26.8	55	-10.2	21.5	9
Week 72-77	15	76.3	38.4	71	25.4	60.7	13
Week 98-104	15	83.5	39.7	82	20.9	26.6	26
Week 124-129	11	85.8	42.0	91	20.3	36.6	9
Week 150-155	11	70.7	32.9	68	1.0	24.9	7

^a % change of within-subject mean SHBG from baseline (i.e. last screening value)

- During the 1st year mean and median SHBG concentrations were below screening values. Thereafter, values returned to close to or above the screening values.

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Figure 9. Mean, median, interquartile and P05-95 ranges of mean ENG concentrations measured during treatment



— : medians; - : means

- During the 1st 6 weeks after implant insertion the within-subject mean ENG concentration was on average 635 ± 243.3 pg/mL (n=15). The maximum concentrations ranged from 265 to 1710 pg/mL (mean of 894 pg/mL), and they were attained between Day 9 and 23 (mean of 10.4 days). Thereafter, concentrations decreased slowly with time (5th year: 145.5 ± 64.4 pg/mL, n=7).

Figure 10. Mean, median, interquartile and P05-95 ranges of mean ENG concentrations measured post-removal

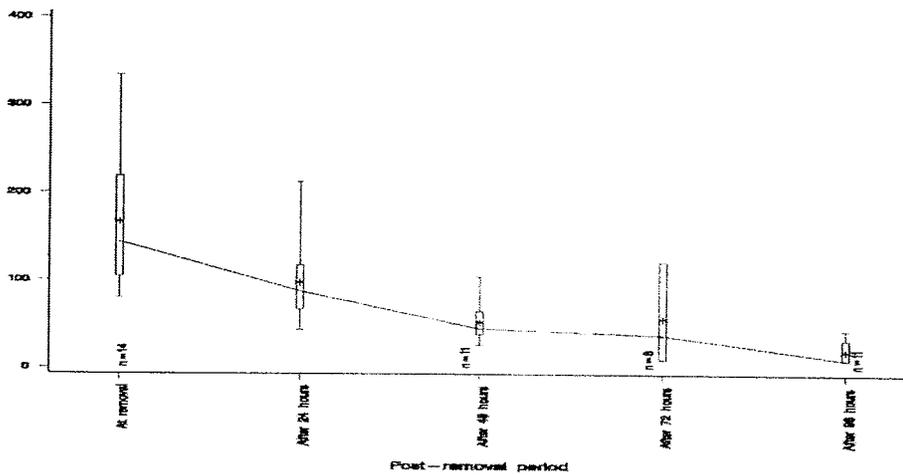


Table 9. Serum post-removal of ENG concentrations

Org 3236	n	Org 3236 (pg/ml)				
		Mean	SD	Minimum	Median	Maximum
At removal	14	166.2	75.8	79	144	334
After 24 hours	14	98.0	45.8	43	87	212
After 48 hours	11	51.9	21.6	26	45	104
After 72 hours	3	56.2	57.6	10	38	121
After 96 hours	11	20.3	13.7	10	10	44

Study 34508 (Phase II): An open, bi-centre, randomized comparative study on ovarian activity in healthy female volunteers with an all EVA one-rod implant (Org 3222) releasing 60 ug 3-ketodesogestrel (Org 3236)/day or with Norplant

An open label, bi-center, randomized study was conducted to compare the effects of Implanon on ovarian function and bleeding pattern with those of Norplant. Subjects were randomly assigned to Implanon or Norplant treatment. The mean age of 16 subjects in the Implanon group was 29.5 ± 6.6 yrs. The mean BMI was 22 ± 2 . The duration of the treatment was 24 months. Serum samples were taken just before implantation and at 0.25, 0.5, 0.75, 1, 2, 4, 8, 12 (optional), 24, 48, and 72 hours post-insertion. Blood samples were taken at monthly intervals thereafter. In addition, ENG concentrations were to be assed twice weekly during the treatment monitoring periods. On the day of implant removal, serum samples were taken just before removal and subsequently at 0.5, 1, 2, 4, 8, 24, and 48 hours post-removal to determine concentrations of ENG. Nine subjects completed 2 years and 7 completed 3 years of treatment.

Figure 11. Relative changes from baseline (mean, SD) of time-integrated mean SHBG concentrations of Implanon (single line) and Norplant (dotted line)

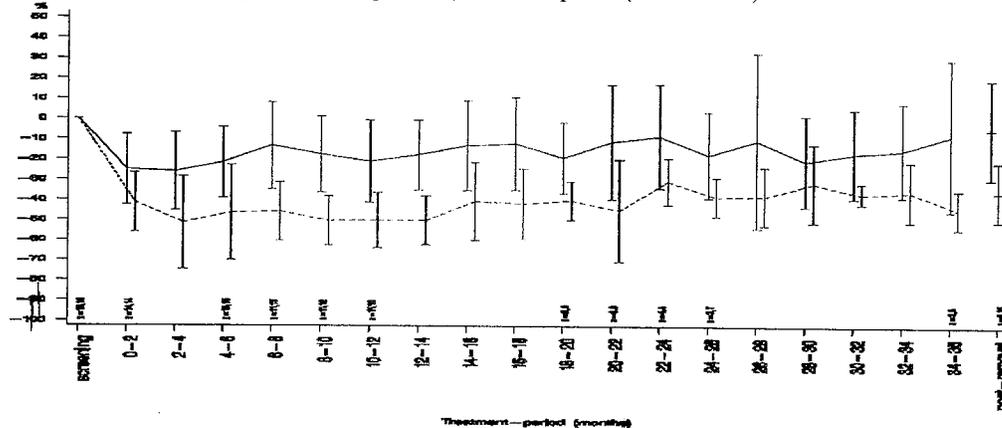
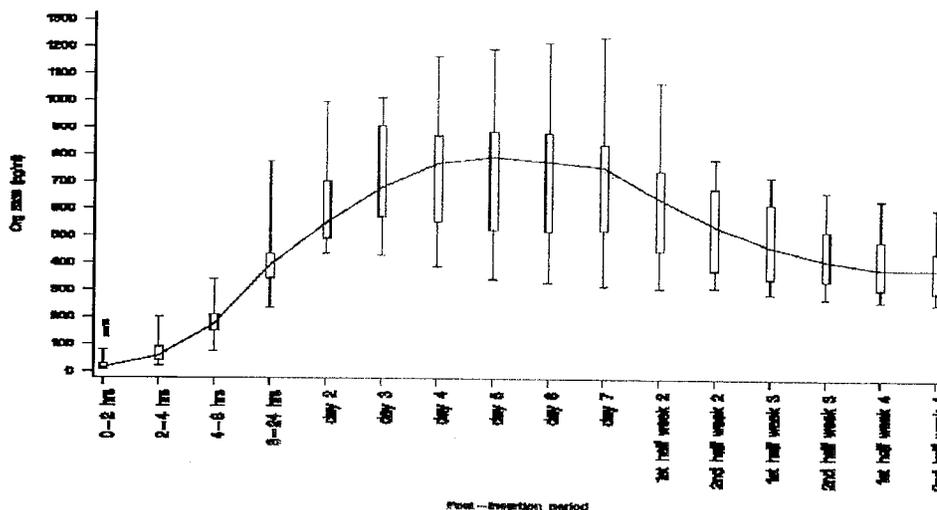
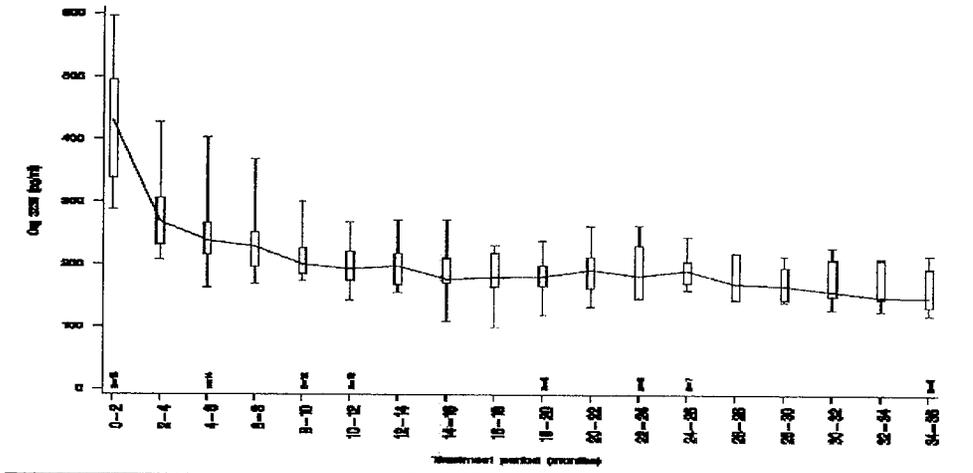


Figure 12. Median, interquartile range and P05-P95 range of time-integrated mean serum ENG concentrations assessed during the 1st 4 weeks after implant insertion



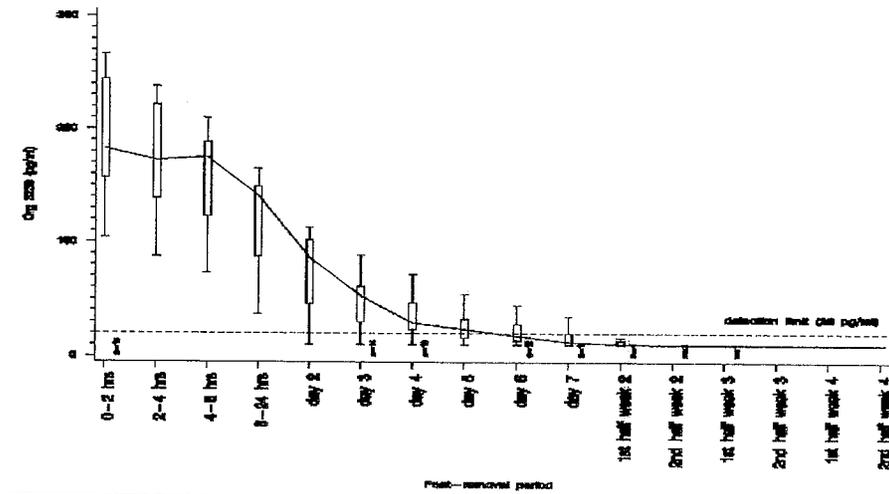
- After Implanon insertion, serum ENG showed a rapid rise, resulting in concentrations >90 pg/mL after on average 6 hrs (range, 2 – 8 hrs).
- Maximum concentrations were attained between Day 1 and 13 and, on average at Day 4. These maximum concentrations ranged between 472 and 1270 pg/mL, with a mean of 813 pg/mL.

Figure 13. Median, interquartile range and P05-P95 range of time-integrated serum mean ENG concentrations assessed during treatment



- At Day 366, the time-integrated serum concentrations were on average 196 pg/mL and ranged from 150 to 261 pg/mL (n=10). At Day 731 (after 2 years), the time-integrated concentrations were on average 194 pg/mL and ranged from 135 to 265 pg/mL (n=8). At Day 1096 (after 3 years), these concentrations were on average 156 pg/mL and ranged from 111 to 202 pg/mL (n=6).

Figure 14. Median, interquartile range and P05-P95 range of time-integrated mean serum ENG concentrations assessed after removal of the implant



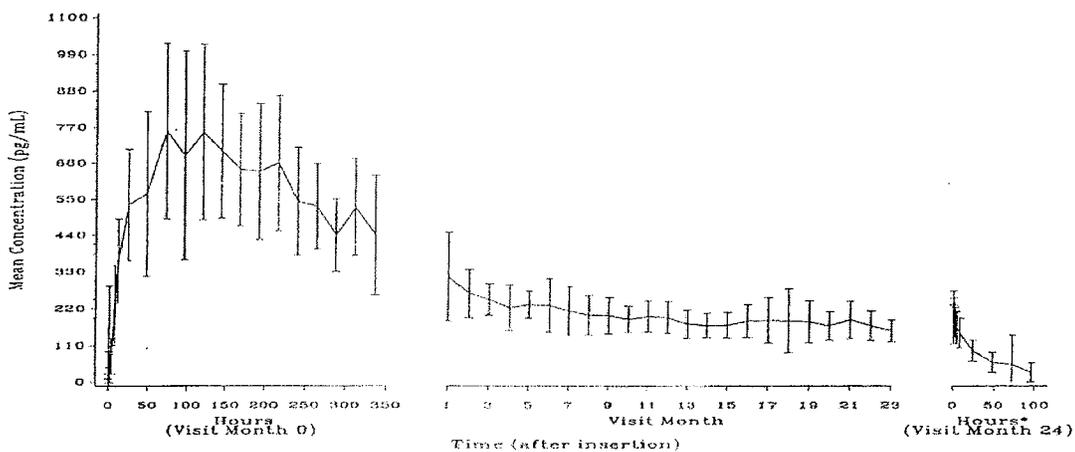
- After removal of the implant, ENG concentrations showed a decrease resulting in values <90 pg/mL after on average 42 hrs (range, 0-126 hrs, n=15).
- The concentrations on the 1st post-removal day were on average 138 pg/mL and ranged from 53 to 185 pg/mL (n=15). On the 2nd day, they averaged 73 pg/mL and ranged from 10 to 113 pg/mL (n=15); whereas on the 3rd day, they averaged 48 pg/mL and ranged from 10 to 88 pg/mL (n=14).

Study 069001 (Phase III): PK of ENG during 2 years of Implanon use in a subset of population (n=20)

An open-label, non-comparative, multi-center, clinical trial was conducted in 330 healthy female subjects with normal menstrual cycles to determine contraceptive efficacy and safety of Implanon during 2 years of use, with subsets for PK measurements. The objective of this subset study was to evaluate the PK parameters of ENG in a subset of 20 subjects participating in the main efficacy and safety study at one study center. The implant was inserted on the inside of the upper arm between the 1st and the 5th day of the subject's menstrual flow. Blood samples for determination of ENG concentrations were drawn at pre-dose (immediately prior to implant insertion), 0.25, 0.5, 0.75, 1, 2, 4, 8, and 24 hr post-insertion on Day 1, once every 24 hr from Day 2 to Day 14, then every month during treatment (Months 1-24). The elimination rate was evaluated by collecting blood samples at 0 (just before implant removal), 0.5, 1, 2, 4, 8, 24, 48, 72, and 96 hr post-removal of implant (Month 24). Serum SHBG levels were measured from blood samples collected at 0 (immediately prior to implant insertion) and once every month during treatment. The mean baseline BMI of 330 subjects was 23.6±2.6 (range, 16.5 – 33.8)

Of 20 subjects enrolled in the PK subset, 8 subjects underwent early removal of the implant (Subjects 02, 06, 12, 13, 14, 16, 19, 20). The mean age of subjects was 27.9 ± 6.7 yrs (range, 18 – 39 yrs), and the mean weight was 64.0 ± 11.9 kg (range, 42 – 92 kg). The subset population was predominantly Caucasians (2 Asians, 2 Blacks, and 16 Caucasians). Twelve women completed the 24 months treatment period. PK parameters (C_{max} , t_{max} , λ_z , $t_{1/2}$) were estimated using non-compartmental methods (WinNonlin Version 1.1).

Figure 15. Mean (SD) Serum Concentrations of ENG over Time



- The absorption/release profile of ENG following implantation was characterized by an initial burst effect (mean C_{max} of 781 pg/mL, median T_{max} of 144 hrs) followed by a slow decline in concentrations over time.

- The C_{max} ranged from 323-1560 pg/mL and occurred at 24-263 hrs following implantation, except for Subject 03 (Caucasian, 24 yrs old, 72 kg, 168 cm) whose highest serum concentrations were measured during Month 1.
- At 2 weeks following implantation (visit Month 0, 336 hr), the mean concentration was 441 pg/mL. After the initial burst release, mean ENG concentrations slowly declined to 192 pg/mL at 12 months and to 160.3 pg/mL at 24 months.

Table 10. Individual PK Parameters and summary statistics for ENG

Subject	C_{max} (pg/mL)	T_{max} (hours)	LAMBDAz (hours ⁻¹)	$T_{1/2}$ (hours)
11001	693	120	0.0124	55.9
11002	610	168	0.0206	33.6
11003	680	*	0.0204	33.9
11004	1560	72	0.0254	27.2
11005	517	74	0.0237	29.3
11006	1220	216	0.0158	43.7
11008	949	144	0.0335	20.7
11009	913	24	0.0258	26.8
11011	695	119	**	**
11012	894	153	**	**
11013	901	144	0.0292	23.7
11014	323	263	0.0136	50.4

* C_{max} for this subject occurred at Visit Month 1. This T_{max} value has not been included in the calculation of summary statistics.

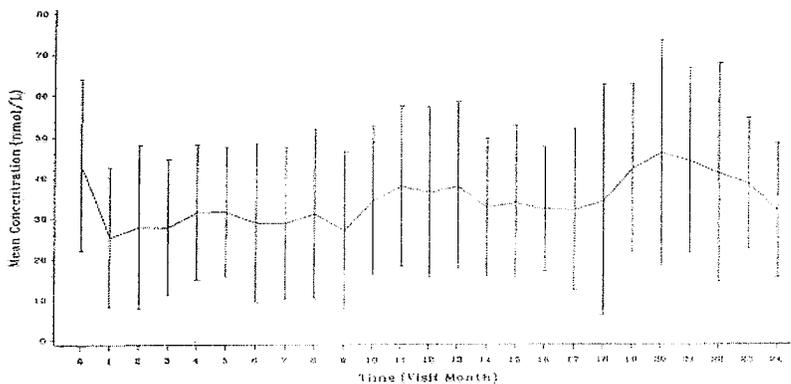
** Values not estimable.

NOTE: Estimates of C_{max} and T_{max} for some subjects may be associated with some error because of the presence of missing Org 3256 concentrations at some timepoints on Visit Month 0.

NOTE: T_{max} estimates correspond to Visit Month 0.

- The parameters λ_z and $t_{1/2}$ were estimated following removal of the implant at Visit Month 24 (or following early removal of the implant for subjects who discontinued early from the study). Serum ENG decreased gradually, with a mean $t_{1/2}$ of 34.6 hrs (range, 20.7 – 55.9 hrs). ENG serum concentrations were undetectable within one week after removal.
- For 3 subjects (11, 12, 20), λ_z and $t_{1/2}$ were not estimable.

Figure 16. Mean (SD) serum concentrations of SHBG over time



- Mean SHBG concentrations decreased significantly after insertion of implant (from pre-implantation, 43.1 ± 20.9 nmol/L to Month 1, 25.3 ± 17.2 nmol/L), and remained at these levels until Month 9 (27 ± 19.3 nmol/L). A trend toward return to baseline was observed after Month 9.

Study 34523: An open, non-randomized, group comparative study to evaluate the effects of Implanon compared to the use of an IUD on lactation and to study the transfer of ENG to breast milk in lactating healthy female volunteers (Thailand)

A single-center, open-label study was conducted in 42 mothers (aged 18 – 40 years, BMI of 18 – 29) and their 42 children (28 – 56 days post-partum) in Thailand to determine the concentrations of ENG in breast milk and compare these to the concentrations in the maternal serum. Maternal blood and breast milk samples were taken prior to implant insertion and 1, 2, and 4 months after Implanon insertion. An additional maternal serum sample was taken just prior to implant removal. The 24-hour volume of breast milk was to be determined by weighing of the infant to the nearest 10g before and after each breast-feeding prior to the start of treatment and after 1, 2 and 4 months of treatment. No pregnancies occurred.

The 24-hour volume was defined as the sum of all feedings in 24 hours, measured by the newborn's weight difference from before to after the feeding divided by 1.03 (specific gravity of the breast milk). The daily ENG dose per time point given to the infant via breast milk was calculated as D_{infant}^1 (ng/kg/d) = ENG_{milk} (ng/mL) x V_{milk} (mL/kg/d) where ENG_{milk} is the breast milk concentration and V_{milk} is the volume of breast milk ingested by the infant over a period of 24 hrs per kg body weight of the infant at corresponding time points. The daily ENG dose per time point was calculated using the following formula: D_{infant}^2 (ng/kg/d) = ENG_{milk} (ng/mL) x 150 (mL/kg/d) assuming milk intake of the infant is defined as 150 mg/kg/d.

Table 11. Mean (SD) ENG concentrations, the ingested volume of breast milk/kg body weight infant/day (V_{milk}) and PK parameters for all subjects

Parameter (Units)	Month 1			Month 2			Month 4		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
ENG _{serum} (pg/mL)	41	399.0	130.7	38	347.8	77.2	38	278.1	80.7
ENG _{milk} (pg/mL)	41	177.7	81.9	38	153.1	77.6	38	131.4	78.1
Milk over Serum ratio	40	0.448	0.176	38	0.442	0.181	37	0.498	0.256
V_{milk} (mL/kg/day)	41	114.2	24.9	38	101.0	28.8	38	80.6	24.3
D_{infant}^1 (ng/kg/day)	41	19.86	9.19	38	15.08	7.88	37	10.45	6.27
Hypothetical D_{infant}^2 (ng/kg/day)	41	26.65	12.29	38	22.96	11.64	37	20.19	11.49

¹ daily ENG dose per kg ingested by the infant based on the actual amount of breast milk ingested

² daily ENG dose per kg based on a hypothetical breast milk volume of 150 mL/kg/day taken from the literature

- The mean transfer of ENG to the infant for up to 4 months was highest at Month 1 and amounted to 19.86 ng/kg/day. Concentrations decreased with time. In the comparison of the D_{infant}^1 an overall statistically significant difference was found with time. The D_{infant}^1 was significantly higher for Month 1 compared to Month 2 and the dose was significantly higher for Month 2 compared to Month 4.
- The initial release rate of Implanon is about 67 ug ENG per day after insertion. This results in a maternal daily ENG dose per kg of around 1200 ng/kg/d for a mean maternal weight of 55.9 kg. With a daily ingested infant ENG dose of 19.86 ng/kg/d at Month 1, it can be shown that 1.7 % of the maternal daily dose per kg was ingested by the infant via breast milk.
- With a daily infant ENG dose of 26.65 ng/kg/d at Month 1, calculated with a milk consumption of 150 mL/kg/d, it can be shown that 2.2% of the maternal daily dose per kg would be ingested by the infant via breast milk.
- The mean maternal serum ENG concentration decreased over time and this decrease was accompanied by a decrease in mean breast milk ENG concentration
- The serum ENG concentration was significantly higher for Month 1 (399 pg/mL) compared to Month 2 (347.8 pg/mL) and the concentration was significantly higher for

Month 2 compared to Month 4 (278.1 pg/mL). This is most likely caused by a decrease of the release rate of the implant.

- The mean daily infant ENG dose calculated with the assumption that the infant had drunk 150 mL/kg/d (D_{infant}^2) showed a gradual decrease over time during the 4 treatment months. In the comparison of the D_{infant}^2 an overall statistically significant difference was found with time and also for Month 4 minus Month 1 and Month 3 minus Month 2.
- The milk over serum ENG concentration ratio did not show a statistically significant change over time

Table 12. Time comparisons performed on the log-transformed ENG concentrations, milk/serum ENG concentration ratio and D_{infant}

Parameter	Month 2/Month 1 ratio			Month 4/Month 2 ratio			Month 4/Month 1 ratio		
	LCLR	PER	UCLR	LCLR	PER	UCLR	LCLR	PER	UCLR
ENG _{serum}	0.82	0.87 ^a	0.92	0.75	0.79 ^a	0.84	0.65	0.69 ^a	0.73
ENG _{milk}	0.74	0.87	1.02	0.70	0.83 ^a	0.95	0.61	0.72 ^a	0.85
M/S	0.84	0.99	1.18	0.89	1.05	1.25	0.88	1.05	1.24
D_{infant}^1	0.63	0.75 ^a	0.89	0.56	0.66 ^a	0.79	0.42	0.50 ^a	0.59
D_{infant}^2	0.74	0.87	1.02	0.70	0.83 ^a	0.95	0.61	0.72 ^a	0.85

Data were taken from Analyses 9-1 to 9-5 in Appendix B.

^a statistically significant difference ($p \leq 0.05$)

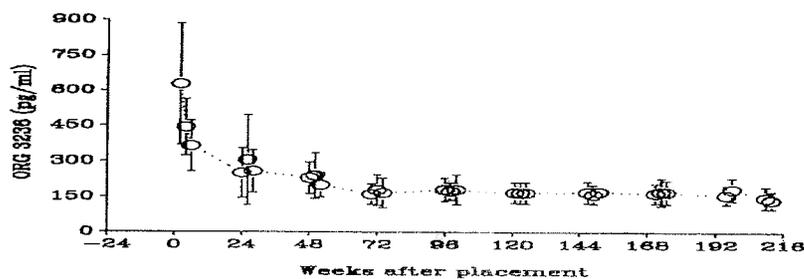
ENG: etonogestrel; D_{infant}^1 : ingested by the infant; D_{infant}^2 : calculated with the breast milk value of 150 mL/kg/day taken from the literature; PER: point estimate of the ratio; LCLR: lower 95% confidence limit of the ratio; UCLR: upper 95% confidence limit of the ratio

Study RM01 (China, PK/PD, Supportive study b/c of GCP could not be confirmed)

A PK/PD study with Implanon in healthy female subjects (CHINA)

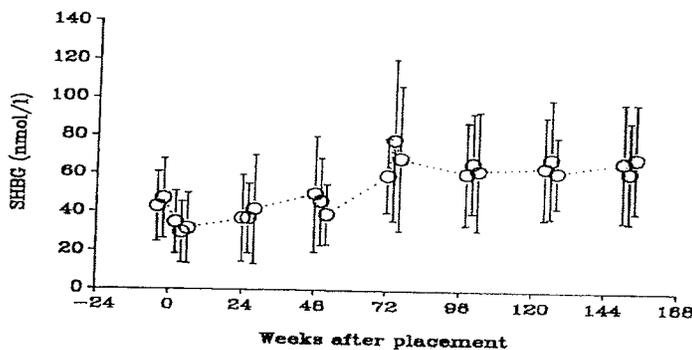
An open-label, non-comparative, PK/PD study was conducted in China to evaluate the effect of ENG on pituitary-ovarian function and bleeding pattern of menstrual cycle in 16 healthy Chinese female subjects (mean baseline weight: 59.8 ± 5.4 kg, range: 50 – 70 kg). In addition, the PK profile of ENG was observed after implantation. Blood samples were taken at ~4 weeks or earlier, -2, 2, 4, 6, 24, 26, 28, 48, 50, and 52 weeks after implant insertion. During the 2nd year, blood samples were taken at 72, 74, 76, 98, 100, and 102 weeks after insertion. In the 3rd year, blood samples were taken at 124, 126, 128, 150, 152, and 154 weeks after insertion, in the 4th and 5th year at 170, 172, 174, 192, 194, 208, 210, 218, 220, 234, and 236 weeks after insertion. Upon removal, blood samples were taken immediately after removal, and 1, 2, 3, and 4 days after removal. Serum concentrations of E_2 , progesterone, ENG, and SHBG were determined. The SHBG concentrations were determined by Farnos immunoradioassay or by Delfia fluoroimmunoassay. The ENG concentrations were determined by RIA. Three subjects (006, 011, 106) discontinued after 11, 23, and 10 months of use, respectively, due to prolonged bleeding and spotting. Thirteen subjects completed the study. No pregnancy occurred.

Figure 17. Mean (SD) serum concentrations of ENG after Implanon



- The mean serum ENG concentrations reached the peak value of 627.3 ± 257.8 (322 – 1061) pg/mL 2 weeks after implantation, and then declined to 364.3 ± 106.5 pg/mL at Week 6. The serum concentrations of ENG continuously decreased to 198.4 ± 52.3 pg/mL at the end of the 1st year.
- Serum ENG concentrations maintained stable from Week 70 to the end of the study: ranging from 160.5 ± 43.6 to 178.5 ± 63.3 pg/mL in the 2nd year, 157.6 ± 38.7 to 169.0 ± 29.2 pg/mL in the 3rd year and 156.3 ± 39.7 to 180.6 ± 47.9 pg/mL in the 4th year. In the 5th year, the mean serum ENG concentrations slightly declined to 145.0 ± 45.8 (Week 208), 135.8 ± 36.4 pg/mL (Week 210), and 152 ± 35 pg/mL (4.5 years).
- A rapid decline of serum concentrations of ENG from 139.5 ± 43.5 pg/mL to 23.3 ± 11.8 pg/mL was observed after 4 days implant removal.

Figure 18. Mean (SD) serum SHBG concentrations during the first 3 years after Implanon



- Serum SHBG levels significantly decreased (29.6 ± 15.7 nmol/L at 4 weeks, 37.1 ± 18.7 nmol/L at 26 weeks) during the 1st half year after implantation compared to the baseline levels (47.1 ± 20.7 nmol/L at -2 weeks). SHBG levels significantly exceeded the baseline levels from Week 72 (59 ± 20.2 nmol/L) and remained elevated up throughout the study.

Table 13. Distribution of maximum serum progesterone values (nmol/L)

Category	Weeks after placement												
	-4 to 0	0-6	23-28	46-51	70-75	95-101	120-125	146-151	170-173	192-199	207-212	217-222	234-239
N	16	16	16	14	14	13	13	13	13	13	13	13	13
<10nmol/l	0	15(93.8)*	16(100)	14(100)	14(100)	10(76.9)	13(100)	11(84.6)	12(92.3)	13(100)	13(100)	13(100)	13(100)
10-23nmol/l	1(6.2)	1(6.2)	0	0	0	3(23.1)	0	2(15.4)	0	0	0	0	0
>=30nmol/l	15(93.8)	0	0	0	0	0	0	0	1(7.7)	0	0	0	0

* inside of () is percentage

- No subject had progesterone levels exceeding 10 nmol/L during the 1st 75 weeks. During Week 95 to 101, 3 of 16 subjects (003, 013, 014) had maximum progesterone levels of 22.8, 14.5, and 10.4 nmol/L, respectively.
- Subject 003 and 013 had maximum progesterone levels of 12.6 and 10.1 nmol/L during Week 146 to 151.

A PK Integrated Analysis of Implanon

The compiled database contained data from the following 4 studies: 069001 (U.S.), 34502 (Thailand), 34508 (Finland/Sweden), and RM01 (China). To compare the serum ENG concentrations in these studies, the AUCs of consecutive 3-months intervals (defined as 91.5 days) were calculated for each subject by linear interpolation of the observations. By dividing these AUCs by 91.5 days, time-integrated average ENG concentrations were obtained for consecutive intervals starting with the 6-9 month intervals. Time-integrated average ENG concentrations calculated for consecutive 3-month intervals were used as dependent variables in a repeated measurement analysis.

Table 14. Demographics of 59 subjects

Parameter	study protocol				
	069001	34502	34508	RM01	Total
Number of observations	17	15	13	14	59
Age (years)					
Mean (SD)	27.2 (6.7)	26.0 (5.4)	30.9 (6.3)	32.3 (2.4)	28.9 (6.0)
Min - Max	18-39	20-37	20-39	27-35	18-39
18-24 years N(%)	8 (47.1)	8 (53.3)	3 (23.1)	0	19 (32.2)
25-29 years N(%)	2 (11.8)	2 (13.3)	3 (23.1)	2 (14.3)	9 (15.3)
30-40 years N(%)	7 (41.2)	5 (33.3)	7 (53.8)	12 (85.7)	31 (52.5)
Weight (kg)					
Mean (SD)	62.3 (10.5)	52.7 (6.8)	58.2 (6.2)	59.9 (5.8)	58.5 (8.4)
Min - Max	42-80.8	42-64	50-69.5	50-70	42-80.8
< 45 kg N(%)	1 (5.9)	3 (20.0)	0	0	4 (6.8)
45-<50 kg N(%)	1 (5.9)	2 (13.3)	0	0	3 (5.1)
50-<60 kg N(%)	5 (29.4)	9 (60.0)	7 (53.8)	5 (42.9)	27 (45.8)
60-<70 kg N(%)	6 (35.3)	1 (6.7)	6 (46.2)	6 (42.9)	19 (32.2)
≥ 70 kg N(%)	4 (23.5)	0	0	2 (14.3)	6 (10.2)
Body mass index (kg/m²)					
Mean (SD)	22.9 (3.4)	22.3 (2.8)	22.0 (2.2)	22.9 (2.2)	22.5 (2.7)
Min-Max	16.9-31.6	17.5-26.3	18.5 - 25.5	18.4-27.3	16.9-31.6
< 20 kg/m ² N(%)	1 (5.9)	3 (20.0)	2 (15.4)	1 (7.1)	7 (11.9)
20-<25 kg/m ² N(%)	12 (70.6)	9 (60.0)	10 (76.9)	11 (78.6)	42 (71.2)
≥ 25 kg/m ² N(%)	4 (23.5)	3 (20.0)	1 (7.7)	2 (14.3)	10 (16.9)

Figure 19. Mean (SE) of time-integrated averaged ENG concentrations over consecutive 3-month intervals (AUCs/91.5) during treatment stratified for BMI categories (<20 kg/m², 20-25 kg/m², ≥25 kg/m²)

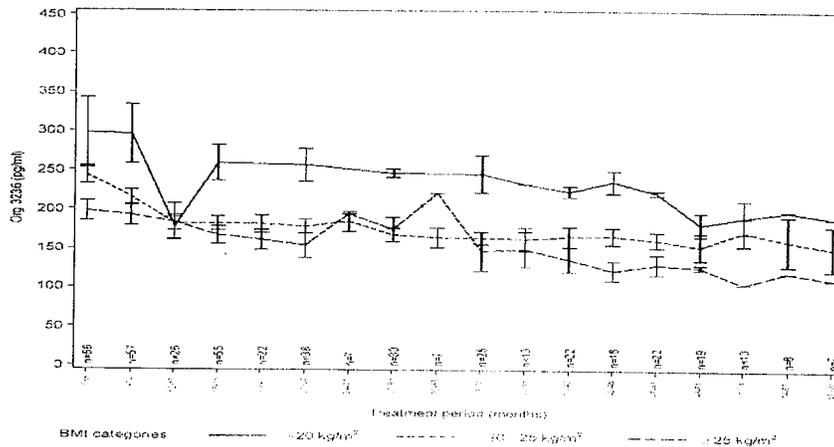


Table 15. Results of repeated measurements analysis based on the reciprocal time profile

Independent variables	Regression coefficient	SE	P-value
Intercept	4.68	0.07	
Reciprocal of time (1/T)	97.75	10.35	<0.0001
(1) BMI < 20 kg/m ²	0.3844*	0.1032	0.0018
(2) 20 ≤ BMI kg/m ² < 25 kg/m ²	0.1266*	0.07245	
(3) 25 kg/m ² ≤ BMI	0.0		
Time-integrated average change of baseline in body weight	-0.0114**	0.0053	0.0335

* implies that the mean is $\exp(0.3844)=1.47\%$ (47%) and $\exp(0.1266)= 1.13$ (13%) larger than the mean associated with (3) and that the mean of (1) is $\exp(0.3844-0.1266)=1.29=29\%$ larger than the mean of (2).

** implies that 5 kg increase of body weight gives a mean level that is $\exp(5 \cdot -0.011)=0.94$ (6%) lower mean in comparison with no change in body weight.

- ENG concentrations for women < 20 kg/m² were on average about 47% higher than women with BMI ≥25 kg/m².
- ENG concentrations for subjects 20-25 kg/m² were on average about 13% higher than subjects with BMI ≥25 kg/m².
- Subjects with BMI <20 kg/m² showed an average 29% higher serum ENG concentrations than the majority of subjects (71.2%) with BMI between 20 and 25 kg/m².
- The interaction of time and BMI categories was not significant (p=0.25) indicating that this observed difference of 47% and 13% between mean time-integrated averaged ENG concentrations was consistent over time.

IVIVC for Implanon

Two types of in vitro/in vivo correlations were attempted by using two different approaches. In the first approach, the correlation between the *in vitro release rate* and the *in vivo release rate* was attempted. The second approach investigated the correlation between the *in vitro release rate* and the *in vivo absorption rate*. The difference between the two in vitro/in vivo correlations reflects the difference between the amount of ENG released in vivo and the amount absorbed in vivo (the amount of ENG that has actually entered the circulation).

Correlation between in vitro and in vivo release rates

Implants used in clinical studies were tested for residual ENG content after being removed from study subjects at various times up to 5 years of use. The amount of ENG released in vivo (in situ) was calculated by extracting the amount remaining in the implant after removal from the mean content of the batch of implants. The in vivo released amounts of ENG at various in-situ time periods (as calculated from the ENG determinations of the ex-vivo implants) were compared with the in vitro released amounts in water measured during the same time periods.

Table 16. In vivo/in vitro correlation of release rates

Fiber Code	Batch	Correlation In vivo/In vitro released amounts of ENG	
		Coefficient (R ²)	Slope
P 88.1006	CP 088007	0.90	0.88
	CP 088066		
P 90.1040	CP 090032	0.79	0.77
TD 93.1249	CP 092124	0.79	0.81
TD 95.1223	CP 095160	0.83	0.83
MEAN VALUES		0.81	0.82

There is a linear correlation between the in vivo and in vitro released amounts. It can be seen from the slopes that the mean in vivo released amount is approximately 20% lower than the in vitro released amount. One likely explanation is the formation of a tissue capsule around the inserted implant. The capsule may act as an additional membrane that causes a decrease in the release rate of ENG in situ. It can be concluded that the mean in vivo release rate of ENG from Implanon is approximately 0.8 times the in vitro release rate.

Correlation between in vitro release rate and in vivo absorption rate (Report, R&DRR NL0038861)

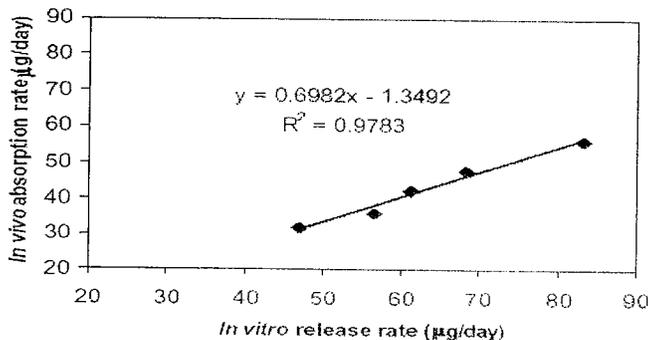
Data from the following studies were used: Study 34507 (batch CP090032) in 8 healthy female subjects with the implant in situ for 2 years and i.v. administrations of ENG before insertion, after 1 year in situ and after removal of Implanon, and Study 069001 (batch CP092124) in 20 healthy female subjects with the implant in situ for 2 years.

To develop an IVIVC model, the in vivo absorption rates were calculated by means of numerical deconvolution using the mean serum ENG concentrations during Implanon use and serum ENG concentrations after i.v. administration as reference formulation, followed by linear regression on in vitro release rates and corresponding in vivo absorption rates (data from Study 34507).

Internal predictability: calculation by numerical convolution of ENG serum concentrations for Study 34507 from IVIVC model to predict in vivo absorption rates.

External predictability: calculation by numerical convolution of ENG serum concentrations for Study 069001 from IVIVC model to predict in vivo absorption rates.

Figure 20. The in vitro release rates versus the in vivo absorption rates



- A linear relationship between the in vitro release rate (R_{rel}) and in vivo absorption rate (R_{abs}) over the in vitro release range 47-83 µg/day for Implanon was developed resulting in the IVIVC model $R_{abs} = -1.3492 + 0.6982 R_{rel}$.

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Table 18. External prediction data for Study 069001

Observed <i>in vitro</i> data				Calculated by IVVC			Calculated by convolution	Observed <i>in vivo</i> data	Prediction errors	
Time (hours)	Time (days)	Time (weeks)	<i>In vitro</i> release rate (µg/day) observed	<i>In vivo</i> absorption rate (µg/day) predicted	Cum. absorbed <i>in vivo</i> (mg) predicted	<i>In vivo</i> ENG conc. (pg/mL) predicted	<i>In vivo</i> ENG conc. (pg/mL) observed	Prediction error (PE) (%)	Absolute PE (%)	
24	1	0.1		102.0	0.102	389.9		26.9	26.9	
48	2	0.3		72.0	0.174	367.5		35.2	35.2	
72	3	0.4		66.4	0.240	373.1		50.7	50.7	
96	4	0.6		63.6	0.304	376.4		44.9	44.9	
120	5	0.7		62.9	0.367	378.9		49.7	49.7	
144	6	0.9		60.1	0.427	370.6		46.8	46.8	
168	7	1.0		59.4	0.486	366.7		42.7	42.7	
192	8	1.1		58.0	0.544	360.0		43.2	43.2	
216	9	1.3		56.6	0.601	352.6		46.5	46.5	
240	10	1.4		56.6	0.658	350.0		35.5	35.5	
264	11	1.6		55.2	0.713	343.1		34.9	34.9	
288	12	1.7		55.2	0.768	340.9		22.5	22.5	
312	13	1.9		54.5	0.823	336.9		35.8	35.8	
336	14	2.0		53.6	0.876	332.8		24.5	24.5	
744	31	4.4		50.6	1.736	309.7		1.4	1.4	
1464	61	8.7		44.6	3.073	273.0		-3.1	3.1	
2208	92	13.1		40.6	4.331	248.6		-0.8	0.8	
2928	122	17.4		37.6	5.460	230.3		-3.6	3.6	
3672	153	21.9		36.1	6.579	221.1		4.5	4.5	
4392	183	26.1		34.6	7.618	212.1		7.2	7.2	
5136	214	30.6		32.9	8.639	201.7		5.1	5.1	

b(4)

Observed <i>in vitro</i> data				Calculated by IVVC			Calculated by convolution	Observed <i>in vivo</i> data	Prediction errors	
Time (hours)	Time (days)	Time (weeks)	<i>In vitro</i> release rate (µg/day) observed	<i>In vivo</i> absorption rate (µg/day) predicted	Cum. absorbed <i>in vivo</i> (mg) predicted	<i>In vivo</i> ENG conc. (pg/mL) predicted	<i>In vivo</i> ENG conc. (pg/mL) observed	Prediction error (PE) (%)	Absolute PE (%)	
5856	244	34.9		32.0	9.599	196.1		1.7	1.7	
6600	275	39.3		31.1	10.564	190.5		3.8	3.8	
7320	305	43.6		30.4	11.475	186.2		0.4	0.4	
8064	336	48.0		29.8	12.399	182.4		6.9	6.9	
8784	366	52.3		29.1	13.271	178.2		7.2	7.2	
9528	397	56.7		27.9	14.137	171.1		0.7	0.7	
10248	427	61.0		27.3	14.957	167.3		0.6	0.6	
10992	458	65.4		26.4	15.774	161.4		4.4	4.4	
11712	488	69.7		25.4	16.537	155.8		14.6	14.6	
12456	519	74.1		24.7	17.304	151.5		17.7	17.7	
13176	549	78.4		24.4	18.037	149.7		18.1	18.1	
13920	580	82.9		24.0	18.781	146.9		18.5	18.5	
14640	610	87.1		23.5	19.486	144.0		14.1	14.1	
15384	641	91.6		23.1	20.202	141.5		24.1	24.1	
16104	671	95.9		22.9	20.889	140.3		16.5	16.5	
16848	702	100.3		22.5	21.586	137.7		10.4	10.4	
17568	732	104.6		21.8	22.240	133.6		22.8	22.8	

b(4)

- The mean ± SD absolute PE was 19.7 ± 16.7 % (range, 0.4 – 50.7%). Limiting the prediction to the *in vitro* release of range 47 – 83 µg/day corresponding to Day 275 and Day 9 respectively, the mean ± SD PE was 15.4 ± 16.1% (range, 0.8 – 46.5%).

Dose-finding studies

Dose-finding studies (Diaz S et al. Contraception 1991;44:393-408 and SDGRR 2904) were performed to determine which subdermal ENG dose was sufficient to inhibit ovulation. Prototype ENG-containing implants (either capsules or EVA rods covered and contained about 7 – 28 mg of ENG) were used in the dose-finding studies. The initial daily *in vitro* release rate was between 10 and 40 µg/day. The *in vitro* release rates measured at various periods in time were compared with serum progesterone levels. Only women with serum progesterone levels above 9.5 nmol/L on one or more occasions during implant exposure were scored positive for having experienced ovulation

b(4)

Diaz S et al.	Inhibition of ovulation
ENG > 0.09 ng/mL	57/59 blood samples (97%)
ENG < 0.09 ng/mL	39/75 blood samples (52%)

- There were 3 pregnancies with ENG implants with a release rate of 20 mcg/day or less but no pregnancies were reported with ENG implants with 30 mcg/day and 40 mcg/day.
- ENG implants releasing approximately 40 mcg/day and providing ENG concentrations above 0.09 ng/mL showed efficient contraception protection (Diaz et al. 1991).

Table 19. Combined serum progesterone data (Diaz et al 1991 & SDGRR 2904)

Dose of ENG (RR in µg / day)	Occurrence of serum P concentrations compatible with ovulation (numbers and percentages)				
	Diaz 1991		SDGRR 2904		Average
	n / N	%	n / N	%	%
40 - 31	1 / 28	3.6	-	-	3.6
30 - 21	3 / 26	11.5	11 / 30	36.7	24.1
20 - 10	12 / 33	36.4	23 / 44	52.2	44.3
< 10	9 / 12	75.0	9 / 10	90.0	82.5

- No data available

- Based on the data collected, the sponsor decided to develop an implant that would give an in vitro release rate of approximately 30 µg/day at the end of 3 years. Taking into account that the release rates of implant systems decrease by about a factor of two during their semi-steady state release period, an initial release rate of approximately 60 µg/day was required.

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Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-529	Brand Name	Implanon	
OCPB Division (I, II, III)	DPE II	Generic Name	Etonogestrel implant	
Medical Division	DRUDP	Drug Class	Progestin	
OCPB Reviewer	Myong-Jin Kim	Indication(s)	Contraception	
OCPB Team Leader	Ameeta Parekh	Dosage Form	Implant	
		Dosing Regimen	68 mg ENG, every 3 years	
Date of Submission	SEP-30-2003	Route of Administration	Subdermal	
Estimated Due Date of OCPB Review		Sponsor	Organon USA Inc.	
PDUFA Due Date	OCTOBER-30-2004	Priority Classification	3S	
Division Due Date				
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	1			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				Lactation study
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	5			
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				

II. Biopharmaceutics				
Absolute bioavailability:	2			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):	2			
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	17			
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	Myong-Jin Kim, Pharm.D.			
Secondary reviewer Signature and Date	Ameeta Parekh, Ph.D.			

CC: NDA 21-529, HFD-850 (L. Lesko, S. Huang), HFD-580 (B. Wesley, S. Monroe), HFD-870 (H. Malinowski, J. Hunt, A. Parekh), CDR (B. Murphy)
CP&B Briefing attendees on October 7, 2004: S. Apparaju, J. Bullock, L. Furlong, S. Huang, J. Hunt, K. Lam, J. Lazor, H. Malinowski, A. Mitra, S. Monroe, S. Ortiz, A. Parekh, H. Sun, B. Wesley.

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Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: NDA 21-529
Compound: Etonogestrel subdermal implant
Sponsor: Organon USA Inc.
Date: NOV-14-2003
Reviewer: Myong-Jin Kim

Background:

Implanon (etonogestrel subdermal implant) is a progestin-only contraceptive for subdermal use and it contains 68 mg of etonogestrel (ENG). It is designed to continuously deliver ENG for a period of up to 3 years. ENG is the biologically active metabolite of desogestrel and is formulated for use as a single rod for subdermal use. After insertion, ENG is slowly released through the rate-controlling skin. It is proposed that plasma concentrations of ENG are inversely related to body weight and decrease with time after insertion. The clinical experience with Implanon in obese women in the 3rd year of use is limited.

Formulation:

Implanon is a co-axial rod consisting of an ethylene vinyl acetate (EVA) copolymer core (28% vinylacetate) containing 68 mg ENG, surrounded by a 60 um skin of EVA (14% vinylacetate). All formulations used in the clinical trials are identical and the same as the to-be-marketed formulation, except for the lot used in Study 34504. The implant used in Study 34504 was a leached implant prepared by extracting approximately 20 mg of ENG using ethanol-water mixtures. This resulted in a release rate of approximately 40 ug/day.

Table 3 List of formulations

Components	Clinical Batches		Market Formula
	Implanon™	Leached Implant used in study 34504	Implanon™
Etonogestrel (Active Ingredient) EVA Copolymer (28% Vinylacetate: Core Polymer) EVA Copolymer (14% Vinylacetate: Skin Polymer)	68 mg	50 mg	68 mg

b(4)

Table 4 List of batch numbers used in clinical trials

Fiber code	P.88.1.006			P.90.1.040	TD93.1240	TD95.1223
Batch number	CP 088007	CP 088066	CP 088135 *	CP 090032	CP 092124	CP 095160
Study	34502 34503 RM01	34505 34506 34508 RM02 RM04	34504	34505 34507 34509 34510 34511 34512	069001 34507CDM 34515	34523

* CP 088135 was a leached implant, prepared from batch CP 088007

Dose Finding Studies: Prototype ENG-containing implants were used in these studies. They differ from the final Implanon design with respect to their dimensions and materials as well as in their ENG content and ENG release rate.

- Report SDGRR 2904 and a study performed by Diaz et al, Contraception 1991;44:393-408

Study 069001 (Phase III): PK of ENG during 2 years of Implanon use in a subset of population (n=20)

- An open label, noncomparative efficacy and safety Phase III study in healthy female subjects with subsets of PK measurements, ophthalmological assessments, carbohydrate metabolism, lipid metabolism and endometrial morphology.
- ENG and SHBG concentrations were measured.
- C_{max} , T_{max} , $t_{1/2}$, and λ_z were estimated.

Studies 34502, 34503, 34504 (using a leached implant), 34508, RM01: ENG serum concentrations over time (PK/PD) in healthy female subjects

- 17β -estradiol (E2), progesterone (P) and SHBG were measured.

Studies 34515, 34507: Absolute bioavailability of ENG from Implanon

- The sponsor did not analyze the data from the Study 34515 due to protocol-related procedural errors.

Study 34523: (ENG concentrations in breast milk and serum, n=42 women and their children)

- A single-center, open-label, group-comparative study conducted in Thailand to compare ENG concentrations in breast milk and in maternal serum in a four-month lactation period.
- The mean of the ENG concentrations in serum and breast milk and the ratio, the ingested volume of breast milk/kg body weight of infant/day, and the daily ENG dose ingested by the infant are assessed at month 1, 2 and 4.

Studies 34505 (pilot efficacy/safety), 34506 (pilot efficacy/safety), 34509, 34510, 34511, 34512, RM02, RM04: A single ENG serum concentration measurement just prior to removal of Implanon.

Implanon PK Meta-Analyses:

1) Compiled database from Studies 34502, 34503, 34508, and RM01

- Because there were some differences between the serum concentrations of ENG in the various Implanon studies, a meta-analysis was performed to examine the effect of demographic variables, time from insertion, and in-treatment body weight changes on the observed serum concentrations of ENG.

2) Report SDGRR 5138-Integrated analysis of ENG measurements

- A meta-analysis to evaluate the relationship between ENG serum concentrations (determined just prior to implant removal at various times during the study) and body weight.
- Evaluable pre-removal samples from 1063 subjects in studies 069001, 34502, 34503, 34505, 34506, 34507, 34507CDN, 34508, 34509, 34510, 34511, 34512, 34515, RM01, RM02 and RM04.
- The sponsor concluded that ENG concentrations are lower with longer duration of use and higher body weight. When the individual ENG values were extrapolated to a 3-year

use of Implanon a similar trend was seen: highest serum concentrations for women with a body weight < 50 kg followed by intermediate concentrations for the 50-60 and 60-70 subsets and the lowest for subjects \geq 70 kg.

IVIVC:

Two types of IVIVC were determined using two different approaches; (1) the correlation between the in vitro release rate and the in vivo release rate was determined (SDGRR 4675, SDGRR 4676), and (2) the correlation between the in vitro release rate and the in vivo absorption rate was determined (R&DRR NL0038861).

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-529 is fileable.

Myong-Jin Kim, Pharm.D.

Date

Ameeta Parekh, Ph.D., Team Leader

Date

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this page is the manifestation of the electronic signature.**

/s/

Myong-Jin Kim
10/26/04 02:48:21 PM
PHARMACOLOGIST

Ameeta Parekh
10/27/04 12:57:23 PM
BIOPHARMACEUTICS
The analysis to address effect of weight on drug
exposure is currently ongoing.