Division of Reproductive and Urologic Drug Products

Clinical Review

NDA 21-529

Implanon™

(Etonogestrel Implant)

Organon USA Inc.

Final Review

October 28, 2004

Date submitted
September 30, 2003

Review completed
October 29, 2004

Reviewers
Barbara Wesley, M.D., M.P.H. (Principal Reviewer – Safety and Efficacy)

Daniel Davis, M.D. (Section reviewer – General Safety)
Phill Price, M.D. (Section reviewer – Efficacy
Theresa van der Vlugt, M.D. (Section reviewer – Special Safety Assessments)

Applicant
Organon USA Inc.
375 Mt. Pleasant Ave.
West Orange, NJ 07052

Proposed indication
Prevention of pregnancy in women of childbearing potential

Proposed Trade Name
Implanon™

Chemical names for the product
Etonogestrel
(17α) 13-ethyl-17-hydroxy-11-methylene-18, 19-dinorpregn-4-en-20-yn-3-one

Dosage form
A rod consisting of an ethylene vinylacetate (EVA) copolymer core, containing 68 mg of etonogestrel (ENG), surrounded by an EVA copolymer skin.

Route of administration
Subdermal implant: to be replaced every 36 months

Related INDs
IND: 42,877

Related NDAs

Norplant™: 19897 (Population Council)
Norplant™: 20,088 (Wyeth-Ayerst)
Jadelle: 20,544 (Population Council)

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EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1 Recommendation Regarding Approval

1.1.1 Approvability

This reviewer recommends an approvable action for Implanon™ (etonogestrel implant) for the prevention of pregnancy in reproductive age women for three years. Approval is contingent on the following:

- (1) Resolution by Organon of deficiencies identified by the Dutch Medicines Evaluation Board inspectors and the (2) Division's conclusions that the clinical data submitted in NDA 21-529 are sufficient (a) to support the conclusion that Implanon is safe and effective for prevention of pregnancy in women and (b) to allow labeling of Implanon that accurately reflects the safety and efficacy profile of Implanon™.
- A satisfactory inspection report from the Office of Compliance regarding the sterilization facility
- Completion of a final label. b(4)

1.1.2 Basis for Recommendation regarding Approvability (Risk/Benefit Analysis)

Because of potential serious issues concerning (1) the clinical conduct of the Principal Studies supporting the safety and effectiveness of Implanon™ and (2) lack of adequate monitoring and oversight by the Applicant of the these studies, the accuracy and adequacy of the data submitted to date in NDA 21-529 to support the safety and effectiveness of Implanon™ for prevention of pregnancy in women cannot be assured. Until these issues are resolved, approval cannot be recommended.

If these issues can be satisfactorily resolved, and the data submitted in NDA 21-529 are deemed to accurately reflect the safety and effectiveness of Implanon™, it can be concluded that Implanon is a safe and highly effective method of contraception that does not compromise future fertility. For most women, the benefits would outweigh the risks.

The benefits of Implanon™ include the following:

- Compliance non-dependant
- Single rod
- Highly effective (< 1% failure rate)
- Rapid onset of action
- Rapid reversibility and return to fertility

The major disadvantages are that a minor surgical procedure is required for use and there is a high rate of frequent/prolonged vaginal bleeding. These bleeding irregularities can be a major nuisance, but do not cause a safety concern.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

1.2.1 Risk Management Program (Training of Healthcare Providers)

A Steering Committee will be formed to develop a training program. All attendees will be required to attend a Faculty Development program to become trained as faculty for training other clinicians at their clinical sites. Each training session will include clinical information, insertion/removal/localization procedures, hands on training using model arms, and patient counseling. Upon completion of the program, the attendees will receive a model arm, practice kit and a CD-Rom to review the training. Only those clinicians who complete the program will be able to order and insert Implanon. Effectiveness of the training programs will be monitored in the following ways:

- Evaluation forms and surveys
- The Clinical Contact Specialists to review the skills of clinicians
- The Steering Committee to review issues that have arisen and the progress of the training programs, surveys and evaluations

Organon should develop a Phase 4 monitoring program in the U.S. for insertion and removal related adverse events

1.2.2 Additional Data to Support 3 Years of Use

It is recommended that the Applicant conduct an additional clinical trial(s), or supply additional confirmatory treatment data obtained through an observational study or registry that would further support the 3-year treatment regimen (effectiveness during treatment Year 3 of a single Implanon implant).

2. SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

2.1.1 Drug

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 of [redacted] (ethylene vinylacetate copolymer with a vinylacetate content of 28%), surrounded by a 60 μm skin [redacted] ethylene vinylacetate copolymer with a vinylacetate content of 14%). Etonogestrel, structurally derived from 19-nortestosterone, is the biologically active metabolite of desogestrel. 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. b(4)

2.1.2 Design of the Clinical Program

NDA 21-529 provided data from approximately 1803 subjects in 19 completed Phase II and III studies plus one ongoing phase II study, who were treated with Implanon™ for up to 2-5 years in 16 different countries (including studies in Southeast Asia, Europe, North America and South America). The clinical development program was designed to evaluate contraceptive efficacy

and safety. In addition, dedicated studies on the pharmacokinetics, pharmacodynamics and metabolic safety of Implanon™ were performed.

Four studies were considered to be the principal efficacy and safety studies by this reviewer and the Applicant (Studies 069001, 34505, 34507, and 34507-CDN). All were non-comparative, historical controlled studies. In addition to efficacy and safety, these 4 studies also provide data on clinical pharmacology, including drug levels (subsets of Studies 069001 and 34507), lipid metabolism, carbohydrate metabolism, ophthalmological parameters, and endometrial histology (subsets of Study 069001). An overview of the number of subjects enrolled in each of the principal safety and efficacy studies and brief summaries of these studies are provided below.

Study 069001- Study 069001 (United States) was an open-label, non-comparative, historically controlled multicenter (16 centers) efficacy and safety study in healthy female subjects. The duration of treatment was up to 24 months. Subsets of Study 069001 evaluated pharmacologic parameters, ophthalmological variables, lipid metabolism, carbohydrate metabolism, and endometrial morphology. Three hundred and thirty (330) subjects were enrolled and treated for a total of 6,198 cycles (based on 28-day cycles and equivalent to 474 women-years of use). One hundred sixty one (161) subjects discontinued in the first 2 years (49% of 330 subjects), and 169 subjects completed 2 years (51%, 169 of 330 subjects).

Study 34505- Study 34505 (Thailand) was an open-label, single-center, non-comparative, historically controlled efficacy and safety study. The duration of treatment was 24 months with an option for a 1 year or 2 year extension period. Upon removal of the implant, subjects were monitored for a 3-month follow-up period. One hundred (100) subjects were enrolled and treated for a total of 3,836 cycles (equivalent to 296 women-years of use). Eighty (80) subjects completed 2 years; 68 subjects extended for 3 years, and 60 completed the 3rd year; 51 subjects extended for 4 years and 47 completed the 4th year. In total, 32 subjects (32% of 100 subjects) discontinued Study 34505, of which, eight were lost to follow-up.

Study 34507- Study 34507 (Europe and Chile) was an open-label, multicenter (21 sites) non-comparative, historically controlled efficacy and safety study. Study 34507 was conducted primarily in Europe (Germany, Belgium, France, Netherlands, Sweden, Hungary, and Austria) but did have a single study site in South America (Chile). The treatment duration was up to 24 months. Study centers in Santiago, Chile and Budapest, Hungary extended the treatment duration to up to 3 years. Upon removal of the implant, subjects were monitored for a 3-month follow-up period. Six hundred and thirty-six subjects (636) were enrolled in Study 34507; 635 subjects received the implant. Four hundred thirty-six (436) subjects completed 2 years, 199 subjects discontinued in the first 2 years; 147 subjects extended for 3 years, 10 subjects discontinued during year three, and 137 subjects completed 3 years. A total of 205 subjects discontinued the study and 4 subjects were lost to follow-up,

Study 34507 CDN- Study 34507 CDN was an open-label, single-center, non-comparative efficacy and safety study. The duration of treatment was up to 24 months. Fifty-two (52) subjects were enrolled and received an implant, 19 subjects discontinued (36.5%, 19 of 52 subjects), and 33 subjects completed 2 years (63.5% of 52 subjects) of treatment.

Four studies specifically addressed the pharmacokinetics (PK) and pharmacodynamics (PD) of Implanon™, in particular examining ovulation inhibition and plasma levels of etonogestrel (Studies 34502, 34508, and 34515). In addition, one 2-year study (Study 34504) was performed

with a "leached" implant to provide information on the in vivo release of Implanon in the 2nd year of use.

A further six studies explored specific safety parameters, particularly for effects on hemostasis (Study 34509), lipid metabolism (Studies 34510, 34512), carbohydrate metabolism, adrenal and thyroid function (Study 34511), bone mineral density (BMD) parameters (Study 34522) and the effects of Implanon™ on lactation and development of infants (Studies 34523).

Data from five additional studies that were performed in China, Russia, and Mexico were also submitted and considered by the Applicant as additional information in support of the claim of preventing pregnancy.

Five studies conducted in Indonesia (not included in the 19 studies) were disqualified because of significant Good Clinical Practice violations. The Applicant had classified two of the five studies as principal safety and efficacy studies and enrolled 649 subjects.

2.2 Efficacy

Principal Efficacy Studies.
The Applicant submitted data from four adequate and historically controlled clinical trials (principal studies 069001-U.S., 34505-Thailand, 34507-Europe, and 34507 CDN-Canada) to support the efficacy of Implanon for the prevention of pregnancy for up to 3 years. These 4 clinical trials had similar inclusion/exclusion criteria and enrolled 1117 reproductive aged, healthy female subjects.

The table below summarizes the annual Pearl Index and annual exposure to Implanon for subjects ≤ 35 years old.

Annual Pearl Index and Annual Exposure to Implanon™ (Subjects ≤ 35 years old at entry)

Parameter	Year 1	Year 2	Year 3
Pearl Index	0.5	0	0
95% CI	(0.1, 1.2)	(0, 0.5)	(0, 1.8)
Woman Years of Use	886	691	202

Source: Response to Information Request, 9 SEP 04

Through Two Years of Use. Overall, the total number of 28-day cycle equivalents was 22,695 with 1,746 woman-years of exposure. Conception for four pregnancies were estimated by the FDA medical reviewer to have occurred (n=3) or may have occurred (n=1) within 7 days of implant removal. Based on these four pregnancies, the cumulative Pearl index for women ≤ 35 years of age was calculated to be 0.27 (95% CI: 0.08 to 0.69) through two years of treatment. This value is well within an acceptable pregnancy rate reported with other methods of hormonal contraception.

Third Year of Use. A total of 215 subjects, from two centers in study 34507 (Chile and Hungary) and one center in Study 34505 (Thailand), entered into the third year of treatment and 195 subjects completed three years of use (90.6% of subjects). There were no reported pregnancies in Year 3 for these studies. For these studies combined, there were 218.8 woman-years of exposure equivalent to 2,844.4 cycles of exposure. The Pearl index for these subjects

was 0 [95% CI: (0, 1.7)]. Among women ≤ 35 years of age there were 183.9 woman-years of exposure equivalent to 2,391 cycles of exposure. The Pearl index for these subjects was 0 [95% CI: (0, 2.0)]. Although the total number of subjects studied in Year 3 was less than that which is usually requested for a contraceptive product, the upper bound of the 95% CI of 2.0 for women ≤ 35 years supports the effectiveness of Implanon throughout 3 years of use.

Supportive Studies
No pregnancies were reported to have occurred in any of the supportive clinical pharmacology, special safety, or additional studies. There was a rapid return of fertility after removal of the implant for subjects who desired to become pregnant.

2.3 Safety

2.3.1 Exposure to Study Drug

Principal Studies. A total of 1117 subjects were exposed to Implanon in the principal safety studies for a total of 26,787 cycles and 2,054 woman-years. Of these, 549 subjects completed 2 years, 197 subjects completed 3 years and 47 subjects completed 4 years.

Principal and Clinical Pharmacology Studies Combined. The mean duration of exposure to Implanon™ for the subjects in studies conducted in U.S./Europe/Singapore/Thailand was 685.8 days with a total exposure for 1,411 subjects of 2,649.2 woman years or 34,557 cycles. Most subjects in this population were exposed for 1 to <3 years (63.6%). A total of 1,112 subjects (78.8%) were exposed to Implanon™ for at least one year, and 214 subjects (15.2%) were exposed to Implanon™ for at least 3 years.

2.3.2 General Safety Findings in Clinical Trials

Deaths
In the clinical development program, no deaths were reported to have occurred in any study.

Discontinuations in the Principal Safety Studies:
A total of 323 out of 1117 (29%) of subjects in the principal safety studies discontinued due to an adverse event. Regional differences were observed, such that the incidence of discontinuations due to AEs was generally higher in the U.S. compared to Europe/Canada/Thailand. A total of 119 out of 330 (36%) subjects in the U.S. study discontinued due to AEs. In the studies conducted in Europe/Thailand, 204 out of 787 subjects (26%) discontinued due to AEs

The most frequently reported reasons for discontinuation (>1%) were bleeding irregularities (n=166, 14.9% subjects), weight increase (n=29, 2.6% subjects), emotional lability (n=23, 2.1% subjects), acne (n=13, 1.2% subjects), headache (n=12, 1.1% subjects), and amenorrhea (n=12, 1.1% subjects).

A total of 161 out of 330 subjects (48.8%) discontinued from U.S. Study 069001. The most common reason for discontinuation was adverse experience, with 119 subjects (36.1%) discontinuing primarily for this reason. Of these subjects discontinuing for an adverse experience, 43 subjects (13.0% of enrolled subjects) discontinued because of adverse menstrual experiences (bleeding irregularities) as the primary reason, and 76 subjects (23.0% of enrolled subjects) discontinued with other adverse experiences being the primary reason.

Adverse Events in the Principal Safety Studies

Serious Adverse Events. Sixty-two (62) out of 1117 subjects (5.5%) in the principal safety studies conducted in U.S./Europe/Thailand had at total of 83 serious adverse events (SAEs) Twelve (12) of the 83 SAEs were thought to be possibly, probably, or definitely drug-related. These included two cases of ovarian cyst and single cases of gastrointestinal disorders not otherwise specified, breast fibroadenosis, breast neoplasm benign, uterine fibroid, depression, cyst not otherwise specified, cerebrovascular disorder (a case of A-V malformation), headache, chest pain, and tachycardia.

Treatment-related Adverse Events. Within the population of subjects from the 4 principal safety studies (U.S./Europe/Thailand), the system-organ classes with the highest incidence of treatment related AEs were: Reproductive Disorders, Female, (212/1117 subjects or 19%); skin and appendages disorders(192/1117 subjects or 17.2%; CNS disorders (164/1117 subjects or 14.6%; and Psychiatric disorders (159/1117 subjects or 14.2%).

Individual drug-related adverse events *(other than uterine (vaginal) bleeding)* in this population and the percentage of subjects reporting them included acne (14.3%), headache (12.6%), weight increase (11.0%), breast pain (10.0%). emotional lability (5.4%), and dysmenorrhea (4.8%)

The overall vaginal bleeding pattern associated with Implanon™ ranged from amenorrhea to heavy bleeding and was primarily unpredictable. In the principal and clinical pharmacology non-comparative studies combined, Implanon™-treated subjects (completers and non-completers combined) experienced a mean of 18.36 bleeding-spotting days per 90-day reference period. The hematology parameters measured in the US Study 069001 and Study 34507 (Austrian site only) did not show a clinically significant lowering of hemoglobin.

Systolic and diastolic blood pressure posed no safety concerns any studies; however, a gradual increase in body mass index over time was noted. The number of subjects with a >10% increase in body mass index from baseline at least once during treatment was 59 out of 330 (18.3%) in the U.S study, and 268 out of 1401 (19.1%) in the non U.S. Principal and Clinical Pharmacology Studies.

Laboratory parameters (hematology, blood chemistry, and urinalysis) were assessed in U.S. Study 069001 and in non-U.S. study 34507 (Austria). No clinically meaningful laboratory abnormalities were noted. Parameters of lipid metabolism (studies in the U.S., U.K. and Thailand) did not reveal any adverse effects. The mean Bone Mineral Density (BMD) parameters were not adversely affected by the use of Implanon.

Summary statistics for implant insertion times in the clinical trials showed a mean insertion time of 84.3 seconds and a mean removal time of 244.1 seconds; a total of 15 subjects (1.1%) experienced complications at implant insertion and 27 subjects (2.0%) experienced complications at implant removal.

2.3.3 Safety Issues of Particular Concern

Thromboembolic Adverse Events. No cases of pulmonary embolus or myocardial infarction, one case of an intracranial hemorrhage associated with a congenital vascular malformation, and one case of DVT were reported among a total of 1803 subjects who participated in the clinical trials.

Insertion/Removal Adverse Events. Since the market introduction of Implanon™, Organon has received over 450 complaints of insertion and removal problems. Problems with insertion of Implanon™ are thought to be the major factor that contributed to unintended pregnancies. The consequence of improper insertion also resulted in removal difficulties. These have included 'non-palpable Implanon™', 'otherwise difficult localization of Implanon™', 'broken Implanon™', 'difficult removal of Implanon™', and 'loss of implants'.

Organon has submitted a Risk Management Program regarding healthcare provider training in insertion and removal of Implanon™. This program is similar to those used with other implants..

2.3.4 Serious Postmarketing Safety Reports

On September 9, 2004, Organon submitted a cumulative listing of all selected postmarketing events from August 1998 – September 1, 2004. The number of implants sold during this period was approximately . Rates of death, pulmonary embolus, cerebrovascular accident, deep vein thrombosis and myocardial infarction worldwide, and for Europe only (in number of events per 100,000 woman-years of use) are outlined in the Table that follows: b(4)

Cumulative Listing-of Selected Serious Postmarketing Adverse Events

	Number of events worldwide	Number of events Europe[a] only	Worldwide rates (events per 100,000 woman-years of use)[b]	Europe[a] only rates (events per 100,000 woman-years of use)[b]
Death	5	3	0.15	0.17
Pulmonary embolus	10	7	0.31	0.41
Deep vein thrombosis[c]	18	14	0.55	0.82
(Venous thromboembolic events (VTE))[d]	(28)	(21)	(0.86)	(1.22)
Cerebrovascular accident (CVA)	14	12	0.43	0.70
Myocardial infarction	1	1	0.03	0.06

[a]The following countries were included for Europe: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Sweden, United Kingdom, Czech Republic, Finland, Malta, Norway, Slovak Republic, Spain, Switzerland, Norway and Iceland.
[b] Both medically confirmed and medically unconfirmed reports are included.
[c] Superficial venous thrombosis is excluded from this analysis. Cases in which it is unclear whether it involves a deep or superficial thrombosis (e.g. only "thrombosis" was reported) are included.
[d]Venous thromboembolic events is the total rate of pulmonary embolus and deep vein thrombosis.

Source: Response to information request, 9Sep04

2.3.5 Overall Assessment of the Safety Profile for Implanon

Based on the safety data from the clinical trials for Implanon supported by the applicant submitted in NDA 21-529 and post marketing safety reports, the safety profile of Implanon is acceptable for a highly effective contraceptive drug product. The most common adverse event, irregular uterine (vaginal) bleeding does not pose a safety concern.

2.4 Dosing

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, etonogestrel is slowly released over a period of 3 years. The initial release rate is approximately 67 µg /day and the release rate over the entire period of three years is approximately 41 µg/day. The Applicant selected this release rate because it was the lowest dose that reliably prevented ovulation in Phase 2 clinical trials. Implanon must be removed no later than 3 years after implantation and replaced by a new Implanon implant

2.5 Special Populations

Ethnicity. There are no separate race or ethnicity considerations about safety or efficacy. The principal U.S. study is the only study that collected data on race. Since the number of non-Caucasian subjects in the U.S. study was small, no formal analyses by race for either efficacy or safety were performed. Two of the four in-treatment pregnancies in the clinical development program occurred in the U.S.: both subjects were Caucasian.

Age (Pediatric Population). The product is intended for use only in reproductive age women. A separate pediatric program is not required. Hormonal contraceptive drug products are considered safe and effective in post-menarchal females. No formal studies involving subjects less than 18 years of age have been required by the Division for this class of drug products. This product is not intended for pre-menarchal use.

Pregnancy and Renal or Hepatic Impairment. This drug is contraindicated in pregnancy. The pharmacokinetics of Implanon™ was not evaluated in patients with renal or hepatic impairment. Labeling will address these latter areas.

Appears This Way
On Original

Clinical Review

1. INTRODUCTION AND BACKGROUND

1.1 Drug

Established Name	Etonogestrel Implant
Proposed Trade Name	Implanon™
Drug Class	Progestin Contraceptive
Indication	Prevention of pregnancy
Dose	68 mg implant
Dosing Regimen	A single subdermal implant for up to three years of continuous use

1.2 State of Armamentarium for Indication(s)

Oral contraceptives containing either an estrogen and a progestin or a progestin alone are highly effective and are used by a large percentage of women who wish to prevent pregnancy. All approved oral contraceptives require daily administration of a tablet for at least 21 days during a 28 day period. Failure to adhere to the approved dosing regimens significantly reduces the effectiveness of these products. Highly effective contraceptives that have a dosing regimen other than by daily oral tablet include medicated and inert IUDs, a vaginal ring (NuvaRing), a weekly transdermal patch (OrthoEvra), a 90-day depot injectable progestin (depot medroxyprogesterone acetate), and levonorgestrel containing subdermal implants. The presently approved subdermal contraceptive implants in the U.S. are a 6-rod system (Norplant™) and a 2-rod system (Jadelle™). Neither is currently marked in the U.S.

1.3 Important Milestones in Product Development

- On 15 April 1993, the FDA held a pre-IND meeting to discuss Organon's proposed studies and the overall development plan for Implanon™.
- On 18 October 1995, the FDA held a pre-NDA meeting. The Applicant was planning to submit the NDA in 1997. Three adequate and well-controlled studies would be pivotal (a 2 year U.S. multicenter study, European multicenter study; and Southeast Asia multicenter study). The acceptability of basing approval for a three year indication on non-U.S. studies was discussed. The FDA asked the Applicant to continue the U.S. study for three years, but they said it would not be possible. It was decided by the Division to allow the foreign data to be the basis for a three year indication instead of a two year indication.
- On 15 May 2002, the Applicant submitted a letter describing the proposed elements of the electronic data sets and requesting a waiver from submitting electronic patient profiles; and
- On 15 July 2003, the FDA agreed that all adverse events could be coded by WHOART classification and that all post marketing adverse events could be coded by MedDRA.

There was a several year delay in the submission of this NDA to the FDA following the pre-NDA meeting in Oct 1995 (submission on 30-Sept-2003). The Applicant gave the following explanation for this delay:

"The original NDA submission was planned in parallel with the submission in Europe in 1997. These timelines were determined by the completion dates of the various clinical trials. Shortly after submission in Europe, Organon encountered some unforeseen problems in the production of Implanon™, which required a redesign of some of the production facilities and equipment. Finally, the original application needed to be updated with all newly acquired clinical information as well as re-formatted to comply with the electronic submission guidelines, which also affected the final submission date of the NDA".

Medical Officer's Comments

- **The pivotal studies submitted for this NDA were in accordance with those that were discussed at the pre IND meeting on April 15, 1993 and the pre NDA meeting on October 18, 1995. The Applicant adequately explained the delay of seven years to submit this NDA. A significant consequence of this delay was completion of more supportive studies and the accrual of more postmarketing information, thereby contributing more data.**

1.4 Other Relevant Information

Two levonorgestrel containing subdermal implants are approved for marketing in the U.S. They are a 6-rod system (Norplant™) and a 2-rod system (Jadelle™). Neither, however, is currently marked in the U.S. Implanon™ is approved for marketing in approximately 57 countries worldwide (see Table 46) and registration is pending in approximately 20 other countries (Table 47. The Applicant states that there have been no rejections by a regulatory agency for approval of Implanon for marketing in any countries in which an application has been submitted.

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). ENG, structurally derived from 19-nortestosterone, is the biologically active metabolite of desogestrel. 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. Currently, one ENG-containing product (NuvaRing®) 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) approved by the FDA for marketing in 2001.

1.5 Important Issues with Pharmacologically Related Agents

Women who are unable to tolerate estrogen or in whom estrogen is contraindicated can use Progestagen-only based contraceptives. The major disadvantages of progestagen-only contraception are unpredictable menstrual bleeding changes such as short cycles, spotting, breakthrough bleeding, and less frequently, amenorrhea. These menstrual cycle changes often are the cause of early discontinuation of progestin-only contraceptives because of the lack of acceptability by the user.

Three different types of progestagen-only contraception are presently approved for marketing in the U.S., i.e., progestin-only oral contraceptive pills (POPs) that are to be taken every day, an

injectable progestin (i.e., depot medroxyprogesterone acetate [DMPA], Depo-Provera™, administered once every 3 months), and two progestin-only subdermal implants. Norplant™ (NDA 19-897) is a non-biodegradable six-rod levonorgestrel releasing implant system that provides efficacy for up to 5 years. A two-rod levonorgestrel-containing system called Jadelle ®(NDA 20-544) that provided efficacy for up to 5 years was first approved for marketing in the U.S. in Nov. 1996 for 3 years, then in Nov. 2002 for five years; however, neither of these implants are currently marketed in the U.S. The failure rates for Depo-Provera™ and the Norplant™ implants are reported as 0.3% and 0.05%, respectively.

Depo-Provera™ requires compliance with an intramuscular injection once every three months. When discontinued, the depot formulation continues to release drug substance for weeks, or in some cases months. Thus, the recovery of ovulatory ovarian function and regular menstrual cycles after discontinuation of Depo-Provera™ is delayed and ovulation may not occur for up to one year. Use of Depo-Provera™ is associated with a decrease in bone mineral density (BMD) and use for more than 2 years may cause a clinically significant decrease in BMD in many women. No clinically important decreases in bone mineral density have been reported for users of Norplant™ or Jadelle.

Neither Norplant™ or Jadelle™ inhibit ovulation consistently and with time the risk of pregnancy due to method failure increases. Insertion and removal of the Norplant™ system also can be difficult and time consuming.

2. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

2.1 Chemistry

The sterilization facility at The Netherlands was not ready for inspection; therefore, the facility could not be inspected. At this time, the Office of Compliance has given a "Withheld" recommendation.

Since sterility is an important parameter dealing with product safety, it is recommended that the application remains approvable pending a satisfactory inspection report from the Office of Compliance.

2.2 Animal Pharmacology and Toxicology

The following information was obtained from the review of Dr Krishan Raheja, the FDA toxicologist.

Preclinical Pharmacology: No safety pharmacology was submitted; however, safety is established based on approval of NDA 20-071 for Desogen tablets (desogestrel & ethinyl estradiol) and NDA 21-187 for 3-keto-desogestrel/ethinyl estradiol vaginal ring (NuvaRing).

Toxicology: Based on review of the preclinical studies reviewed under NDA 21-187 and those under IND 38,795, there are no toxicological concerns.

Genetic Toxicology: 3-keto-desogestrel (3-KDSG) was negative in the in vitro (Ames and chromosomal assays) and in the in vivo (mouse micronucleus assay) genotoxicity tests.

Carcinogenicity: 3-KDSG was not carcinogenic in the 2-year rat carcinogenicity study using subcutaneous implants.

Reproductive and Developmental Toxicology: Based on pre-clinical findings and clinical experience with 3-KDSG, there is no safety concern.

Conclusion: Essentially all preclinical study data was cross-referenced to that submitted for 3-KDSG/EE (NDA 21-187, NuvaRing). The FDA preclinical Pharmacology Reviewer (Dr. Raheja) had no toxicological concerns and recommended approval of NDA 21-529.

2.3 Statistics

The FDA statistician (Ms. Ng) provided the following summary:

> "The effectiveness of Implanon™ in the prevention of pregnancy has been demonstrated for women who completed 2 years of treatment. The results are based on 4 studies: 1 U.S. study (069001) and 3 Non-U.S. studies (34505, 34507, and 34507 CDN). They are open label, noncomparative, multicenter studies to evaluate the safety and contraceptive efficacy of Implanon™ in women who chose to use the contraceptive implant for the prevention of pregnancy".
>
> "The sponsor reports no pregnancies in any of the 4 studies. The medical reviewer requested calculation of the Pearl Index and Life-Table Pregnancy Rate including post-treatment pregnancies conceived within 14 days after discontinuation of the study drug. Two pregnancies in the U.S. study and 2 pregnancies in the Non-U.S. studies were included based on the recommendation of the medical reviewer. The Pearl indices for the U.S. study is 0.42 [95% CI: (0.05, 1.5)], and for the Non-U.S. studies are 0 [95% CI: (0, 2.0)], 0.01 [95% CI: (0, 0.5)] and 1.26 [95% CI: (0.03, 6.72)] for studies 34505, 34507, 34507 CDN, respectively. The Pregnancy Rates for the U.S. study is 0.7% [95% CI; (0%, 2%)], and for Non-U.S. studies are 0.2% [95% CI: (0%, 0.5%)], and 2% [95% CI: (0%, 7%)] for studies 34507 and 34507 CDN, respectively".

2.4 Other Consultations

2.4.1 Division of Drug Marketing, Advertising, and Communications (DDMAC)

Comments were provided on the draft labeling for Implanon™. These comments were reviewed and all were considered in FDA revised labeling. FDA revised labeling was significantly different from that proposed by the Applicant. Final labeling was pending at the time of completion of this review.

2.4.2 Division of Surveillance, Research, and Communication Support

The Division of Surveillance, Research, and Communication Support (DSRCS) recommended: that the patient package insert should be written in a Medication Guide question and answer type format. DSRCS also the suggested to use the class labeling for estrogen and progestin containing products for postmenopausal women as a template for revising patient information for contraceptive products and to keep the insertion and removal information at the end of the leaflet.

Medical Officer's Comments

- **Until the patient package inserts for all contraceptive products are revised, the patient package insert for this product will follow that for other presently approved contraceptive products.**

2.4.3 Division of Medication Errors and Technical Support

In their last review, dated February 2, 2004, (ODS Consult # 03-0311), DMETS did not have any objections to the use of the proprietary name, Implanon.

3. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

3.1 Pharmacokinetics (PK)

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 of (ethylene vinylacetate copolymer with a vinylacetate content of 28%), surrounded by a 60 µm skin of (ethylene vinylacetate copolymer with a vinylacetate content of 14%). ENG, structurally derived from 19-nortestosterone, is the biologically active metabolite of desogestrel. 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. b(4)

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 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 8 studies (34505, 34509, 34510, 34511, 34512, 34522, RM02, RM04).

The mean peak serum ENG concentrations were between 781 and 894 pg/mL and were reached within the 1st few weeks after insertion. Serum ENG concentrations gradually declined to 192 – 261 pg/mL at the end of the 1st year. The mean serum ENG concentrations were between 156 and 177 pg/mL at the end of the 3rd year. In 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. These ENG concentrations are significantly lower than the concentrations released by the Nuva Ring® (etonogestrel + ethinyl estradiol). See Table 1.

Table 1 Comparison of ENG exposures in Women with NuvaRing® or Implanon™

Mean (SD) PK Parameters of ENG in Women using NuvaRing®						
1st Week (pg/mL)	2nd Week (pg/mL)	3rd Week (pg/mL)	C_{max} (pg/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	CL (L/hr)
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 in Women using Implanon™ (Study 069001)				
1st Year (pg/mL)	2nd Year (pg/mL)	C_{max} (pg/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
192	160.3	781 (323-1560)	median, 144 (24-263)	34.6 (21-56)

Source: NuvaRing label; Original NDA 021529; 30 Sep 03

During the 4-month lactation period, the mean daily ingested infant ENG doses were about 1.7% of the maternal daily dose/kg.

- *ENG concentrations for subjects with BMI<20 kg/m^2 were about 47% and 29% higher than subjects with BMI ≥ 25 kg/m^2 and 20-25 kg/m^2, respectively.*

One study was conducted to assess the absolute bioavailability of ENG from Implanon™ (a subset of study 34507). The bioavailability of Implanon™ was close to 100%.

The recommendation of the Biopharmaceutical Reviewer (Dr. Myong–Jin Kim) was that the overall human pharmacokinetic and pharmacodynamics section is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics /Division of Pharmaceutical Evaluation II.

3.2 Pharmacodynamics (PD)

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

Medical Officer's Comment

- **Data to support the Applicant's claim that the contraceptive effect of Implanon is primarily achieved by suppression of ovulation is not provided in the principal clinical trials.**

Dose-finding studies (by Diaz et al. 1991 Contraception, and an Organon study performed in China) were performed to determine which subdermal dose of ENG was sufficient to obtain ovulation inhibition. In these studies, prototype ENG-containing implants were used, differing from the final Implanon™ design with respect to their dimensions and materials as well as in their ENG content and ENG release rate. These implants contained approximate quantities of ENG between 7 and 28 mg. Five different doses with *in vitro* release rates of 10-40 µg/day of ENG were evaluated. There were no pregnancies at release rates of 30 µg and 40 µg/day of ENG. At a release rate of 20 µg/day or less, three pregnancies occurred. Ovulation was inhibited in 97% of subjects with ENG plasma levels >0.09 ng/mL: ovulation was inhibited in only 52% of subjects with ENG plasma levels <0.09 ng/mL. ENG implants releasing ~40 µg/day and providing plasma levels ~0.09 ng/mL showed efficient contraception protection.

Based on these data, it was decided to develop an implant that would show an in vitro release rate of approximately 30 µg/day at the end of its projected duration of use of three 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 is required. The in-vitro release rate profile of Implanon™ is about 60-70 µg/day during week 5-6, decreasing to about 35-45 µg/day at the end of the first year, to about 30-40 µg/day at the end of the second year, and about 25-30 µg/day at the end of the third year.

The clinical experience with Implanon™ in obese women in the 3rd year of use was 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 kg. Body weight and BMI contributed to the differences in mean ENG serum concentrations. Serum ENG concentrations were inversely related to body weight and decreased with time after insertion. Although the contraceptive effect in obese women during the 3rd year of use may be lower, no pregnancies were observed in the clinical trials in the higher weight categories.

Medical Officer's Comments

- **There is limited PD/PK data for 3rd year of use, particularly in women who were above 130% ideal body weight. This product should be restricted to women who are between 80% and 130% ideal body weight. The label should contain a warning for the use of this product in women whose body weight is greater than 130% of ideal body weight.**

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Sources of Clinical Data

4.1.1 Original NDA Submission

NDA 21-529 provides data from 1803 subjects in 19 completed Phase II and III studies plus one ongoing phase II study. Subjects were treated with Implanon™ for up to 2-5 years in 16 different countries (including studies in Southeast Asia, Europe, North America [U.S. and Canada], and South America). With the exception of Study 34504, all studies were designed to collect pregnancy, vaginal bleeding, and safety data. Study 34504 assessed the pharmacokinetic and pharmacodynamic profiles of a leached implant (Implanon™) with an initial etonogestrel (ENG) release rate similar to that observed at the start of the second year of use).

The clinical development program of Implanon™ was designed to evaluate the contraceptive efficacy, and safety (including vaginal bleeding patterns, a major aspect of acceptability). In addition, dedicated studies on the pharmacokinetics, pharmacodynamics and metabolic safety of Implanon™ were performed.

On Mar. 23, 2004, Organon Inc. informed the Division of Reproductive and Urologic Drug Products (DRUDP) that there were *significant* Good Clinical Practice violations at the Jakarta, Indonesia site (R1001) and the Semarang Indonesia site (R1007). During the monitoring visit in preparation for an upcoming FDA inspection, several instances of misconduct were uncovered. These issues involved five of the studies submitted in the original NDA. Affected studies included "principal" Studies 34506 and 34520; pharmacodynamic Study 34503, lipid metabolism Study 34510 (Indonesia site only), and endometrial histology Study 34514. These studies involved the data for 720 Indonesian subjects. On a subsequent teleconference with the Applicant, there was a mutual agreement to remove these studies and all related data from for the analyses supporting the safety and efficacy of Implanon.

The remaining data were initially considered to be of adequate quality for review and is derived from 20 Phase II and III studies that are described below and listed in Table 2. However, the adequacy of the studies was later reassessed (see Section 5.4).

Medical Officer's Comments

- **Removal of Studies 34506 and 34520 has had a significant impact on the adequacy of the data submitted in support of this NDA since both were considered by the Applicant to be principal efficacy and safety studies. In additional, both studies provided efficacy and safety data for a third year of use, data that was provided by only 3 other centers.**

Principal Safety and Efficacy Studies (4 Studies)

Four studies (that enrolled 1117 subjects) were considered the principal safety and efficacy studies (Studies 069001, 34505, 34507, and 34507 CDN). In addition to efficacy and safety, these 4 studies also present data on clinical pharmacology, including drug levels (subsets of Studies 069001 and 34507), lipid metabolism, carbohydrate metabolism, ophthalmological parameters, and endometrial histology (subsets of Study 069001).

Supportive Clinical Pharmacology Studies (4 Studies)

Four studies (that enrolled 56 subjects) specifically addressed the pharmacokinetics (PK) and pharmacodynamics (PD) of Implanon™, in particular examining ovulation inhibition and plasma levels of ENG (Studies 34502, 34508, and 34515). In addition, one 2-year study (Study 34504) was performed with a "leached" implant. This implant was prepared by extracting the amount of ENG normally released within the first year of use (i.e. approximately 20 mg), resulting in an implant simulating Implanon™ from its second year of use onwards. This implant was used to investigate ovulation inhibition, cervical mucus effects and blood levels of ENG representative for the (simulated) second and third year of use.

Supportive Special Safety Studies (6 Studies)

A further six studies (that enrolled 226 subjects)explored specific safety parameters, particularly for effects on hemostasis (Study 34509), lipid metabolism (Studies 34510, 34512), carbohydrate metabolism, adrenal and thyroid function (Study 34511), bone mineral density parameters (Study 34522) and the effects of Implanon™ on lactation and development of infants (Studies 34523).

Additional Supportive Studies (5+1 Studies)

Data from five additional studies that were performed in China (Studies RM01, RM02, and RM04- not conducted under good clinical practices), Russia (Study 34525) and Mexico (Study 34524-for registration in Mexico) were also submitted and considered by the Applicant as additional information in support of the claim of preventing pregnancy (all five) and ovulation inhibition (Study RM01). An additional study is ongoing: study E-1729 Malaysia, Venezuela, Austria, and Germany. These studies were not reviewed in detail and were reviewed only for significant safety issues).

Table 2 Listing of Clinical Trial Studies

Principle Safety and Efficacy Studies (4)
069001 (U.S.) – Open label, noncomparative, multicenter, safety and efficacy study of Implanon™ in 330 women age 18-40 for 2 years
34505 (Thailand) – Open label, noncomparative, single center, safety and efficacy study of Implanon™ in 100 women age 18-39 for 2 to 4 years
34507 (Europe/Chile) – Open label, noncomparative, multicenter, safety and efficacy study of Implanon™ in 635 women age 18-40 for 2 to 3 years
34507 CDN (Canada) – Open label, noncomparative, single center, safety and efficacy study of Implanon™ in 52 women age 18-40 for 2 years
Supportive Clinical Pharmacology (4) and Special Safety Studies (6)
34502 (Thailand) – Open label, noncomparative PK/PD study of Implanon™ in 15 women age 20-37 for 2 to 5 years
34504 (UK) – Open label, noncomparative PK/PD leached implant study of Implanon™ in 15 women age 28-37 for 1 to 4 years
34508 (Finland; Sweden) – Open label, randomized, comparative (vs. Norplant™), PK/PD study of Implanon™ in 16 women (16 women- Norplant™ group) age 18-39 for 2 to 3 years
34515 (Singapore) – Open label, single center, absolute bioavailability study of Implanon in 10 women age 27-39 for 2 years
34509 (Finland; Sweden) – Open label, randomized, comparative (vs. Norplant™), hemostasis and liver function study of Implanon™ in 43 women (43 women- Norplant™ group) age 19-40 for 2 years
34510 (Thailand) – Open label, randomized, comparative (vs. Norplant™), lipid metabolism study of 15 women (15women-Norplant™ group) age 19-37 for 2 years
34511 (Singapore) – Open label, randomized, comparative (vs. Norplant™), carbohydrate metabolism, thyroid and adrenal function study of Implanon™ in 40 women (40 women-Norplant™ group) age 19-39 for 2 years
34512 (Finland) – Open label, randomized, comparative (vs. Norplant™), lipid metabolism study of Implanon™ in 40 women (40 women-Norplant™ group) age 19-40 for 2 years
34514 (UK) - Open label, randomized, comparative (vs. Norplant™), endometrium study of Implanon™ in 30 women (30 women in Norplant™ group) age 18-40 for 2 to 3 years
34522 (The Netherlands, Chile, Finland) – Open label, randomized, comparative (vs. IUD), bone mineral density study of Implanon™ in 46 women (30 women-IUD group) age unavailable for 2 years
34523 (Thailand) – randomized, comparative (vs. IUD), lactation and development of infants study of Implanon™ in 42 women (38 women-IUD) age 18-40 for 2 years to 4.5 years
Additional Supportive Studies (5 + 1 ongoing)
34524 (Mexico) – Open label, noncomparative, non randomized, safety and efficacy study of Implanon™ in 58 women age 18-36 for 2 years
34525 (Russia) – Open label noncomparative, non randomized, safety and efficacy study of Implanon™ in 60 women age 18-40 for 1 year
RM01 (China) – Open label, noncomparative PK/PD not good clinical practice study of Implanon™ in 16 women age 26-35 for 2 to 4.5 years
RM02 (China) – Open label, noncomparative, safety and efficacy not good clinical practice study of Implanon™ in 200 women age not available for 2 to 4 years
RM04 (China) – Open label, randomized, comparative (vs. Norplant™) not good clinical practice study of Implanon™ in 100 women (100 women Norplant™ group) age not available for 2 to 4 years
E-1729 Malaysia, Venezuela, Austria, Germany - Ongoing - Open label, noncomparative, multicenter, safety, efficacy study of Implanon™ planned in 211 women for 3 years

Table 2 Listing of Clinical Trial Studies (Continued)

Disqualified Studies (5)
34506 (Indonesia) – Open label, noncomparative, multicenter study of Implanon™ in women age 20-35 for 2 to 4 years
34520 (Indonesia) – Open label, comparative (vs. Norplant™) multicenter, safety, acceptability study of Implanon™ in women age 18-40 for 2 to 3 years
34503 (Indonesia) – Open label noncomparative PK/PD study of Implanon™ in 15 women age 27-34 for 2 to 5 years
34510 (Indonesia; Thailand data included) – Open label, randomized, comparative (vs. Norplant™ and IUD) lipid metabolism study of Implanon™ in 60 women (60 women-Norplant™ group; 45 IUD group) age 19-40 for 2 to 3 years
34514 (Indonesia) Open label, randomized comparative (vs. Norplant™) endometrial histology study in 41 women (40 women-Norplant™ group) age 18-41 for 2 to 3 years

Source: Original NDA 021529; Table 1, ISE, P21, 30 Sep 03.

4.1.2 Information Submitted during the Review

Four Month Safety Update Studies

The four month safety update was submitted on 19-Jan-2004. In addition to providing general updated safety information, the submission included detailed information from two studies: Studies 34525 (Russia) and E-1729 (ongoing study in Malaysia, Venezuela, Austria, and Germany). The updated Investigator's Brochure was also included.

Revised Integrated Summaries of Safety and Efficacy

On 3 May 2004 the Division had a teleconference with the Applicant to discuss the improprieties that occurred during the conduct of the clinical studies at the Indonesian study sites. The Applicant subsequently submitted a major revision to the NDA, which contained the following revised components:

- Human Pharmacokinetics and Bioavailability Summary
- List of Studies
- Clinical Pharmacology Summary
- Integrated Summary of Effectiveness Data
- Integrated Summary of Safety Information

Postmarketing Surveillance Study

The BKKBN study, which was not part of the clinical development program, was a post marketing surveillance study conducted by the National Family Planning Coordination Board in Indonesia.

Health Care Provider training program

On 9 Sep 04 the Applicant submitted (1) a description of their program to train healthcare providers on the proper technique for insertion/removal other aspects of the use of Implanon™, and (2) the evaluation program to monitor the effectiveness of the program. Materials submitted included:

- Program description
- PowerPoint® SlideSets
- Publications referenced on the PowerPoint® SlideSets

Additional sources of clinical data and information (spontaneous submissions by the Applicant and Division requests) included:

- Postmarketing : Unintended pregnancies
- Postmarketing: Adverse events, including a list of all SAEs and deaths
- Postmarketing: Insertion/ Removal Related Events (IRREs)
- Marketing and registration information outside of the U.S.
- Clinical trial listing of SAEs, deaths and specific AEs
- Pregnancy follow-up data, including source sonographic data to assist in assessing conception dates for Pearl index calculations
- Financial disclosure information

4.2 Overview of Clinical Trials

Table 3 is a listing of 22 (3 disqualified studies listed in Table 2 are not listed in Table 3) completed Phase II and III studies submitted by the Applicant. The studies are presented in the table in the following study groupings: Principal Safety and Efficacy Studies; Supportive Clinical Pharmacology Studies; Disqualified Studies.

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Table 3 Overview of Clinical Trials

Study number (No. of Sites) Country Start Date End Date	Study design	Age range (mean age) Race (%)	Treatment and dose	Number of subjects/total months of exposure	Maximum duration of drug treatment
Principal Safety and Efficacy Studies – (4)					
Study 069001 (Main Study) (16 sites) **Country: U.S.** Start: November 1993 End: July 1996	Open label, noncomparative, multicenter, safety, efficacy	18-40 yr (26.1 yr) White: 70.9% Black: 12.1% Asian: 2.1 Other: 14.8	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG	330/6,196	2 years
Substudies (6 sites)	Open label, noncomparative, pharmacokinetic, ophthalmology, carbohydrate metabolism, lipid metabolism, and endometrial morphology	PK 18-39 yr (27.9 yr) Ocular 19-36 yr (25.7 yr) Carbohydrates 20-36 yr (25.3 yr) Lipids 18-37 yr (26.6 yr) Endo 18-40 yr (27.5 yr)		PK 20/492 Ocular 20/297 Carbohydrates 25/450 Lipid 40/822 Endo 22/404	2 years
Study 34505 (1 site) **Country: Thailand** Start: January 1991 End: February 1996	Open label, noncomparative, single-center, safety, efficacy	18-39 yr (26.3 yr)	**Implanon™:**	100/3,863	2 years, extended to 4 years
Study 34507 (27 sites) **Countries: Austria; Belgium; Germany; France; UK; Hungary; Netherlands; Chile; Sweden** Start: November 1991 End: January 1997	Open label, noncomparative, single-center, safety, efficacy	18-40 yr (29.1 yr)	**Implanon™:**	635/15,653	2 years (extended to 3 years in Hungary and Chile)
Study 34507 (1 site) **Country Canada** Start December 1993 End December 1996	Open label, noncomparative, single-center, safety, efficacy	18-40 (24.0)	**Implanon™**	52/1,085	2 years

Table 2 Overview of Clinical Trials (cont)

Study number (No. of Sites) Country Start Date End Date	Study design	Age range (mean age) Race (%)	Treatment and dose	Number of subjects/total months of exposure	Maximum duration of drug treatment
Supportive Clinical Pharmacology or Special Safety Studies (16+1 submitted later)					
34502 Thailand (1 site) Start: September 1989 End: June 1995	Open label, noncomparative, pharmacokinetic, pharmaco-dynamic	20-37yr (26.0yr)	**Implanon**: Subdermal Implant with initial daily release rate of 67 µg ENG	15/755	2 years, extended to 5 years
34504 UK (1 site) Start: January 1990 End: September 1994	Open label, noncomparative, pharmacokinetic, pharmaco-dynamic Leached Implant	28-37yr (32.0yr)	**Implanon™** Subdermal Implant with initial daily release rate of 40µg ENG	15/306	1 years, extended to 4 years
34508 Finland; Sweden (2 sites) Start: March 1991 End: December 1994	Open label, randomized, comparative (vs. Norplant™ pharmacokinetic;pharmaco-dynamic	**Implanon™** 18-39yr (29.5yr) **Norplant™** 20-37 (27.7)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **Norplant™** 6 subdermal implants with initial daily release rate of 85 µg levonorgestrel	**Implanon™** 16/420 **Norplant™** 16/355	2 years, extended to 3 years in Finland
34509 Finland; Sweden (4 sites) Start: January 1992 End: March 1995	Open label, randomized, comparative (vs. Norplant™) efficacy and safety (hemostasis and liver function)	**Implanon™** 19-40yr (28.2yr) **Norplant™** 19-38yr (28.4yr)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **Norplant™** 6 subdermal implants with initial daily release rate of 85 µg etonogestrel	**Implanon™** 43/789 **Norplant™** 43/842	2 years

Table 2 Overview of Clinical Trials (cont)

Study number (No. of Sites) Country Start Date End Date	Study design	Age range (mean age) Race (%)	Treatment and dose	Number of subjects/total months of exposure	Maximum duration of drug treatment
Supportive Clinical Pharmacology or Special Safety Studies (Cont)					
34510 Thailand (1 sites) Start: March 1992 End: July 1996	Open label, randomized, comparative (vs. Norplant™) lipid	**Implanon™** 19-36yr (28.5yr) **Norplant™** 20-37yr (27.7yr)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **Norplant™** 6 subdermal implants with initial daily release rate of 85 µg levonorgestrel **IUD** Multiload cu 250	**Implanon™** 15/358 **Norplant™** 15/384	2 years
34511 Singapore (4 sites) Start: November 1992 End: October 1995	Open label, randomized, comparative (vs. Norplant™) carbohydrate metabolism, thyroid and adrenal functions	**Implanon™** 19-39yr (29.1yr) **Norplant™** 22-37yr (29.2yr)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **Norplant™** 6 subdermal implants with initial daily release rate of 85 µg levonorgestrel	**Implanon™** 40/1028 **Norplant™** 40/921	2 years
34512 Finland (2 sites) Start April 1992 End February	Open label, randomized, comparative (vs. Norplant™) lipid	**Implanon™** 19-40 (25.7) **Norplant™** 6 subdermal implants with initial daily release rate of 85 µg levonorgestrel	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **Norplant™** 6 subdermal implants with initial daily release rate of 85 µg levonorgestrel	**Implanon™** 40/728 **Norplant™** 40/811	2 years

Table 2 Overview of Clinical Trials (cont)

Study number (No. of Sites) Country Start Date End Date	Study design	Age range (mean age) Race (%)	Treatment and dose	Number of subjects/total months of exposure	Maximum duration of drug treatment
Supportive Clinical Pharmacology or Special Safety Studies (Cont)					
32514 UK (1site) Start January 1993 End March 1997	Open label, randomized, comparative (vs. Norplant™) endometrium	**Implanon™** 18-40 (27.0) **Norplant™** 18-35 (26.1)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **Norplant™** 6 subdermal implants with initial daily release rate of 85 µg levonorgestrel	**Implanon™** 30/904 **Norplant™** 30/915	2 years extended to 3 years
34515 Singapore (1 site) Start February 1994 End January 1997	Open label, single center absolute bioavailability	27-39 (32.3)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **Reference:** 150 µg ENG (i.v.)	10/253	2 years
34522 The Netherlands, Chile, Finland (3 sites) Start October 1994 End December 1997	Open label, nonrandomized, comparative (vs. IUD) bone mineral density	**Implanon™** 18-39 (30.8) **IUD** 22-39 (31.4)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **IUD** Non-medicated	**Implanon™** 46/1054.3 **IUD** 30/750.3	2 years
34523 Thailand (1 site) Start May 1997 End March 2001	Open label, nonrandomized, comparative (vs. IUD), lactation	18-40 (29.3)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **IUD**: Multiload copper 250	**Implanon™** 42/1,483 **IUD** 38/1,233.6	**Implanon™** 2.7 years **IUD** 2.49 years

Table 2 Overview of Clinical Trials (cont)

Study number (No. of Sites) Country Start Date End Date	Study design	Age range (mean age) Race (%)	Treatment and dose	Number of subjects/total months of exposure	Maximum duration of drug treatment
Supportive Clinical Pharmacology or Special Safety Studies (Cont)					
RM01 China (1 site) Start December 1989 End June 1995	Open label, noncomparative, pharmacokinetic, pharmacodynamic	26-35 (31.5)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG	16/837	2 years, extended to 4.5 years
RM04 China (4 sites) Start May 1991 End December 1995	Open label, randomized, comparative (vs. Norplant™) efficacy and safety	**Implanon™** Age range not available (29.4) **Norplant™** Age range not available (28.7)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **Norplant™** 6 subdermal implants with initial daily release rate of 85 µg levonorgestrel	**Implanon™** 100/4,456 **Norplant™** 100/4,293	2 years, extended to 4 years.
RM02 China Start January 1991 End December 1995	Open label, noncomparative, safety, efficacy	Age range not available (29.8)	**Implanon™**: Subdermal Implant with initial daily release rate of 67 µg ENG	200/8,669	2 years, extended to 4 years
34524 Mexico (2 sites) Start July 1999 End May 2002	Open label, noncomparative, nonrandomized	18-36 (26.1)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG	58/1223	2-3 years
34525 Russia (submitted later-ongoing (2 sites) Start December 2001 End September 2003	Open label, noncomparative, nonrandomized	<18 to > 40 years (Not available)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG	60/ Not available	1 year

Table 2 Overview of Clinical Trials (cont)

Study number (No. of Sites) Country Start Date End Date	Study design	Age range (mean age) Race (%)	Treatment and dose	Number of subjects/total months of exposure	Maximum duration of drug treatment
Supportive Clinical Pharmacology or Special Safety Studies (Cont)					
E-1729 Malaysia, Venezuela, Austria, Germany (12 sites) Start May 2001 End ongoing	Open label noncomparative multi-center efficacy and safety	<18 to 40 years (Not available)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG	211/Not available	3 years planned
Principal Disqualified Studies (2)					
34506 (1 sites) Country: Indonesia Start: November 1990 End: April 1996	Open label, noncomparative, multicenter, safety, efficacy	18-35 yr (28.3 yr)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG	200/8,589	2 years, extended to 4 years
34520 (9 sites) Country: Indonesia Start: November 1992 End: February 1997	Open label, comparative (vs. Norplant™), multicenter, safety, efficacy, acceptability	**Implanon™** 18-40 (29.0) **Norplant™:** 19-40 (29.5)	**Implanon™** Subdermal Implant with initial daily release rate of 67 µg ENG **Norplant™:** 6 subdermal implants wit initial daily release rate of 85 µg levonorgestrel	**Implanon™** 449/16,224 **Norplant™:** 450/17,459	2 years, extended to 3 years

Source: Original NDA 021529, ISE Table 1, P21 30Sep03

4.3 Postmarketing Experience

As of the NDA cutoff date of April 30, 2003, Implanon™ had been approved for marketing in 51 countries worldwide (Table 46) and registration is pending in 20 other countries (Table 47). In the June, 2003 – June 2004 Annual Report it was stated that in six of the countries with a previous pending registration, Implanon™ was subsequently registered and five new registrations are now pending. According to the Applicant's communication dated 9 Sep 04, Implanon™ has not been withdrawn from the market in any country nor has approval been denied for safety or efficacy reasons.

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5. CLINICAL REVIEW METHODS

5.1 How the Review was Conducted

The review was conducted utilizing the following:

- Detailed review of the four principal safety and efficacy studies (Studies 069001, 34505, 34507, and 34507 CDN): paper and electronic submission; less detailed review of the remaining 15 studies.
- Detailed review of all information submitted by the Applicant during the review
- Independent review of the literature
- Consultative meetings with FDA statistician, other medical reviewers, and reviewers from other disciplines regarding the data findings and clinical issues
- Interactions with Applicant for clarification and additional data

5.2 Overview of Materials Consulted in Review

Materials consulted in review included:

- Paper and electronic submissions for NDA 21-529: submission date of 30-Sept-2003
- Subsequent submissions:
  1. 19-Jan-2004 – Four month safety update
  2. 30-Mar-2004 – Investigator's Brochure on Implanon™, edition No. 4; clinical trial reports on studies 34523 and 34524.
  3. 11-May-2004 – Information request: documentation of conception dates in selected pregnancies.
  4. 20-May-2004 – New list of well-controlled studies; revised ISE and ISS.
  5. 27-May-2004 – Information request: dataset for subjects enrolled 2 to 3 years – studies 34505 and 34507.
  6. 28-May-Information request: reason for delay in submission of NDA; status of pending applications; approval issues in other countries.
  7. 30-Jun-2004 – Information request: postmarketing problems with insertion/removal of Implanon™; postmarketing assessment of pregnancy risk and adverse events.
  8. 20-July-2004 – Information request: postmarketing pregnancies information; Implanon™ polymer skin thickness information.
  9. 4-Aug-2004 – Information request: financial disclosure information; additional information regarding "Postmarketing Unintended Pregnancies"; additional safety information.
  10. 9-Sep-2004 – Additional marketing and registration information outside of the U.S.; clinical (SAE) information; labeling information; Health Care Provider (HCP) training program.
  11. 5-Oct-2004 – Updated information for the label

12. 11-Oct-2004- Information request: postmarket exposure, rates of selected adverse events.
13. 11A-Oct-2004- Information request: updated regulatory information (Mutual Recognition Facilitation Group), updated bleeding irregularities and weight changes information.
14. 12-Oct-2004- Information request: uterine bleeding irregularities
15. 14-Oct-2004- Information request: Revised Pearl Calculations
16. 15-Oct-2004- Information request: Dutch Inspectorate Integrated Inspection Report: Evaluation of Implanon non-compliance issues.

- Consultation reports from the other disciplines
- Journal reviews

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

5.3.1 Independent FDA Analysis of Safety and Efficacy Data and FDA Requests for Additional Data and Analysis

During the review cycle for NDA 21-529, the FDA Statistician Moh-Jee Ng, M.S., confirmed the accuracy of the Applicant's primary efficacy analyses (based on listings provided by the Applicant). Her conclusions are summarized in Section 2.3 and are provided in full in her separate statistical review. At the request of the medical officer, the Applicant provided additional information (source clinical records and sonographic) data to determine the number of pregnancies in the 4 principal studies and during the post marketing surveillance.

Several special safety data requests were submitted and reviewed including polymer skin thickness information, postmarketing unintended pregnancy information, postmarketing insertion/removal related events and a clinical trial/postmarketing list of all deaths and thromboembolic events. The Applicant's Health Care Provider training program regarding the technique for insertion /removal of Implanon™ and the evaluation of the effectiveness of this program was reviewed.

To aid in determining the integrity of the data, additional registration information was requested and reviewed.

5.3.2 Division of Scientific Investigation (DSI) Site Inspections

On January 30, 2004, an inspection assignment was issued for inspections of 3 U.S. sites and 2 non-U.S. sites. The non-U.S. sites and the protocols were:

Protocol 34520 (Dr. Dewata, Surabaya, Indonesia, Site RI-008, and Dr. Pramono, Semarang, Indonesia, Site RI-007)

Protocol 34506 (Dr. Affandi, Jakarta Pusat, Indonesia, Site RI-001)

These non-U.S. sites were selected because of large enrollment, data on three years of use of the study drug, and a remarkable lack of reporting of adverse events. Prior to DSI's initiation of inspections, in a letter dated March 23, 2004, Organon alerted DSI to significant GCP violations at the Indonesian sites. As a result, the Applicant withdrew these sites and their clinical data from further consideration.

Subsequently, the non-U.S. sites of Drs. Urbancsek and Croxatto were selected for inspection as they had provided the majority of the remaining data supporting three years use of Implanon™. The domestic sites of Drs. Chez, Poindexter, and Funk were also selected for inspection.

The conclusion in the overall assessment of findings was that the data submitted in support of this application by Drs. Funk, Chez, Poindexter, Croxatto, and Urbancsek appeared adequate in support of this submission. For Drs. Croxatto and Urbancsek this assessment is based upon preliminary reviews.

5.4 Were Trials Conducted in Accordance with Accepted Ethical Standards

The appropriate Institutional Review Boards (IRBs) reviewed the study protocols and amendments. Informed consent was obtained allegedly according to the ethical principles stated in the latest version of the Declaration of Helsinki (Republic of South Africa; 1996), and the applicable guidelines for Good Clinical Practice with one exception: On March 23, 2004 Organon notified the Division of significant Good Clinical Practice violations at the Jakarta, Indonesia study site of Dr. Biran Affandi and the Semarang site of Dr. Pramono. Several instances of misconduct were uncovered, involving five studies included in the NDA and data for 720 Indonesian subjects. Subsequently, the Dutch Medicines Evaluation Board (European Regulatory Agency) decided to initiate their own inspection program at European sites not already inspected by the FDA. The results of these inspections are as follows:

- Several inspections revealed observations that might have implications for the quality of the trial data (e.g. verifiability of data). At the sites inspected inaccuracies were observed, some classified as critical. It was concluded that there was an underreporting of the frequency of side effects in some trials. There were no indications of fraudulent actions.
- It was agreed that there are no reasons for doubts on efficacy and safety of the product provided it be inserted in the appropriate manner. This conclusion was based on the large postmarketing experience and extensive monitoring and reporting.
- Because of the above mentioned conclusions, it was recommended that Organon make several changes to the label, including changes in the occurrence of adverse events and pregnancy rates.

5.5 Evaluation of Financial Disclosure

Organon USA Inc. and NV Organon collected financial disclosure information from all investigators except four, listed in Table 4. The two principle reasons why information could not be obtained were:

1. Investigators/sub-investigators left the clinical site prior to solicitation of the required information. Attempts to contact theses individuals were unsuccessful.
2. Investigators/sub-investigators died prior to solicitation for the required information.

The Applicant notes that all trials listed (except Study 34523) were completed by December 1997, prior to implementation of Financial Disclosure requirements (February 2, 1999)

Table 4 Investigators without Financial Disclosure Information

Investigator	Study	No. of Subjects under Investigator
b(6)	069001-US	7
	069001-US	20
	34507-Europe (Germany-Leipzig)	8
	34507-Canada	52

Source: Response to Information Request, 04Aug04

Medical Officer's Comments

- **The Applicant informed the Division that Principal Investigator for study 34507-Canada is deceased. The 3 remaining investigators without financial disclosure information were responsible for only 1.3% of the total number of subjects in the studies.** b(6)
- **The financial disclosure information is adequate to support approval of this application.**

6. INTEGRATED REVIEW OF EFFICACY

6.1 Brief Statement of Efficacy Conclusions

The efficacy of Implanon™ (etonogestrel implant) has been demonstrated through four adequate and historically controlled clinical trials that entered approximately 1,117 subjects for either 2 or 3 years of treatment. Overall, data supporting the effectiveness of Implanon for the prevention of pregnancy was provided from the equivalent of approximately 22,695 treatment cycles in the 4 principal studies with 1,746 woman-years of treatment. (In this review, a cycle is defined as 28-days of continuous treatment). Of the 1,117 subjects, 330 subjects were treated in the U.S. (Study 069001) for 6,106 treatment cycles and 470 woman-years of treatment. Across the 4 principal studies, 4 pregnancies (2 in the U.S. study) were considered by the Medical Reviewer to have occurred either within 7 days of removal of Implanon (n=3) or may have occurred within this period (n=1) and were classified by the Medical Reviewer as on-treatment pregnancies. Based on use of Implanon for up to 2 years in women 35 yrs or less in age at entry, the overall efficacy was demonstrated by a cumulative Pearl Index of 0.27 (95% CI: 0.08 to 0.69) and a Life Table Analyses estimate of the pregnancy rate of 0.5 (95% CI: 0.01 to 0.9) for women less than 36 years of age. Of the 1117 subjects enrolled in the 4 principal studies (1099 evaluated), 195 subjects were treated for three full years in the extension trials. No pregnancies were reported for these subjects during Year 3 in the extension trials (Year 3 Pearle index of 0 [95% CI: 0.0 to 2.0] for subjects $\leq$ 35 years of age).

The cumulative Pear Index for 2 years of 0.27 is more than adequate to support an efficacy claim for two years of use. The number of treatment cycles during Year 3 was less than originally planned by the Applicant because of the disqualification of all data from Studies 34506 and 34520. However, the Year 3 Pearl Index of 0 (with a 95% upper bound of 2.0) is adequate to support approval for 3 years of use, with a postmarketing commitment by the Applicant to obtain additional supportive efficacy data for Year 3 of treatment.

6.2 General Approach to Review of the Efficacy of the Drug

The Applicant submitted data from four adequate and historically controlled clinical trials (designated the principal clinical trials in this review) to support the efficacy of Implanon™ for prevention of pregnancy for up to 3 years. These 4 clinical trials had similar inclusion and exclusion criteria. Data were reviewed in the following sequence, the US study (069001), the European studies (34507 and 34507-CDN and the Thailand study (034505). Note that the Canadian study has the same number as the European study; this study is similar to the European study but commenced approximately 2 years after the European studies. In the European studies, two centers (Chile and Hungary) extended the use of Implanon for 3 years of treatment; in the Thailand study some subjects were initially extended into 3 years of treatment, and then into 4-years of treatment. Efficacy data was not formally evaluated in the fourth year of treatment because of the small number of continuing subjects and because a claim for 4 years of continuous treatment with a single implant is not being sought. Nevertheless, there were no pregnancies out of 47 subjects in the fourth year of treatment.

6.3 Integrated Efficacy Findings

There were four trials (Studies 069001, 34505, 34507 and 34507-CDN) with the primary objective of assessing efficacy and safety. These studies are considered the principal studies that provided the basis for evaluating the efficacy of Implanon™ for the indication of prevention of pregnancy. Of these four studies, Studies 069001 and 34507-CDN provide evidence of efficacy during two years of use. At 3 of the centers in the other 2 clinical trials, longer-term efficacy data were obtained. For study 34507, the duration of treatment of subjects from two centers (those in Hungary and Chile) was extended to three years. Southeast Asian Study 34505 provided efficacy data for up to four years of use.

6.3.1 Efficacy Population

Subjects in the principal studies had to be healthy females who were sexually active and of childbearing potential with ages between 18 and 40 years. The subjects had to have normal menstrual cycles with a length of 24-35 days and an intra-individual variation of plus or minus 3 days and were not to be currently pregnant or breast-feeding. Body weight was to be between 80% and 130% of the ideal body weight. Subjects had to be willing to return to the clinic for the scheduled visits, to fill in the diary card with information on bleeding, and to give written informed consent.

6.3.1.1 Inclusion/Exclusion Criteria

Study 069001(U.S.)

Inclusion criteria

Eligibility for enrollment in the study included:

- Healthy, sexually active female volunteers in age groups between 18-40;
- Subjects who were at least 80% and at most 130% of their ideal body (Metropolitan Life Insurance Table);
- Subjects with normal menstrual cycles, with a mean length of 24-35 days and an intra-individual variation of ± 3 days;

Exclusion criteria

Subjects were excluded from the study if one or more of the following criteria were met:

- Women for whom progestin-only contraceptives were contraindicated;
- Women who were ≥ 35 years old and who smoked;
- Women who were pregnant or lactating, had given birth, or were post-abortion or miscarried less than one month prior to the start of the study medication;
- Women who use an intrauterine device (IUD) during the study;
- Women who had used an injectable hormonal method of contraception within a period of six months, other hormonal contraceptives within a period of one month, or those who had contraceptive implants removed within a period of two months prior to the start of the study medication;
- Women with past or present significant gynecological disorders;
- Women with a history of ectopic pregnancy;
- Women with a history of pelvic inflammatory disease/salpingitis or herpes gestationis;
- Women with a history of breast discharge in combination with elevated serum prolactin (other than lactation);
- Women with significant uncontrolled endocrine disorders;
- Women with past or present disturbance of liver functions such as cholestatic jaundice, jaundice of pregnancy, jaundice due to previous (oral) contraceptive use, Rotor syndrome or Dubin-Johnson syndrome;
- Women with current or history of hyperlipoproteinemia;
- Women who had hypertension (systolic BP >140 mmHg and/or diastolic BP>90 mmHg);
- Women who used the following drugs during the study: sex steroids, hydantoins, barbiturates, primidone, carbamazepine, rifampin, griseofulvin;
- Women with current or history of alcohol or drug abuse within 12 months prior to study entry;
- Women who received investigational drugs within three months prior to study entry;
- Women with a cervical Papanicolaou (Pap) smear of Class III, IV, or V at the screening phase;
- Women with clinically significant laboratory abnormalities at the screening phase; and

Women with a history of or current thromboembolic disorder were <u>not</u> excluded.

The following medications were not allowed during the primary study: sex steroids, hydantoins, barbiturates, primidone, carbamazepine, rifampin, and griseofulvin.

The use of any contraceptive drug or device other than the study medication was not permitted. *The use of condoms by the subject or her partner for the prophylaxis of sexually transmitted diseases was permitted.* Each subject received one implant that remained in-situ for the duration of the study (24 months).

Medical Officer's Comments

- **Inclusion/exclusion criteria are acceptable. The use of condoms could have easily been reported with daily diary cards to give a more accurate assessment as to whether condom use may have decreased the chance of an individual subject getting pregnant**

Study 34507 (Europe and Canada)

The inclusion criteria were similar to study 069001. The exclusion criteria were also similar with the following exception: women who smoked, who were over 35 years old or who had a history of/or current thromboembolic disease were *not* excluded.

Study 34505 Thailand

The inclusion criteria were the same as in the other 3 protocols except all subjects had to agree that the implant would be their *sole method* of contraception. In addition, there were no ideal body weight requirements as in the US clinical study.

The exclusion criteria were very *similar to the US trial except for the following*:

- Post-abortal women could be enrolled if they were within 2 weeks of an abortion (not 4),
- Women with a hemoglobin of < 10g could not be enrolled,
- Women with clinically significant laboratory abnormalities at screening were not excluded,
- Women with a history of thromboembolic disorder were not excluded,
- Use of an IUD was not specifically excluded (although IUD use was not likely given the subjects potential to afford another method); and
- A history of PID was not specifically excluded.

6.3.2 Dosage Schedule (Insertion/Removal)

For all studies, an implant was to be placed in the upper arm of each subject and was to remain in situ for the duration of the study. In women with normal cycles, insertion of the implant was to be performed on or between the first and the fifth day of the subject's menstrual flow. In post-partum subjects, the implant was to be inserted within 8 weeks after delivery. Implanon™ was to be inserted on the inside of the upper (non-dominant) arm, 6 to 8 cm above the elbow in the groove between the biceps and triceps. The implant was to be located by palpation. At the time of implant removal, the subject's arm was to be washed and antiseptic applied. A small amount of local anesthetic (such as 1% lidocaine) was to be applied under the implant. After making a 2 mm incision, the implant was to be gently pushed toward the incision until the tip was visible.

The implant was then to be grasped with forceps and removed. After removal, the incision was to be closed and bandaged.

6.3.3 Assessments

In general, the baseline assessments for the principal studies consisted of a medical history, gynecological history, recording of pre-existing medical conditions, vital signs, complete physical examination (including a breast examination), and gynecological examination (including pelvic examination and Pap smear). For U.S. Study 069001, a urine pregnancy test was required immediately prior to implant insertion and serum beta-hCG was to be obtained at screening and whenever pregnancy was suspected. The Thailand study also required a pregnancy test to be performed prior to implant insertion; however, this was optional in the European and Canadian studies. After the results of screen assessments were available and the subject was found eligible to enter the study, she was asked to return to the study-site on or between Days 1 and 5 of her most immediate menstrual flow to have Implanon™ inserted within 7 days from the onset of menses. After enrollment, each subject was given daily diary cards on which to record vaginal bleeding events. All subjects were to be scheduled for clinic visits at three-month intervals until the end of their participation in the clinical trial. During the study period, serum pregnancy tests were to be performed if there were signs of suspected pregnancy. At each visit, diary cards to record daily occurrences of vaginal bleeding were to be collected and new ones issued and subjects were to be questioned about the use of concomitant medications and the occurrences of any adverse events from the time of the last visit. In addition, the implant site was to be inspected.

Approximately 3 months after the subject discontinued or completed participation in the study, a post-treatment evaluation was scheduled. The subject was asked about her menses, use of contraceptive methods, and the occurrence of untoward events. A pregnancy occurring between the end of the study and the post-treatment visit was to be followed for pregnancy outcome. The post-treatment evaluation was made during a visit or through information obtained by telephone or letter.

Table 5 presents the assessment schedule during treatment for the principal studies. For comparison of assessments across studies, assessments up to 24 months are presented as follows: blood pressure and body weight (BP/BW) were assessed in all studies at 3, 6, 12, 18, and 24 months, Study 34505 also had BP/BW assessments at 9, 15, and 21 months; physical examinations were performed in all studies at 12 and 24 months, Study 34505 had examinations also at 6 months.

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Table 5 Schedule of Events

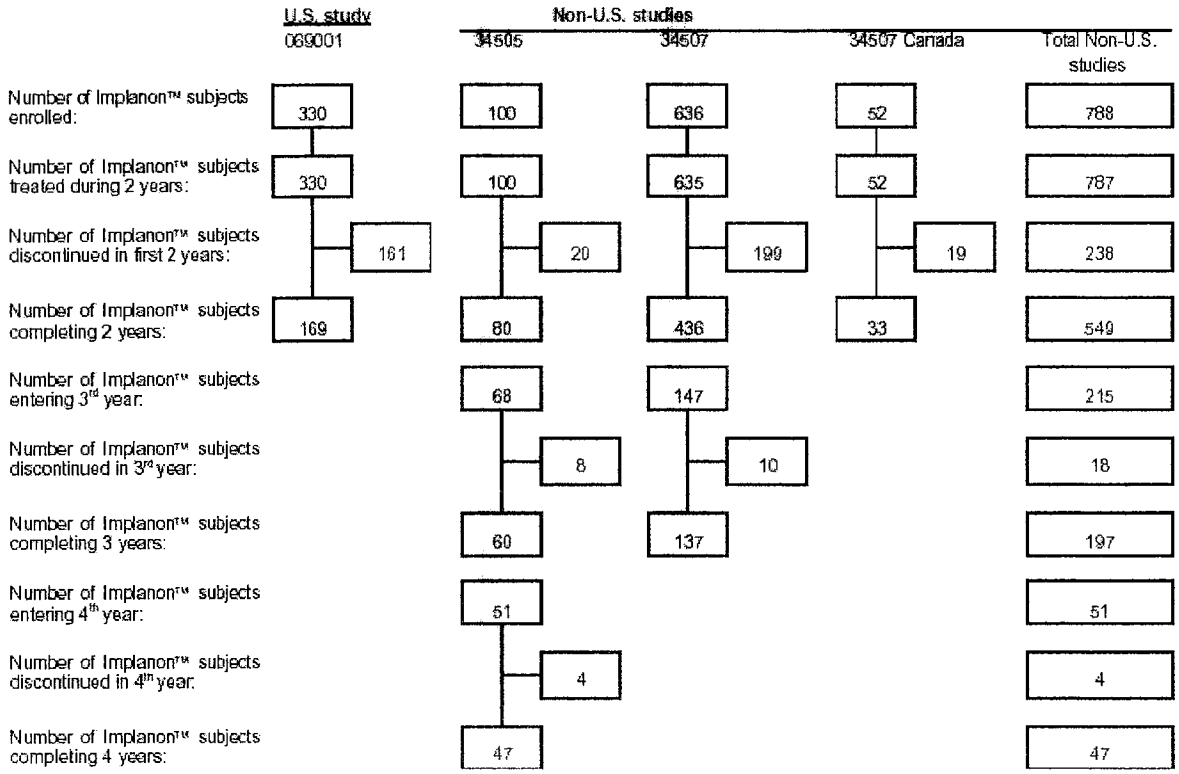
	First year						Second year						Third year				Fourth year		
Time in months	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**
Assessment no.	**2[a]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18[c]**
Study 34505																	
Status at implantation site	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure, body weight		X	X		X		X		X		X		X		X		X
Pelvic examination									X				X				X
Physical examination			X		X				X		X		X		X		X
Pap smear[b]																	X
Hemoglobin		X	X		X		X		X				X				X
ENG concentration																	X
Study 34507 and Study 34507CDN																	
Status at implantation site		X	X	X	X	X	X	X	X	X	X	X	X				
Blood pressure, body weight		X	X		X		X		X	X	X	X	X				
Pelvic examination									X				X[d]				
Physical examination					X				X				X[d]				
Pap smear[b]									X				X[d]				
ENG concentration									X				X[d]				
Gynecological history during study period (including dysmenorrhea)									X				X[d]				
Study 069001																	
Status at implantation site	X	X	X	X	X	X	X	X	X								
Blood pressure, body weight		X	X		X		X		X								
Pelvic and breast examination					X				X								
Physical examination					X				X								
Pap smear[b]					X				X								
Hematology and Chemistry	X		X		X		X		X								

a Screening (Assessment 1) is not included in this overview. During Assessment 2 the implant was to be inserted.
b A cervical (Papanicolaou, Pap) smear was to be scheduled at the end of trial.
c Implant removal assessment. Whenever the implant was removed all assessments as listed under Assessment 18 were to be performed.
d For women who continued into the third year, these investigations were optional.
Source: Original NDA 021529; 30Sep03; Page 9 (Study 34505CLI), page 14 (Study 34507CLI), page 9 [Study 34507CLI (CDN)], and page 15 (Study 069001CLI).

6.3.4 Disposition of Subjects

Figure 1 lists the disposition of subjects in the principal clinical studies, including the number of subjects who were enrolled in each study, number of subjects who received Implanon™, number of subjects who discontinued from each study, and the number of subjects who completed each study.

Figure 1 Disposition of Subjects – Principal Studies



Source: Revised NDA 021529, ISE, Fig 1, P55, 04May04

6.3.5 Demographics and Baseline Characteristics

In the U.S. Study 069001, subjects were 18 to 40 years of age, with most subjects between 21-30 years old and Caucasian. The mean body mass index was 23.6 kg/m^2.

The Implanon™-treated subjects in the non-U.S. studies ranged in age from 18 to 42 years with means of 26.3, 29.1, and 24.0, years for Studies 34505, 34507 and 34507 CDN, respectively. Body mass index (BMI) means, measured in kg/m^2, were 21.7, 22.7, and 22.8, for Studies 34505, 34507, and 34507 CDN, respectively (see Table 6)

Table 6 Demographics – Principal Efficacy Studies

Parameter	Study 069001 (N = 330) n	(%)	Study 34505 N = 100 n	(%)	Study 34507 N = 635 n	(%)	Study 34507 CDN N = 52 n	(%)
Age (years)								
18-20	43	(13.0)	12	(12.0)	39	(6.1)	14	(26.9)
21-25	129	(39.1)	36	(36.0)	147	(23.1)	21	(40.4)
26-30	85	(25.7)	35	(35.0)	192	(30.2)	12	(23.1)
31-35	55	(16.6)	12	(12.0)	167	(26.3)	4	(7.7)
36-40	18	(5.4)	5	(5.0)	86	(13.5)	1	(1.9)
>40	0		0		4	(0.6)	0	
Mean Age (SD)	26.1 (5.1)		26.3 (4.8)		29.1 (5.6)		24.0 (4.1)	
Race								
Caucasian	234	(70.9)						
Black	40	(12.1)						
Asian	7	(2.1)						
Other	49	(14.8)						
Body Mass Index (BMI) (kg/m2)								
≤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 BMI (SD)	23.6 (3.6)		21.7 (2.8)		22.7 (2.8)		22.8 (3.3)	

N = Number of subjects in All-Subjects-Treated Group.
n = Number of subjects with a particular characteristic.
Source: Table 8, P 61, revised ISS; 04 May 04.

Medical Officer's Comments

- **Overall, the population in Europe was slightly older and the population in Canada was slightly younger; however, there were more subjects over 35 years in Thailand.**
- **The variable race was only obtained in the U.S. study; Caucasians comprised over 70% of the population.**
- **The mean BMI was highest in the U.S. (23.6) and lowest in Thailand (21.7).**

6.3.6 Extent of Exposure

The treatment duration (in days) was defined as the time between the date of implant insertion and the date of removal. For those subjects lost to follow-up, the date of their last actual assessment was used. The extent of exposure to the study drug was expressed in both in terms of woman-years and total number of 28-day cycles. The duration of treatment and extent of exposure to Implanon™ for the U.S. and non-U.S. principal clinical studies is listed in Table 7.

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Table 7 Duration of Treatment and Extent of Exposure in the Principal Studies

Study	Duration of treatment (Number of subjects)			Extent of exposure	
	0-2 Yrs	2-3 Yrs	3-4 Yrs	Cycles (28-days)	Woman-yrs
U.S. study					
069001	327[a]	-	-	6,198	475
Non-U.S. studies					
34505	100	68		3,863	296
34507	635	147	-	15,653	1,200
34507 CDN	52	-	-	1,085	83
Total: Non-U.S. studies -	787	215	51	20,601	1,579
Total (U.S. + Non-U.S.)	1114	215	51	26,799	2,054

[a] Three subjects, who had no post-baseline assessments, were not included in the calculation of extent of exposure
Source: Table 14 (Integrated summary of efficacy), amendment submitted on May 4, 2004, page 65/103

6.3.6.1 U.S. Study

In U.S. Study 069001, 330 subjects were exposed to Implanon™ of which 327 were exposed for 6,198 cycles (three subjects had no post-baseline assessments and were not included in the calculation of extent of exposure), equivalent to 475 woman-years of exposure.

6.3.6.2 Non- U.S. Studies

In non-U.S. Study 34505, 100 subjects were exposed to the study medication for 3,863 cycles, equivalent to 296 woman-years of exposure during four years of use. In Study 34507, 635 subjects were exposed to Implanon™ for 15,653 cycles, equivalent to 1,200 woman-years of exposure during three years of use. In Study 34507-CDN, 52 subjects were exposed to Implanon™ for 1,085 cycles, equivalent to 83 woman-years of exposure during two years of use.

6.3.6.3 Summary of Drug Exposure

The data presented show that a total of 330 subjects in the principal U.S. clinical study and 787 subjects in the principal non-U.S. clinical studies had been treated with Implanon™ for up to four years. Total exposure in the U.S. and non-U.S. studies was 475 and 1,579 woman-years (equivalent to 6,198 and 20,600 28-day cycles), respectively.

6.4 Methods for the Assessment and Analysis of Contraceptive Effectiveness

6.4.1 Methods of Assessment

Overview. The assessment of efficacy was based on the occurrence of pregnancies during the treatment period. Pregnancies were categorized as those that occurred pre-treatment (prior to implant insertion but not initially identified), during-treatment (with implant in place), and post-treatment (after removal of implant). During the treatment period, a serum pregnancy test was to be performed if the diary cards showed a sign of suspected pregnancy, such as no vaginal bleeding in the previous 45 days, or if only spotting occurred during this period. If pregnancy was confirmed, the implant was to be removed and the estimated date of conception was to be verified by ultrasound. The subject was to be followed-up for pregnancy outcome and pediatric evaluation of the newborn.

U.S. study. In U.S. Study 069001, a protocol amendment required a urine pregnancy test to be administered immediately prior to the insertion of the implant. During the study period, a serum pregnancy test was to be performed if the diary cards showed a sign of suspected pregnancy, such as no vaginal bleeding for at least 3 days in the previous 45 days or if only spotting occurred during this period. If pregnancy was confirmed, the implant was to be removed and the date of conception was to be sought from the subject. The estimated date of conception was to be verified by ultrasound.

Non-U.S. studies. Non-U.S. Studies 34507 and 34507-CDN required a pregnancy test to be performed prior to implant insertion if there were signs of suspected pregnancy, such as no vaginal bleeding for at least 3 days in the previous 45 days or only spotting occurred prior to implant insertion. Similar to the U.S. study, in non-U.S. Study 34505, a pregnancy test was to be performed prior to implant insertion. During the study period, a serum pregnancy test was to be performed if there were signs of suspected pregnancy, such as no bleeding for at least three days during the last 45 days (all non-U.S. studies). The implant was to be removed if pregnancy was confirmed, and follow-up was expected to occur until delivery. For Study 34507, a serum β-hCG test was to be performed after removal of the implant.

6.4.2 Statistical Analyses of Effectiveness

Contraception effectiveness was based on the occurrence of pregnancies in the All-Subjects-Treated Group (ASTG). In the statistical analysis, ASTG includes all subjects who were implanted with Implanon™ for whom post implantation data were obtained, but excludes 18 subjects at two centers in study 34507 where there was non-compliance with Good Clinical Practice (GCP) standards. Contraceptive efficacy was determined by Pearl Indices and Life-Table Pregnancy Rate analyses. The endpoints of interest for both analyses were the cumulative number of pregnancies that occurred from insertion of the implant through the end of Year 2, the number of pregnancies that occurred during Year 3, and the cumulative number of pregnancies that occurred from insertion of the implant through the end of Year 3. .

The Pearl Index (number of pregnancies per 100 women-years of use) was calculated as the number of pregnancies times 1300 divided by the total number of 28-day exposure cycles during use of Implanon. The Life-Table Pregnancy Rate calculation used SAS procedure Lifetest to estimate the probability of pregnancies in a fixed time period for women during use of Implanon.

6.5 Effectiveness

6.5.1 Applicant's Assessment of Contraceptive Effectiveness

6.5.1.1 Study 069001 (U.S. Study)

Three hundred and thirty (330) subjects enrolled in this study for a period of up to two years (169 subjects completed 2 years). In 6,186 cycles of exposure to Implanon™, there were no pregnancies while Implanon was implanted. There were no pre-treatment pregnancies and 11 pregnancies were reported after removal of the implant.

6.5.1.2 Non U.S. Principal Studies

Seven hundred and eighty seven (787) subjects enrolled in these studies for up to two years (549 subjects completed); 215 of these subjects in Thailand, Chile and Hungary enrolled for up to three years (197 completed); 51 of these subjects in Thailand enrolled for four years

(47 completed). In 20,600 cycles of exposure to Implanon™ in the non-U.S. principal studies, there were no reported pregnancies while Implanon was implanted . There were 4 pre-treatment pregnancies and 32 pregnancies after removal of the implant.

6.5.1.3 Applicant's Summary of Contraceptive Effectiveness

In 26,787 total cycles of exposure to Implanon™ in the U.S and non-U.S. principal clinical studies, the Pearl Index was 0 [95% CI: (0 to 0.18)], see Table 8).

In the U.S. and non-U.S. principal clinical studies, subjects became pregnant 1 to 26 weeks after removal of the implant. Those pregnancies determined to have occurred soon after implant removal in both the U.S. and non-U.S. studies indicate that there was a rapid return to fertility.

Table 8 Summary of Applicant's Cumulative Efficacy Analysis (Principal Studies - Yrs 1-4)

Study	Total No. of women	Total exposure (28-day cycle equivalents	Total exposure (women-yrs)	No. of Pretreatment pregnancy	No. of On-Treatment pregnancy	No. of post-treatment pregnancy	Pearl Index (95% CI) *
U.S. Study							
069001	330	6,186	475	0	0	11	0 (0, 0.77)
Non-U.S. Studies							
34505	100	3,863	296	0	0	6	0 (0, 0.12)
34507	635	15,653	1,200	4	0	24	0 (0, 0.31)
34507 CDN	52	1,085	83	0	0	2	0 (0, 4.27)
Total	*787*	*20,601*	*1,579*	*4*	*0*	*32*	*0 (0, 0.23)*
U.S. and Non-U.S. Studies Combined							
Total	***1,117***	***26,787***	***2,054***	***4***	***0***	***43***	***0 (0, 0.18)***

*: two-sided 95% confidence intervals computed by FDA statistician.
Source: Revised NDA 021529, ISE, Tables 14, 16, 17, P 64, 69, &70, 04May04

6.5.2 FDA's (Medical Reviewer's) Assessment of Contraceptive Efficacy

The FDA Medical Reviewer requested that the calculation of the Pearl Index and Life-Table Pregnancy Rate include all pregnancies for which conception occurred while Implanon was implanted as well as post-treatment pregnancies (1) determined to be conceived within 7 days after discontinuation of the study drug and (2) for which a conception date within 7 days of implant removal could not be excluded. After reviewing clinical and ultrasound data, the Medical Reviewer identified four post treatment pregnancies that met these criteria. (Table 9).

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Table 9 Pregnancies with Estimated Conception Dates within 7 Days of Implanon Removal or for which a Conception Date within This Interval Could not be Excluded.

Study	Subject Number	Age	BMI	Weight (kg)	Treatment Duration Days (Cycle)	Estimated day of conception (post Implanon™ removal)
069001	05014	27	24	69.5	172 (7)	7
	10017	19	25	58.1	100 (4)	6
34507	00550	21	29	78.0	198 (8)	0-14
3450-CDN	00864	23	20	54.0	232 (9)	7

Source: Calculated by Medical Reviewer, refer to subject no., Table17, P77, revised ISE

6.5.2.1 Cumulative Efficacy Through Two Years of Use (FDA Assessment)

Study 069001 (U.S. Study)

No conceptions in 330 subjects were identified while Implanon was inserted. Two pregnancies estimated to have occurred within 7 days of implant removal (Subject Nos. 05014 and 10017, see Table 9) were included in the analyses of efficacy. The Pearl Index was calculated to 0.42 (95%CI: [0.05, 1.5]) for all subjects and 0.68 (95%CI: [0.06, 1.61]) for subjects ≤ 35 years of age at entry (see Table 10). The life table estimate of the pregnancy rate for subjects ≤ 35 years of age was 0.7% (95% CI: [-0.3%, 2%]).

Studies 34507, 34507-CDN and 34505 (non-U.S. Studies)

Eighteen (18) subjects were removed from analysis of the non-U.S. studies (2 sites – GCP violations). Although 787 subjects were enrolled, only 769 subjects were analyzed.

No conceptions in these 769 subjects were identified while Implanon was inserted. Two pregnancies estimated to have occurred within 0-14 days of implant removal (Subject Nos. 00550 and 00864, see Table 9) were included in the analyses of efficacy. The Pearl Index was calculated to 0.16 (95% CI: [0.02, 0.57]) for all subjects and 0.19 (95% CI: [0.02, 0.68]) for subjects ≤ 35 years of age at entry (see Table 10). The life table estimate of the pregnancy rate for subjects ≤ 35 years of age was 0.4% (95% CI: [-0.1%, 0.8%])

Summary of Cumulative Efficacy Through Two Years of Use (All Principal Studies).

No conceptions in 1099 subjects were identified while Implanon was inserted. Four pregnancies estimated to have occurred within 0-14 days of implant removal (Subject Nos. 05014, 10017, 00550, and 00864, see Table 9) were included in the analyses of efficacy. The Pearl Index was calculated to 0.23 (95% CI: [0.06, 0.6]) for all subjects and 0.27 (95% CI: [0.08, 0.69]) for subjects ≤ 35 years of age at entry (see Table 10). The life table estimate of the pregnancy rate for subjects ≤ 35 years of age was 0.5% (95%CI: [0.01%, 0.9%]).

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Table 10 Efficacy Analyses Through 2 Years of Exposure (Study Days 1 – 730)

Study Age range	# of subjects	Total cycle of exposures (Women-years)	# of Pregnancy	Pearl Index (95% CI)	Life-Table Pregnancy Rate % (95% CI)
U.S. Study					
069001					
Total	330	6105.9 (469.7)	2	0.42 (0.05, 1.50)	0.7% (0%, 2%)
≤ 35 year old	307	5698.4 (438.4)	2	0.68 (0.06, 1.61)	0.7% (0%, 2%)
> 35 year old	23	407.3 (31.3)	0	0.00 (0, 10.80)	-
non-U.S. Studies					
34505					
Total	100	2,358.8 (181.5)	0	0 (0, 2.0)	-
≤ 35 year old	92	2,158.4 (166)	0	0 (0, 2.18)	
> 35 year old	8	200.4 (15.4)	0	0 (0, 19.2)	
34507					
Total*	617	13,196.8 (1012.2)	1	0.01 (0, 0.5)	0.2% (0%, 0.5%)
≤ 35 year old	497	10,495.8 (807.4)	1	0.12 (0.006, 0.7)	0.2% (0%, 0.7%)
> 35 year old	120	2,700.9 (207.8)	0	0.00 (0, 1.75)	-
34507 CDN					
Total	52	1,032.6 (83.5)	1	1.26 (0.03, 6.72)	2% (0%, 7%)
≤ 35 year old	51	1,006.6 (77.4)	1	1.29 (0.03, 6.88)	2% (0%, 7%)
> 35 year old	1	26.1 (2.0)	0	0.00 (0, 48.6)	-
non-U.S. studies combined					
Total	769	16,587.8 (1276.0)	2	0.16 (0.02, 0.57)	0.3% (0%, 0.7%)
≤ 35 year old	640	13,660.9 (1050.8)	2	0.19 (0.02, 0.68)	0.4% (0%, 0.8%)
> 35 year old	129	2,927.4 (225.2)	0	0.00 (0, 1.62)	-
All Studies combined					
Total	1099	22,694.7 (1745.7)	4	0.23 (0.06, 0.6)	0.4% (0.01%, 0.8%)
≤ 35 year old	947	19,360.0 (1489.2)	4	0.27 (0.08, 0.69)	0.5% (0.01%, 0.9%)
> 35 year old	152	3,334.6 (256.5)	0	0.00 (0, 1.42)	

* 2 centers (B_004 and F_041) excluded from study 34507: 18 subjects, which provided 27.8 woman-years of exposure (362.2 cycles) had been removed from total of exposures non-US studies: 1 in cycle 8, 1 in cycle 9 and 1 in cycle 40

- no assessment of life-table pregnancy rate due to 0 pregnancy

Source: FDA Statistical Report, Table 5

Medical Officer's Comments

- **There was a rapid return to fertility after removal of Implanon for subjects who desired to become pregnant**
- **The cumulative Pearl index through 2 years of use in subjects ≤ 35 years of age at entry of 0.27 [95% CI: (0.08, 0.69)] is well within the acceptable pregnancy rate considered by the Division for marketing approval of other hormonal contraceptive products.**
- **Based on this Pearl Index, it is the opinion of this reviewer that a single Implanon™ implant is highly effective for prevention of pregnancy for least 2 years of use.**

6.5.2.2 Effectiveness during Year Three of Use (FDA Assessment)

As stated earlier, two centers in Study 34507 (Chile and Hungary) extended the use of Implanon™ into a third treatment year and one center in Study 34505 (Thailand) allowed subjects to continue treatment into a third and fourth year.

Implanon™ exposure between the second and third year of treatment is summarized in Table 11. Also listed in the Table are the Pearl Index values for subjects during Year 3 of use. These data consider all subjects with treatment exposure from 731 up to 1095 days. Among these subjects were some subjects whose treatment extended slightly beyond 2 years (i.e. Day 731) but who were not formally considered to be enrolled in a third year of treatment. There were no pregnancies in Year 3 for any subjects enrolled in studies 34505 and 34507. For these studies combined, there were 218.8 woman-years of exposure equivalent to 2,844.4 cycles of exposure during Year 3. The Pearl Index for these subjects was 0 [95% CI: (0, 1.7)]. For subjects ≤ 35 years of age at entry the Pearl Index was 0 [95% CI: (0, 2.0)].

Table 11 Exposure to Implanon and Pearl Index Values Based on Treatment Year 3 (Study Days 731-1095; All Subjects with Use of Implanon after Study Day 730)

Study	# of women	Total cycle of exposures (Women-years)	# of Pregnancies	Pearl Index (95% CI)
Non-U.S. Studies				
34505				
Total *	77	825.9 (63.5)	0	0 (0, 5.7)
≤35 year old	70	734.8 (56.5)	0	0 (0, 6.4)
> 35 year old	7	91.1 (7.0)	0	0 (0, 40.9)
34507				
Total**	349	2,018.4 (155.3)	0	0 (0, 2.4)
≤ 35 year old	270	1,655.6 (127.4)	0	0 (0, 2.9)
> 35 year old	79	362.8 (27.9)	0	0 (0, 12.9)
Non-U.S. Studies Combined				
Total *	426	2,844.4 (218.8)	0	0 (0, 1.7)
≤ 35 year old	340	2,390.5 (183.9)	0	0 (0, 2.0)
> 35 year old	86	453.9 (34.9)	0	0 (0, 10.3)

* Includes some subjects whose treatment extended slightly beyond 2 years (day 731) but who did not formally enter into a third year of treatment.
**: 2 centers (B_004 and F_041) excluded from study 34507
Source: FDA Statistical Report

Two hundred and fifteen (215) subjects formally entered into the third year of treatment and according to the FDA statistician, 195 subjects completed three years of use. In the European trial, 147 subjects entered into the third year and 136 completed the third year of treatment (92.5% completers). In the Thailand trial, 68 subjects entered into the third year and 59 completed 3 years of treatment (86.7% completers). Therefore, 90.6% of all subjects who entered into the third year of treatment completed 3 years of treatment.

There were no pregnancies in the 195 subjects completing the third year (Table 12). For the combined non-U.S. studies, there were 195 women with 2535 cycles of exposure. The Pearl Index for all subjects was 0 [95% CI: (0, 1.87)]. The Pearl Index for all subjects ≤ 35 years of age at entry was 0 [95% CI: (0, 2.23)].

Table 12 Exposure and Pearl Index Values Based on Treatment Year 3 (Study Days 731-1095) (Subjects Who Completed Year 3)

Age Group	# of women	Total cycle of exposures	# of Pregnancies	Pearl index	Upper bound of the 95% CI *
All subjects	195	2535	0	0	1.87
≤ 35 year old	164	2132	0	0	2.23
> 35 year old	31	403	0	0	11.23

From Non-US Studies 34505 and 34507 Combined
* Confidence intervals are 2-sided
Source: FDA Statistical Report, addendum to statistical review.

Medical Officer's Comments

- **Comparison of accrued cycles from a similar implantable product that received an approval in the past 3 years is pertinent. This product was studied in a similar study period from 1990 to 1998 and was studied in the US and multiple international sites. At the time of completed review, 722 subjects completed 3 full years of treatment. The annual Pearl indices calculated by the FDA statistician ranged from 0.09 to 0.12 over 3 years of treatment and increased to 0.57 in the fifth year of treatment.**
- **The cumulative Pearl Index for Implanon™ over 2 years of use was 0.23 and is similar to the compared product but has less studied cycles. The number of subjects/cycles (195/2535) based on treatment Year 3 was less than for previously approved implantable products. However, when the ≤35 year old group (the most fertile group) was analyzed in the Implanon studies, the Pearl Index was 0, and the upper limit of the 95% confidence interval for the Pearl Index was 2.23, which is acceptable to support approval for a third year of use for a single implant.**
- **However, it is recommended that the Applicant conduct, or supply confirmatory treatment data in a Phase IV commitment that would provide additional support for the 3-year treatment regimen.**

6.5.2.3 Summary of Effectiveness Through Four years of Use

There were no pregnancies in 47 subjects completing the fourth year. There were too few subjects entering a fourth year of treatment to obtain meaningful 4 year efficacy data, and Organon is not seeking an indication for four years of treatment.

6.5.3 Postmarketing Contraceptive Failure Data

The Applicant provided the following information about postmarketing reports of pregnancy in the original NDA submission. Table 13 lists the groups, which reflect the reasons for the occurrence of a pregnancy in women using Implanon

Table 13 Pregnancy Analysis Groups which Reflect the Reasons for the Occurrence of a Pregnancy in Women Using Implanon™

Groups	Subgroups
1. Presence of pregnancy not confirmed	
	• Presence of pregnancy not confirmed
2. No active implant present	
	• Implanon not in situ • Blue placebo training rod or other non-active parts inserted
3. Conception took place outside period of Implanon use	
	• Already pregnant before insertion of Implanon* • Pregnant after removal of Implanon*
4. Contraceptive method failure	
	• Contraceptive method failure

Groups	Subgroups
5. Reason for pregnancy cannot be determined with complete certainty	
	• Presumed contraceptive method failure • Reporter states that woman was already pregnant, but no confirmation with data on gestational age • Conception around date of insertion* • Conception around date of removal* • Untimely insertion • Doubt about the presence of Implanon • Insufficient data to determine if insertion or removal of Implanon was before or after date of conception • Presence of Implanon has not been investigated

* See Figure 1.
Note: in cases where more than one reason is applicable, the most important reason according to NV Organon is used for the final classification.

Source: Table 1, p3, Four month safety update, 19Jan04

Overall 621 pregnancies were reported to Organon's Drug Safety Surveillance Department (DSSD) from market introduction in August 1998 through 1 September 2003. From these 621 reports, 594 reports were medically confirmed (including 24 ectopic pregnancies). .. Market use, based on implants sold, was estimated to be Implanon™ implants during this same period. An overview of reported postmarketing pregnancies provided by the Applicant that provides additional information about the possible relationship of the pregnancies to the use of Implanon (likelihood that the pregnancy represented a true contraceptive failure) is provided in Table 14.

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Table 14 Pregnancy Rates for Implanon™ Based on Post-Marketing Data

	Pregnancy [redacted] 100 sold implants*	Number of cases*
Overall	0.046 (0.048)	
Excluding Group 2*	0.030 (0.032)	
Excluding Group 2* and 3**	0.027 (0.029)	
Group 4***	0.0042 (0.0045)	

b(4)

* Number between brackets also include the medically unconfirmed reports
* Group 2: No active implant present
** Group 3: Conception took place outside of Implanon use
*** Group 4: Contraceptive method failure

Source: Table9, p14, Four month safety update, 19Jan04

The Applicant presented the following additional information about the reported and medically confirmed postmarketing pregnancies:

- in cases no active implant was present
- in cases conception took place outside the period of Implanon™ use
- in cases the reason for the occurrence of a pregnancy could not be determined with complete certainty
- in cases the occurrence of a pregnancy could not be confirmed
- in cases no explanation other than a true contraceptive method failure of Implanon™ could be found

b(4)

These latter cases were considered to be "contraceptive failures" by the Applicant.

A pregnancy rate of 0.046 pregnancies per 100 sold implants was calculated if all of the medically confirmed pregnancies were considered to represent a contraceptive failure due to any cause. The rate for contraceptive method failures (based on the Applicant's highly restrictive definition of a method failure) was estimated at 0.0042 pregnancies per 100 sold implants.

Medical Officer's Comments

- **Problems with insertion of Implanon™ were the major factor that contributed to unintended pregnancies (see Section 7.12.1).**
- **The Applicant's classifying only medically confirmed (total) reported pregnancies as contraceptive failures cannot be supported. All reported pregnancies (whether due to implantation error by the healthcare provider or true device failure) should be considered as a pregnancy in an Implanon user.**

b(4)

- **If all reported pregnancies are considered and all sold devices are assumed to have been implanted (an over estimate of actual use), the pregnancy rate is 0.046 pregnancies per 100 sold implants.**
- **If it is assumed that (1) all sold implants were inserted, (2) the average implant was in place for one year, and (3) only 1 in 50 pregnancies were reported to the Applicant, the estimated Pearl Index would be 2.4 pregnancies per 100 woman years of use. This**

"extreme case" value would be acceptable based on the estimated "actual or typical use" failure rate of about 5% for combination oral contraceptive users.

- **In 26 medically confirmed pregnancy cases a suspected drug interaction was reported. In 23 of these 26 cases an interaction may have occurred between Implanon™ and anti-epileptic drugs. In 2 of these 26 cases an interaction may have occurred between Implanon™ and St. John's wort. In one case, rifampicin was used. In 18 of the 26 cases the interaction may have led to a contraceptive method failure of Implanon™. The drugs that interact with Implanon™ to decrease its' effectiveness must be clearly delineated in the label.**

6.5.3.1 Ectopic Pregnancies

In total, 24 medically confirmed ectopic pregnancies were reported since market introduction of Implanon™. Three ectopic pregnancies occurred in Group 2. In these cases, the etonogestrel level was below the LOQ, thus implying that no active implant had been inserted. In Group 3 one ectopic pregnancy occurred, in which the woman became pregnant after the removal of Implanon™. In Group 4, 9 ectopic pregnancies occurred for which no reason other than failure of contraceptive action of Implanon™ could be identified based on the information supplied to NV Organon. In 11 of the 289 reports in Group 5 an ectopic pregnancy was reported in association with Implanon™ use. Concerning these 11 reports, the Applicant noted that:

- In 4 cases no information was provided to determine the estimated date of conception accurately, thus it is not clear whether the patient had conceived prior to or just after Implanon™ insertion.
- In 2 cases the presence of Implanon™ was not clear.
- In 4 cases the estimated date of conception was around the date of insertion of Implanon™.
- In 1 case the reporter stated that the woman was already pregnant before insertion of Implanon™.

<u>Medical Officer's Comments</u>

- **Assuming that all 24 ectopic pregnancies were associated with the use of Implanon, 24 medically confirmed pregnancies (or 4%) were ectopic. This is about 2-fold higher than the generally reported rate for ectopic pregnancies in women not using contraception (2 ectopic pregnancies per 100 pregnancies). Although the *proportion* of reported pregnancies that were ectopic pregnancies was higher in the Implanon users than the *proportion* in a population using no contraception or combination oral contraceptives, it was similar to, or lower than, the proportion seen in women using other progestin-only contraceptives. Moreover, the *absolute number of ectopic pregnancies* was *less* than would be expected in a population of similar women at risk for pregnancy who used no contraception.** b(4)
- **Clinicians/women are more likely to report ectopic pregnancies versus normal pregnancies, thus explaining, in part, the relatively high proportion of pregnancies reported to be ectopic.**
- **The label should alert physicians about the possibility of ectopic pregnancy.**

6.5.3.2 Pregnancies by Year of Use

On June 8, 2004, the Applicant was asked to submit an updated summary of reported post marketing pregnancies and to summarize the data based on the estimated date of conception relative to months after insertion of the implant. The following information was submitted:

From market introduction (28 August 1998) up to 11 June 2004 NV Organon received a total of 830 medically confirmed and medically unconfirmed spontaneous pregnancy reports. These 830 pregnancy reports can be subdivided into 3 groups:

- Pregnancy not confirmed: **9 cases**.
- Conception did not take place while Implanon™ was in situ: **336 cases**.
- Conception took place while Implanon™ was in situ, or conception *possibly* took place while Implanon™ was in situ: **485 cases.**

These cases were subdivided into 5 categories based on the estimated date of conception relative to the months after insertion of Implanon™ (see Table 15).

Table 15 Number of Pregnancies Based on Time of Conception post Insertion of Implanon

Time of Conception (months post insertion)	Number (%) of Reported Pregnancies N=485	
0-12	121	25%
12-24	50	10%
24-36	19	4%
>36	0	0%
Unable to determine	295	61%

Source: Information Request Response, 30 June 04

Medical Officer's Comment

- **The greatest number of pregnancies occurred in the first year of use, which may be related to problems that occurred with insertion. There was no observed increase in the rate of pregnancies in years 2 or 3. Theoretically, a drop in the etonogestrel level over time could lead to an increase rate of pregnancy by year three: this was not observed, although under-reporting of events during the postmarketing surveillance must be considered. The total postmarketing pregnancy rate continued to be low. This data provides support to the clinical trial data to approve Implanon™ for three years.**

6.6 Medical Reviewer's Overall Summary of Effectiveness of Implanon™

The efficacy of Implanon™ (etonogestrel implant) has been demonstrated through four adequate and historically controlled clinical trials that entered approximately 1,117 subjects for either 2 or 3 years of treatment.

Through Two Years of Use:
Overall, data supporting the effectiveness of Implanon for the prevention of pregnancy was

provided from the equivalent of a total of approximately 22,695 treatment cycles in the 4 principal studies with a total of 1,746 woman-years of treatment. In this review a cycle is defined as 28-days of continuous treatment. Of the 1,117 subjects, 330 subjects were treated in the U.S. (Study 069001) for 6,106 treatment cycles and 470 woman-years of treatment. Conceptions for four pregnancies were estimated by the FDA medical reviewer to have occurred (n=3) or may have occurred (n=1) within 7 days of implant removal. Based on these four pregnancies, the cumulative Pearl index was calculated to be 0.23 (95% CI 0.06, 0.6) through two years of treatment. For subjects ≤ 35 years of age, the cumulative Pearl index was calculated to be 0.27 (95% CI 0.08, 0.69) through two years of treatment. This value is well within an acceptable pregnancy rate reported with other methods of hormonal contraception.

Third Year of Use:
A total of 215 subjects, from two centers in study 34507 (Chile and Hungary) and one center in Study 34505 (Thailand), entered into the third year of treatment and 195 subjects completed three years of use (90.6% of subjects). There were no reported pregnancies in Year 3 for these studies. For these studies combined, there were 218.8 woman-years of exposure equivalent to 2,844.4 cycles of exposure. The Pearl Index for these subjects was 0 [95% CI: (0, 1.7)]. Among subjects ≤ 35 years of age, there were 183.9 woman-years of exposure equivalent to 2,390.5 cycles of exposure. The Pearl Index for these subjects was 0 [95% CI: (0, 2.0)]. Although the studies of Implanon™ included less treatment cycles of use compared to a similar long-term product, the trend is positive for subjects to continue with 3 years of treatment. In addition, there were no pregnancies in the limited number (47) of subjects who continued into the fourth year.

No pregnancies were reported to have occurred in any of the supportive clinical pharmacology, special safety, or additional studies. There was a rapid return of fertility after removal of the implant for subjects who desired to become pregnant.

Limitations of the dating pregnancies in the clinical trial program include inconsistent pregnancy testing at the time of implant insertion and removal and inconsistency in performing early ultrasounds for all pregnancies occurring near treatment.

Post Marketing Experience:
During the postmarketing phase of product use, the highest number of reported pregnancies occurred during the first treatment year, which may have been due to insertion related problems. If it is assumed that (1) all sold implants were inserted, (2) the average implant was in place for one year, (3) only 1 in 50 pregnancies were reported to the Applicant, and (4) all reported pregnancies occurred while the implant was supposedly in situ, the estimated Pearl Index would be 2.4 pregnancies per 100 woman years of use. This "extreme case" value would be acceptable based on the estimated "actual or typical use" failure rate of about 5% for combination oral contraceptive users. In 26 medically confirmed pregnancy cases a suspected drug interaction was reported.

The rate of reported ectopic pregnancy in post marketing data was similar to that seen with other progestin-only contraceptives.

Conclusion:
In conclusion, Implanon™ should be granted an initial 3-year treatment indication. However, it is recommended that the Applicant conduct, or supply additional treatment data from a Phase IV commitment that would provide confirmatory support for the 3-year treatment regimen.

7. INTEGRATED REVIEW OF SAFETY

7.1 Brief Statement of Safety Findings

The extent of exposure to Implanon™ in the Applicant's clinical development program in conjunction with more than 5 years of postmarketing safety is adequate to assess the safety of Implanon™ for the prevention of pregnancy. In the principal safety studies and supportive pharmacology studies conducted by GCP criteria at least 1411 subjects were exposed to Implanon. Among these subjects 1,112 subjects were exposed to Implanon for at least one year; 789 for at least two years; 214 for at least 3 years; and 47 for at least 4 years.

In the clinical development program, no deaths occurred in any study. There were no serious adverse events of concern (including cardiovascular/thromboembolic events). Bleeding irregularities were the most frequently reported adverse event, occurring in more than 85% of subjects). The most common reasons for discontinuing Implanon™ in the Principal Studies and the percentages of subjects discontinuing because of them were bleeding irregularities (43/330-U.S. Study; 123/788-non U.S. Studies). More than 19 % of 1401 subjects had a > 10% increase in Body Mass Index from baseline. Laboratory parameters (hematology, blood chemistry, and urinalysis) were assessed in U.S. Study 069001 and in non-U.S. study 34507 (Austria). No clinically meaningful laboratory abnormalities were noted. Parameters of lipid metabolism (studies in the U.S., U.K. and Thailand) did not reveal any adverse effects. In study 069001, analysis of liver function parameters showed a few treatment differences that reached statistical significance; however, these results were not clinically important. Mean bone mineral density (BMD) parameters measured at different sites were generally higher than those reported for a reference population in the U.S. and in Europe.

Since the start of marketing of Implanon in 1998, more than units have been sold as of 30 April 2003. Selected postmarketing safety data (SAEs) submitted to the FDA on 9 Sep 04, included reports of 4 deaths (3 deaths due to pulmonary embolus; one death due to bacterial infection). Serious cardiovascular adverse events have consisted of 10 reports of pulmonary emboli, 14 reports of CVAs, and 17 reports of DVTs. Implanon has not been withdrawn from any market because of safety issues. The most common significant postmarketing safety issues has related to adequate training of healthcare providers, a problem that was most common following the initial marketing of the product. b(4)

Medical Officer's Comments

- **Review of all submitted safety studies from the principal and supportive safety studies did not reveal any significant safety concerns.**
- **The number and types of serious post marketing adverse events reported by the Applicant are compatible with those to be expected with a hormonal contraceptive product that has been used by more than women.** b(4)
- **This reviewer believes that the safety data provided in this application support a recommendation for approval of this product for prevention of pregnancy.**

7.2 Studies Supporting the Safety of Implanon™

7.2.1 Overview of Studies and Distribution of Subjects (All Studies)

The studies conducted by the Applicant to support the safety of Implanon™ and the number of subjects in each of them are listed in Table 16. A total of 1803 subjects were treated with Implanon™ in 20 completed Phase II and III studies (cutoff date, 30 April 2003). These studies consisted of:

1. Four Principal Safety and Efficacy Studies (designated by the Applicant as "adequate and well controlled studies" (U.S./Europe/Thailand)- 1117 subjects
2. Ten clinical Pharmacology and Special Safety Studies (Europe/ Singapore/Thailand)- 297 subjects,
3. Five additional supportive studies (primarily conducted in China and Mexico) – 389 subjects

Table 16 Clinical Studies Supporting the Safety of Implanon™

Study Type	Region	Studies and Study Sites Included	Implanon™
Adequate and Well Controlled Studies	U.S.	069001–All Sites	330
	Europe[a]/Thailand	34505 –All Sites	100
		34507 –All Sites	635
		34507 CDN	52
		Total Europe[a]/Thailand	787
	Total U.S./Europe[a]/Thailand		1117
Clinical Pharmacology Studies	Europe/Singapore/Thailand	34502 –All Sites	15
		34508 –All Sites	16
		34509 –All Sites	43
		34510 –Excluding Indonesian Sites	15
		34511 –All Sites	40
		34512 –All Sites	40
		34514 –Excluding Indonesian Sites	30
		34515 –All Sites	10
		34522 –All Sites	46
		34523 –All Sites	42
		Total Europe/Singapore/Thailand	297
Total Adequate and Well Controlled + Clinical Pharmacology Studies U.S./Europe[a]/Singapore/Thailand			1414
Additional Clinical Pharmacology Studies[b]	China	RM01	16
	Europe	34504 (Leached implant)	15
Controlled Study	China	RM04	100
Uncontrolled Studies	China	RM02	200
	Mexico	34524	58
Grand Total –All Subjects Treated			1803

[a] Including Chile and Canada.

[b] Studies RM01 and 34504 were not integrated with the remaining Clinical Pharmacology Studies. RM01 did not conform to GCP, and 34504 used a leached implant. Study 34513 is excluded from this table as the study was discontinued before any subjects received Implanon™

Source: Table 2, P 53, revised ISS, 04 May 04

Medical Officer's Comments

- **There were 720 additional subjects in disqualified trials held in Indonesia: 649 in two controlled clinical trials and 71 in three clinical pharmacology trials. These subjects are not included in the above Table. The Applicant removed all the Indonesian subjects from the database supporting the safety of Implanon because of Good Clinical Practice (GCP) violations (see Section 4.1)**

7.2.1.1 Principal Safety Studies

An overview of the number of subjects enrolled in each of the Principal Safety Studies and brief summaries of these studies are provided below. Disposition of these subjects is provided in Figure 2

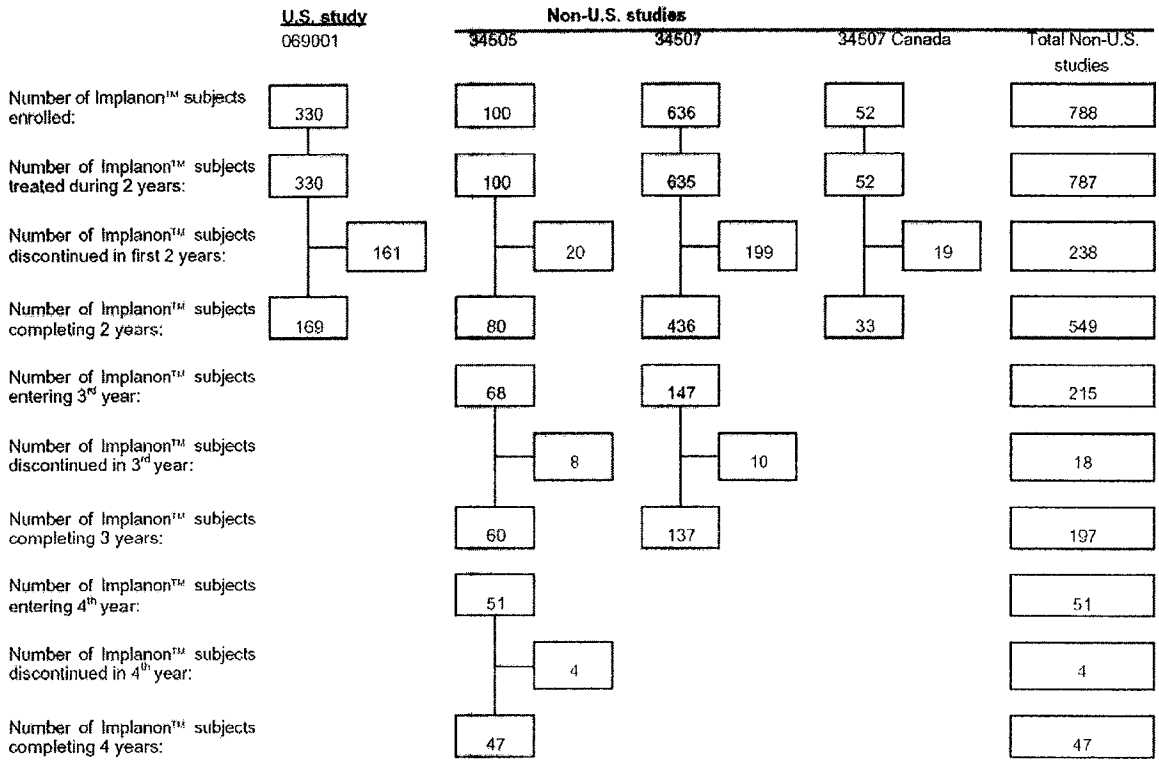
Study 069001- Study 069001 (United States) was an open-label, non-comparative, historically controlled multicenter (16 centers) efficacy and safety study in healthy female subjects. The duration of treatment was up to 24 months. Subsets of Study 069001 evaluated pharmacologic parameters, ophthalmological variables, lipid metabolism, carbohydrate metabolism, and endometrial morphology. Three hundred and thirty (330) subjects were enrolled and treated for 6,198 cycles (based on 28-day cycles and equivalent to 474 women-years of use). One hundred sixty one (161) subjects discontinued in the first 2 years (49% of 330 subjects), and 169 subjects completed 2 years (51%, 169 of 330 subjects).

Study 34505- Study 34505 (Thailand) was an open-label, single-center, non-comparative, historically controlled efficacy and safety study. The duration of treatment was 24 months with an option for a 1 year or 2 year extension period. Upon removal of the implant, subjects were monitored for a 3 month follow-up period. One hundred (100) subjects were enrolled and treated for 3,836 cycles (equivalent to 296 women-years of use). Eighty (80) subjects completed 2 years; 68 subjects extended for 3 years, and 60 completed the 3rd year; 51 subjects extended for 4 years and 47 completed the 4th year. In total, 32 subjects (32% of 100 subjects) discontinued Study 34505, of which, eight were lost to follow-up.

Study 34507- Study 34507 (Europe and Chile) was an open-label, multicenter (21 sites) non-comparative, historically controlled efficacy and safety study. Study 34507 was conducted primarily in Europe (Germany, Belgium, France, Netherlands, Sweden, Hungary, and Austria) but did have single study site in South America (Chile). The treatment duration was up to 24 months. Study centers in Santiago, Chile and Budapest, Hungary extended the treatment duration to up to 3 years. Upon removal of the implant, subjects were monitored for a 3 month follow-up period. Six hundred and thirty-six subjects (636) were enrolled in Study 34507; 635 subjects received the implant. Four hundred thirty-six (436) subjects completed 2 years, 199 subjects discontinued in the first 2 years; 147 subjects extended for 3 years, 10 subjects discontinued during year three, and 137 subjects completed 3 years. A total of 205 subjects discontinued the study and 4 subjects were lost to follow-up,

Study 34507 Canada- Study 34507 Canada was an open-label, single-center, non-comparative efficacy and safety study. The duration of treatment was up to 24 months. Fifty-two subjects were enrolled and received an implant, 19 subjects discontinued (36.5%, 19 of 52 subjects), and 33 subjects completed 2 years (63.5% of 52 subjects) of treatment. .

Figure 2 Disposition of Subjects in Principal Safety Studies



Note Data in this figure were obtained from Figure 1 (069001CL1, 34505CL1, 34507CL1and 34507 (CDN)CL1).

Source: Fig 1, P55, revised ISE, 04 May 04

7.2.1.2 Supportive Clinical Pharmacology Studies

A listing of the clinical pharmacology studies with the number of subjects enrolled in each is presented in Table 16. A total of 297 subjects (using Implanon™) were enrolled across 10 sites in Europe, Singapore and Thailand.

7.2.1.3 Comparative Clinical Pharmacology Studies

In many of the supportive clinical pharmacology studies, some additional subjects at selected sites used either a Norplant™ implant or an IUD, instead of Implanon™ for prevention of pregnancy. Table 17 lists the studies and the number of subjects in each of the studies in which a comparative method of contraception was used. Subjects who used Implanon™ in these comparative studies are a subset of subjects in the studies listed in Table 16). In the clinical pharmacology studies that also included a comparator, 272 subjects used Implanon™; 184 subjects used Norplant™, and 68 subjects used an IUD for prevention of pregnancy. In an additional study conducted in China (Study RM04), 100 subjects used Implanon™ and an additional 100 subjects used Norplant™ for prevention of pregnancy (Table 17).

Table 17 Distribution of Treated Subjects in Clinical Studies that Included a Comparator

Study Type	Region	Studies and Study Sites Included	Treatment Groups		
			Implanon™	Norplant™	IUD
Clinical Pharmacology Studies	Europe/ Singapore/ Thailand	34508 –All Sites	16	16	-
		34509 –All Sites	43	43	-
		34510 –Thailand	15	15	-
		34511 –All Sites	40	40	-
		34512 –All Sites	40	40	-
		34514 –UK	30	30	-
		34522 –All Sites	46	-	30
		34523 –All Sites	42	-	38
		Total Europe/Singapore/Thailand	272	184	68
Controlled Study	China	RM04	100	100	-
Grand Total –All Subjects Treated			372	284	68

Note: Cells containing hyphens indicate that the given treatment group did not exist for a given study.

Source: Table 3, P54, Revised ISS, 4May04

Medical Officer's Comment

- **The comparative studies do not appear to have been randomized. The one exception is Study RM04; however, this study was not conducted under Good Clinical Practices. No firm conclusions can be drawn from the comparator studies.**

7.3 Subject Demographics and other Baseline Characteristics

General subject information, including demographic and subject characteristic data, such as date of birth, height, and weight were collected during the screen period. Also collected during the screening period was gynecological history including menstrual characteristics, gravity, parity, and previous contraceptive use.

For each study grouping, descriptive summaries of the following demographic characteristics were collected: age (18-20, 21-25, 26-30, 31-35, 36-40, and >40), body mass index (BMI), number of previous pregnancies, and number of deliveries. All are summarized in tabulation form by presenting the number (and percent) of subjects in each category. BMI was calculated as weight/height (kg/m^2) and categorized as follows: $\leq$20, >20-22, >22-24, >24-26, >26 (kg/m^2). The mean and standard deviation for age, body weight, height, and BMI were also calculated.

7.3.1 Principal Safety Studies and Supportive Clinical Pharmacology Studies

Demographic characteristics for subjects in the Principal Safety Studies are listed in Table 18.

Table 18 Demographics – Principal Safety Studies

Parameter	Study 069001 (N = 330) n	(%)	Study 34505 N = 100 n	(%)	Study 34507 N = 635 n	(%)	Study 34507 CDN N = 52 n	(%)
Age (years)								
18-20	43	(13.0)	12	(12.0)	39	(6.1)	14	(26.9)
21-25	129	(39.1)	36	(36.0)	147	(23.1)	21	(40.4)
26-30	85	(25.7)	35	(35.0)	192	(30.2)	12	(23.1)
31-35	55	(16.6)	12	(12.0)	167	(26.3)	4	(7.7)
36-40	18	(5.4)	5	(5.0)	86	(13.5)	1	(1.9)
>40	0		0		4	(0.6)	0	
Mean (SD)	26.1 (5.1)		26.3 (4.8)		29.1 (5.6)		24.0 (4.1)	
Race								
Caucasian	234	(70.9)						
Black	40	(12.1)						
Asian	7	(2.1)						
Other	49	(14.8)						
Body Mass Index (BMI) (kg/m2)								
≤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 BMI (SD)	23.6 (3.6)		21.7 (2.8)		22.7 (2.8)		22.8 (3.3)	

N = Number of subjects in All-Subjects-Treated Group.
n = Number of subjects with a particular characteristic.
Source: Table 12, P 12, Revised ISS 4May04

Demographic characteristics for subjects in the supportive clinical pharmacology studies are listed in Table 19.

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Table 19 Demographics – Supportive (Clinical Pharmacology) Studies

Parameter	Supportive Clinical Pharmacology Studies (N = 297) n	(%)
Age (years)		
18-20	26	(8.8)
21-25	74	(24.9)
26-30	92	(31.0)
31-35	67	(22.6)
36-40	38	(12.8)
>40	0	
Mean (SD)	28.4 (5.6)	
Body Mass Index (BMI) (kg/m2)		
≤20	46	(13.9)
>20-22	84	(25.4)
>22-24	74	(22.4)
>24-26	46	(13.9)
>26	80	(24.2)
Mean BMI (SD)	23.6 (3.6)	

N = Number of subjects in All-Subjects-Treated Group.
n = Number of subjects with a particular characteristic.
Source: Table 13, P 68, revised ISS 04May04

Medical Officer's Comments

- **Demographic and other subject characteristics for the pooled analysis of the Principal Studies and Supportive Clinical Pharmacology Studies (n=1414 subjects) showed the mean age of subjects was 27.8 years in studies conducted in U.S./Europe/Singapore/Thailand, with most subjects ranging in age from 21 to 35 years. Most of these 1414 subjects had prior pregnancy(s), with most having 1 to 3 prior deliveries.**
- **The mean body mass index for this population was 22.8 kg/m^2. The mean weight at enrollment was 70 ± 9.6 kg (154 ± 21 lb.). No special studies were done in obese women.**
- **Within this population, the most common prior contraceptive method used was oral contraceptives, and at screening the mean usual duration of menstrual bleeding was 4.7 days. The population studied clearly represents the target population for this product.**
- **Although there were no subjects under age 18, there is no clinical reason to suspect that Implanon™ will not be safe and effective in younger women. In the comparative studies, the characteristics of the limited number of subjects treated with Implanon™ did not differ from those treated with Norplant™ or a non-hormonal IUD.**
- **Data on the variable "race" was not collected in the non-U.S. studies and is only available for U.S. Study 069001 (N = 330).**

7.4 Reasons for Discontinuations and Subject Disposition

In this section, reasons subjects discontinued are presented by primary reason for discontinuation for each study grouping: principal safety studies, supportive clinical pharmacology studies, and comparative studies.

7.4.1 Principal Safety Studies

Within the principal safety studies, the predefined choices for reasons for discontinuation in the *U.S. clinical trial (Study 069001)* differed from the Non-U.S. Principal Safety Studies. The reasons for discontinuation of subjects from this study that were recorded on the Termination Case Report forms (CRF) were as follows:

- The subject was not willing to or could not cooperate further, for reasons not related to the protocol;
- Protocol violations (e.g., incorrect use of selection criteria, use of drugs or other treatments interfering with study treatment, and failure to comply with scheduled visits);
- Emergence of an intercurrent illness, which either by its severity or duration or by the required treatment, violated the conditions of the trial;
- Emergence of unacceptable adverse experiences;
- Essential data (outcome measures) missing which could not be recovered; and
- Other reasons (must have been specified by the investigator).

For the *Non-U.S. Principal Safety Studies*, specified reasons for discontinuation as described on the Termination Form were coded according to predefined codes. If the primary reason for discontinuation reported on the Termination Form was not 'end of the study', then a subject was considered a premature termination. If a subject did not wish to participate in the extension of a given study, she was not considered a premature termination. The primary reasons for termination were categorized, using the predefined codes into one of the following categories:

- Amenorrhea;
- Bleeding irregularities;
- Adverse event (medical problems other than bleeding-related);
- Lost to follow-up;
- Other reasons (all remaining codes)

Subject disposition and specific reasons for termination in the 4 principal safety studies are listed in Table 20 and summarized below.

U.S. Study- 069001. A total of 161 out of 330 subjects (48.8%) discontinued from U.S. Study 069001. The most common reason for discontinuation was adverse experience, with 119 subjects (36.1%) discontinuing primarily for this reason. Of these, 43 subjects (13.0%) discontinued because of adverse menstrual experiences (bleeding irregularities) as the primary reason, and 76 subjects (23.0%) discontinued with other adverse experiences being the primary reason.

Non- U.S. - Principal Safety Studies (Studies 34505, 34507, and 34507 CDN). A total of 260 Implanon™-treated subjects (33.0%) discontinued from the Principal Safety Studies

conducted in Europe, Thailand, and Canada. The most common reason for discontinuation among subjects in these studies was adverse event with 204 subjects (20.6%) withdrawing for this reason. Among adverse events, bleeding irregularities with 123 subjects (15.6% of total subjects) discontinued primarily for this reason. Forty three (43) subjects (5.5%) discontinued for "other reasons" and 13 subjects (1.6%) were lost to follow up.

Table 20 Subject Disposition (Reasons for Termination) in Principal Safety Studies

	Number (%) of Subjects			
Study	**69001**	**34505**	**34507**	**34507 CDN**
Number subjects randomized	330	100	636	52
Discontinued Prematurely	161 (49%)	32 (32%)	209 (33%)	19 (37%)
Adverse Event	119 (36.1%)	12 (12%)	180 (28.3%)	12 (23.1%)
Amenorrhea	-*	1 (1%)	11 (1.7%)	-
Bleeding irregularities	43 (13%)	6 (6%)	110 (17.3%)	7 (13.5%)
Other adverse events	76 (23%)	5 (5%)	59 (9.3%)	5 (9.6%)
Lost to follow-up	-	8 (8%)	4 (0.6%)	1 (1.9%)
Protocol violation	4 (1.2%)	-	-	-
Unwilling to continue	8 (2.4%)	-	-	-
Intercurrent illness	1 (0.3%)	-	-	-
Other reasons	29 (9%)	12 (12%)	25 (3.9%)	6 (11.5%)

*: No data available
Source: Protocol 069001 (Table 4), Protocol 34505 Table 5), Protocol 34507 (Table 6), & Protocol 34507 CDN (Table 6).

Medical Officer's Comments

- **A total of 421 out of 1117 subjects (37.3%) prematurely discontinued Implanon™. There were a greater percentage of subjects who discontinued in the U.S., compared to the non-U.S. studies (36.1% vs. 20.6%). Adverse events (including bleeding irregularities) were the most common reasons. An explanation for this is not readily apparent. It is possible that cultural differences dictate that U.S. subjects are less willing to tolerate adverse events. Nonetheless, it is interesting to note that a greater percentage of subjects in the European study discontinued due to bleeding irregularities: 17.3% vs. 13% (U.S.), 13.5% (Canada) and 6% (Thailand). Subjects in Thailand discontinued less frequently than all other studies for both adverse events (12% vs. 36% U.S., 28.3% Europe, and 23.1% Canada) and bleeding irregularities (see above). Again, it is unknown why this is the case; one can speculate that cultural influences are also operating here.**

7.4.2 Supportive Clinical Pharmacology Studies

A summary of reasons for discontinuation in the supportive clinical pharmacology studies is presented in Table 21. Data from Study RM01 and the leached implant study (34504) are not included. As shown in Table 21, 84 Implanon™-treated subjects (28.3%) discontinued from studies conducted in Europe/Singapore/Thailand. The most common reason for discontinuation was bleeding irregularities, with 45 subjects (15.2%) discontinuing primarily for this reason.

Table 21 Number (%) and Reason for Discontinuations in Supportive Clinical Pharmacology Studies

Primary reason for discontinuation[b]	Implanon™ Europe/Singapore/Thailand[a] (N=297)	
	n	(%)
Amenorrhea	2	(0.7)
Bleeding irregularities	45	(15.2)
Adverse experience	17	(5.7)
Other reasons	16	(5.4)
Lost to follow-up	4	(1.3)
Total	84	(28.3)

[a] Studies 34502, 34508, 34509, 34510 (Thailand), 34511, 34512, 34514 (UK), 34515, 34522 and 34523.

Source: Table 7, P58, revised ISS, 04May04

Medical Officer's Comments

- **The most common reason for premature discontinuation of Implanon™ in the supportive clinical pharmacology studies was bleeding irregularities (15.2%) vs. other adverse experiences (5.7%).**

7.4.3 Clinical Pharmacology Comparative Studies

As shown in Table 22, the discontinuation rate among Implanon™-treated subjects was lower than Norplant™-treated subjects (29.8% vs. 37.5%, respectively), but higher than IUD subjects (29.8% vs. 17.6%). For the Implanon™ and Norplant™ treatment groups, the most common reason for discontinuation was bleeding irregularities (16.2% and 15.8%, respectively).

Table 22 Number (%) and Reason for Premature Discontinuations in Comparative Clinical Pharmacology Studies

Primary reason for discontinuation[b]	Europe/Singapore/Thailand[a]					
	Implanon™ (N=272)		Norplant™ (N=184)		IUD (N=68)	
	n	(%)	n	(%)	n	(%)
Amenorrhea	2	0.7	4	2.2	0	
Bleeding irregularities	44	16.2	29	15.8	0	
Adverse experience	16	5.9	14	7.6	2	2.9
Other reasons	15	5.5	14	7.6	5	7.4
Lost to follow-up	4	1.5	8	4.3	5	7.4
Total	81	29.8	69	37.5	12	17.6

[a] Studies 34508, 34509, 34510 (Thailand), 34511, 34512, 34514 (UK), 34522 and 34523.
[b] Categorized using pre-defined code-list from Implant Removal Form

Source: Table 8, P 59, revised ISS, 04May04

Medical Officer's Comments

- **There does not appear to be a significant difference in adverse experiences other than bleeding irregularities (5.9% vs. 7.6%) or bleeding irregularities (16.2% vs. 15.8%)**

between the Implanon™ and Norplant™ groups; however this must be interpreted with caution because of the small number of subjects and lack of random assignment to treatment. There are fewer adverse experiences in the IUD group (2.9%).

7.4.4 Summary of Subject Disposition (Premature Terminations)

Medical Officer's Comments

- **A total of 1414 subjects were treated with Implanon™ in the 4 principal safety and efficacy studies, and 10 supportive clinical pharmacology studies. In addition, 389 subjects were treated in 5 supportive studies; however, most of these studies did not adhere to Good Clinical Practice guidelines.**
- **In the U.S. Principal Safety Study, 161 out of 330 subjects (48.8%) discontinued prematurely. The most common reason for discontinuation was adverse experience, with 119 subjects (36.1%) discontinuing primarily for this reason. Among these 119 subjects, 43 discontinued because of bleeding irregularities.**
- **In the non-U.S. studies Principal Safety Studies (Europe, Canada and Thailand) 204 out of 788 subjects discontinued. The most common reason for discontinuation was an adverse event, with bleeding irregularities (123 subjects - 15.6%) the most common adverse event associated with discontinuation.**
- **In the comparative studies, IUD subjects had the lowest discontinuation rate (17.6%); fewer total Implanon™ subjects (29.8%) than Norplant™ subjects (37.5%) discontinued prematurely.**

7.5 Subject Exposure to Implanon

All subjects who used Implanon™ for prevention of pregnancy received the same dose. Implanon™ is a subdermal single-rod ethylene vinyl acetate copolymer implant containing 68 mg of etonogestrel (ENG). It has an initial release of approximately 67μg/day. The average release rate over the entire period of 3 years is approximately 41 μg/day.

Among the Principal Safety Studies, the maximum duration of exposure in Study 069001 was 2 years. Maximum duration of exposure in Study 34507 was initially 2 years, but the study was extended to 3 years at two sites. Study 34505 was initially 2 years, but was extended to 4 years.

Among the Supportive Clinical Pharmacology Studies, the maximum duration of exposure in Studies 34509, 34510 (Thailand), 34511, 34512, 34515, and 34522 was 2 years. The maximum duration of exposure in Study 34523 was 3 years. Study 34508, was initially 2 years, and then extended to 3 years at particular sites. Study 34514 (UK) was initially 2 years, and then extended to 3 years. Studies 34502 and 34503 were initially 2 years and then extended to 5 years. Study RM01 was initially 2 years and then extended to 4.5 years.

The extent of exposure was converted into "woman-years of exposure" (with a year defined as 365.25 days) and "cycles of exposure" (with a cycle defined as 28 days). These data are summarized by presenting the total woman-years of exposure and total cycles of exposure.

7.5.1 Principal Safety Studies

The extent of exposure to Implanon™ in the Principal Safety Studies is summarized in Table 23. The mean duration of exposure to Implanon™ for the subjects in studies conducted in U.S./Europe/Thailand was 673.3 days with a total exposure for 1114 subjects of 2,053.5 woman-years or 26,786.7 cycles. Most subjects in this population were exposed for 1 to <3 years (62.2%), and 169 subjects (15.2%) were exposed to Implanon™ for 3 years or greater.

Table 23 Extent of Exposure to Implanon in the Principal Studies

	Implanon™		
	US[a]	Europe/Thailand [b]	Total: US/Europe/ Thailand
	(N=327)	(N=787)	(N=1114)
Mean +/- SD	529.7 +/- 256.2	732.9 +/- 357.1	673.3 +/- 343.3
Median	721	736	733
Total exposure			
Woman-years	474.2	1579.2	2053.5
Number of 28-day cycles	6186.2	20600.5	26786.7
Number of subjects exposed by duration			
< 1 year	101 (30.9%)	151 (19.2%)	252 (22.6%)
1 to < 2 years	90 (27.5%)	175 (22.2%)	265 (23.8%)
2 to < 3 years	136 (41.6%)	292 (37.1%)	428 (38.4%)
3 to < 4 years	0	131 (16.6%)	131 (11.8%)
≥ 4 years	0	38 (4.8%)	38 (3.4%)

[a] Study 069001. Extent of exposure was calculated from 327 subjects in Study 069001 (3 subjects had no postbaseline assessments).
[b] Studies 34505, 34507, and 34507 CDN.

Source: Table 18, P 79, revised ISS, 04May04

7.5.2 Principal Safety Studies and Supportive Pharmacology Studies Combined

The extent of exposure to Implanon™ in the Principal and Supportive Clinical Pharmacology Studies combined is summarized in Table 24. The mean duration of exposure to Implanon™ for the subjects in studies conducted in U.S./Europe/Singapore/Thailand was 685.8 days with a total exposure for 1,411 subjects of 2,649.2 woman years or 34,557.5 cycles. Most subjects in this population were exposed for 1 to <3 years (63.6%). A total of 1112 subjects (78.8%) were exposed to Implanon™ for at least one year, and 214 subjects (15.2%) were exposed to Implanon™ for at least 3 years.

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Table 24 Extent of Exposure to Implanon in the Principal and Supportive Clinical Pharmacology Studies Combined

	Implanon™
	US/Europe/Singapore/ Thailand[a] (N=1411)[b]
Treatment duration (days)	
Mean +/- SD	685.8 +/- 342.7
Median	734
Total exposure	
Woman-years	2649.2
Number of 28-day cycles	34557.5
Number of subjects exposed by duration	
< 1 year	299 (21.2%)
1 to < 2 years	323 (22.9%)
2 to < 3 years	575 (40.8%)
3 to < 4 years	167 (11.8%)
≥ 4 years	47 (3.3%)

[a] Studies 069001, 34502, 34505, 34507, 34507 CDN, 34508, 34509, 34510 (Thailand), 34511, 34512, 34514 (UK), 34515, 34522, and 34523.
[b] Three subjects in the US study do not have exposure information. They are excluded from N.

Source Table 21, pg 83, revised ISS, 04May04

Medical Officer's Comments

- **The extent of exposure to Implanon™ in the principal and supportive clinical pharmacology studies is adequate for an overall safety review. In these studies, there were 1,411 subjects with over 2649 woman-years or 34,577 cycles of use [mean exposure was 685 days/subject]. Most subjects in this population were exposed for 1 to <3 years (63.6%). A total of 1,112 subjects (78.8%) were exposed to Implanon™ for at least one year, 789 (55.9%) subjects for at least 2 years, 214 subjects (15.2%) for at least 3 years, and 47 (3.3%) subjects were exposed to Implanon™ for at least 4 years.**

7.6 Adverse Events

In the revised Integrated Summary of Safety (ISS), the Applicant provided a description of adverse experiences listed by WHO system-organ class and preferred terms. Adverse events were further classified as those that were associated with subject deaths, serious adverse experiences, and discontinuations. Common adverse events (those that occurred with an incidence of ≥ 5%) and adverse events that were possibly, probably, or definitely related to the study medication in the opinion of the investigator were summarized.

7.6.1 Deaths

No deaths occurred in any study in the Clinical Development Program for Implanon.

7.6.2 Serious adverse events

7.6.2.1 Principal Safety Studies

Sixty-two (62) out of 1117 subjects (5.5%) in the principal safety studies conducted in U.S./Europe/Thailand had a total of 83 serious adverse events (SAEs) as shown in Tables 23, 24 and 25 of the Applicant's revised ISS. The system-organ classes with the most SAEs and the number of subjects reporting a SAE associated with the system-organ class were Gastro-Intestinal System Disorder: 14/1117 (1.3%), Neoplasms: 9/1117 (0.8%), Liver and Biliary System Disorders: 7/1117 (0.6%), and Reproductive Disorders, Female: 6/1117, (0.5%). All individual SAEs occurred with an incidence less than 1%. The most frequently occurring individual SAEs were gastrointestinal disorder not otherwise specified, occurring in 7 subjects (0.6%); cholelithiasis, occurring in 6 subjects (0.5%); and bone disorder, occurring in 5 subjects (0.4%). Serious adverse events coded as Bone Disorders included four cases of bone fracture and one case of hallux valgus surgery. All other individual SAEs occurred in 3 or fewer subjects.

Twelve (12) of the 83 SAEs were thought to be possibly, probably, or definitely drug-related. These included two cases of ovarian cyst and single cases of gastrointestinal disorders not otherwise specified, breast fibroadenosis, breast neoplasm benign, uterine fibroid, depression, cyst not otherwise specified, cerebrovascular disorder, headache, chest pain, and tachycardia..

All subjects recovered with the exception of one subject (Subject 0544 in Study 34507) who had continuing abdominal pain with an unknown outcome.

Medical Officer's Comments

- **All individual SAEs occurred with an incidence less than 1%. Serious adverse events thought to be related to the study drug all occurred as single cases except for 2 cases of ovarian cyst. This indicates there were no significant trends that would indicate a drug related adverse event problem that might preclude the approval of Implanon™ for prevention of pregnancy.**

7.6.2.2 Principal Safety Studies and Supportive Clinical Pharmacology Studies (Pooled Analysis)

The incidence of SAEs among Implanon™-treated subjects in the pooled analysis of all Principal Safety Studies and the Supportive Clinical Pharmacology Studies by WHO system-organ classification is shown in Table 31 of the Applicant's revised ISS. Seventy-three (73) out of 1414 subjects (5.4%) in the population from studies conducted in U.S./Europe/Singapore/Thailand had at 99 SAEs. The system-organ classes with the most SAEs and the numbers of subjects reporting SAEs in the respective system-organ classes were Gastrointestinal System Disorder: 16/1414 (1.1%), Neoplasms: 11/1414 (0.8%), Reproductive Disorders, Female: 8/1414, (0.6%), Liver and Biliary System Disorders: 7/1414 (0.5%), and Musculoskeletal System Disorders: 7/1414 (0.5%). All individual SAEs occurred with an incidence less than 1%. The most frequently occurring SAEs were Gastrointestinal Disorder not otherwise specified, occurring in 7 subjects (0.5%); Cholelithiasis, occurring in 6 subjects (0.5%); and Bone Disorder, occurring in 6 subjects (0.4%). SAEs coded as Bone Disorder included five cases of bone fracture and one case of hallux valgus surgery. All other SAEs occurred in 4 or fewer subjects.

Sixteen (16) of the 99 SAEs were thought to be possibly, probably, or definitely drug- related. These included two cases each of headache and ovarian cyst and single cases of gastrointestinal disorder not otherwise specified, breast fibroadenosis, breast neoplasm benign, teratoma, uterine

fibroid, asthma, chest pain, fever, cerebrovascular disorder (A-V malformation), depression, cyst not otherwise specified, and tachycardia.

All Implanon™-treated subjects recovered with the exception of one subject (Study 34507, Subject 0544) who had continuing abdominal pain with an unknown outcome.

Medical Officer's Comments

- **There were no SAEs of concern. It is hard to interpret the 6 cases of cholelithiasis in terms of causation. In a large Norplant™ Postmarketing Surveillance Study (NPMS), the incidence rate of gallbladder disease was 1.5 per 1000 woman-years in women who initiated treatment with Norplant™ (a levonorgestrel-only implant). It is also well known that cholelithiasis and cholecystitis are associated with combination hormonal contraception. As with oral contraceptives, a small risk of gallbladder disease may exist for users of Implanon™, but it is difficult to assess the precise risk.**
- **The reviewer table below summarizes the 6 cases of gall bladder disease that were reported from the clinical studies. It is of note that all the subjects completed or continued in their study; three women were from Santiago where there is a high incidence of gallbladder disease in the population; and none of the investigators judged these events to be related to the study medication.**

Cholecystitis and/or Cholelithiasis Cases

Subject Number	Age	Weight (kg)	Diagnosis- Days on drug	Outcome	Comment
0012	24	60	Chronic Cholelithiasis- 30	Laparoscopy	Continued study
0210	39	61	Cholelithiasis- 540	Surgery	Study completed
0519	37	54	Chronic Cholecystitis- 1107	Laparoscopy	Surgery 90 days post 3-yr study
0610	25	51	Cholelithiasis- 575	Surgery	Study completed
0652	28	54	Acute + lithiasis 392	Laparoscopy	Study completed
0660	29	67	Cholelithiasis- 603	Laparoscopy	Study completed

Source: Medical reviewer table

- **None of the 720 subjects in disqualified studies in Indonesia reported SAEs.**

7.6.2.3 Serious Adverse Events of Special Interest

Cardiovascular-Potential Adverse Effects:

Since the late 1960s, the thromboembolic events occurring in women using combination oral contraceptives (COCs) were generally attributed to the estrogen component of the pill. In contrast to COCs, epidemiological studies on the risk of venous thromboembolism (VTE) in progestin-only contraception users are scarce. The World Health Organization study[i] was one of the first studies to evaluate the risks of cardiovascular disease, including VTE, with the use of oral and injectable progestagen-only contraceptives. Although limited by the small number of cases and control subjects, this study and other studies[ii,iii] did not reveal an increased risk of VTE as compared to non-users of hormonal contraceptives.

Table 25 Studies on The Relationship Between Progestin-Only Contraception and the Risk of Venous Thromboembolism (VTE)

Reference	Type of progestagen-only contraception	RR	(95% CI)
WHO (1998) [35]	all oral progestagens continuous POP only progestagen-only injectable	1.74 1.82 2.19	(0.76-3.99) (0.79-4.22) (0.66-7.26)
Heinemann et. al. (1999) [36]	all POPs	0.68	(0.28-1.66)
Vasilakis et. al. (1999) [37]	all progestagens alone for contraception for menstrual disorders	2.4 1.3 5.3	(0.8-6.5) (0.3-6.8) (1.5-18.7)

Source: Original NDA 21529 submission, 30Sep04

Cardiovascular SAEs in Implanon Clinical Trials

Vascular (extracardiac) disorders. In the Clinical Development Program for Implanon™, 4 subjects had SAEs that were categorized as vascular disorders. A brief summary of cases follows.

1. Subject 0558 from Study 34507 [N=635, 21 centers in Europe and Chile] suffered from *varicose veins* and was hospitalized for a varicectomy. In the opinion of the investigator this event was unlikely to be related to Implanon™ use. The subject recovered and completed the study.
2. Subject 0682 from Study 34507 suffered transient loss of vision in the left eye and blurred vision in the right eye. She later had motor problems and paraesthesia of the extremities on the left side that lasted for several hours. The subject was hospitalized for a *suspected transient ischemic attack (TIA)*. The subject had no relevant medical history. A routine MRI in frontal and sagittal planes yielded the following results. Ventricular system: normal appearance (size and position). Hypophysis: normal in size, inhomogeneous in consistency. From the right side of the hypophysis there were signs, which may indicate reduction of volume. The suprasellar cistern was free; the chiasmatic region showed no abnormalities. Otherwise, there were no pathological findings in the brain, and no signs of demyelination. The subject recovered from the event, which was judged by the investigator as possibly related to Implanon™ use. The subject discontinued from the study.
3. Subject 0648 from Study 34507 suffered from headache, vomiting and confusion and was diagnosed with a *rupture of an arteriovenous (AV) left occipital malformation*. The vascular malformation was surgically removed, the residual hematoma was drained, and the subject recovered. The subject discontinued the study. The event was judged by the investigator as unlikely to be related to Implanon™ use.
4. Subject 09003 from U.S. Study 069001 experienced chest pains and was diagnosed with bronchospastic disorder, *vasospasm of the arteries*, drug abuse, and allergic reaction. She was treated with erythromycin and diazepam for the bronchospastic disorder and aspirin for the vasospasm of her arteries. The events were judged by the investigator as unlikely to be related to the use of Implanon™. The subject recovered and completed the study.