

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-529

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION Clinical Studies

NDA/Serial Number: 21-529 / 000

Drug Name: Implanon (68 mg etonogestrel subdermal implant)

Indication(s): Prevention of pregnancy

Applicant: Organon USA Inc.

Date(s): Letter Date: January 16, 2006 PDUFA Date: July 17, 2006

Review Priority: 1S

Biometrics Division: Division of Biometrics 3

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Key Words: Clinical studies, NDA review, complete response to approvable letter

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Implanon contraceptive implant has demonstrated a cumulative 3-year Pearl Index of 0.38 (95% C.I. from 0.14 to 0.82).

1.2 Background

This submission is a complete response to an approvable letter dated June 14, 2005, whose major issues were related to data quality and insufficient number of 28-day cycles collected during the first year of treatment. The Sponsor has submitted one U.S. and 10 non-U.S. clinical studies to demonstrate the safety and efficacy of Implanon contraceptive implant to prevent pregnancy in sexually active women aged 18 to 35 years of childbearing potential over three years of use.

The Sponsor's proposed indication is:

Implanon (etonogestrel implant) is indicated for women for the prevention of pregnancy.

1.3 Statistical Issues and Findings

There was one statistical issue with this submission, an error in calculation of the total number of 28-day cycles for Study E1729. This information was conveyed to the Sponsor who subsequently revised their integrated summary of efficacy report in the May 15, 2006 submission.

Efficacy is based on calculation of pregnancy rate using the Pearl Index in women aged 18 to 35 years. The cumulative 3-year Pearl Index is 0.38 (95% C.I. from 0.14 to 0.82).

2 INTRODUCTION

2.1 Overview

The Sponsor has submitted 11 clinical studies (one U.S. and 10 in Europe, Southeast Asia and South America) designed to demonstrate the safety and efficacy of Implanon over the course of 3 years in sexually active women, 18-35 years of age, who desire pregnancy prevention. Table 2.1 presents a brief summary of these 11 studies.

Table 2.1
Brief Summary of Clinical Studies for Implanon

| Study Number (No. of Centers* / Country) | Design ¹ | No. of All Implanon Subjects in Current Efficacy Database | Treatment Duration |
|---|--|--|-----------------------|
| 069001 (16 / U.S.) | OL, NC, MC, S, E | 330 | 2 years |
| 34502 (1 / Thailand) | OL, NC, PK/PD | 15 | 2 to 5 years |
| 34505 (1 / Thailand) | OL, NC, S, E | 100 | 2 to 4 years |
| 34507 (21 / Europe and Chile) | OL, NC, MC, S, E | 268 | 2 to 3 years |
| 34510 (2 / Thailand and Indonesia) | OL, MC, R, C, lipid metabolism | 15 | 2 years |
| 34511 (1 / Singapore) | OL, R, C, carbohydrate metabolism, thyroid and adrenal function | 40 | 2 years |
| 34512 (2 / Finland) | OL, MC, R, C, lipid metabolism | 20 | 2 years |
| 34515 (1 / Singapore) | OL, absolute bioavailability | 10 | 2 years |
| 34522 (3 / Chile, Finland, Netherlands) | OL, MC, C, bone mineral density | 49 | 2 years |
| 34525 (2 / Russia) | OL, MC, NC, S, E | 30 | 1 to 3 years |
| E1729 (24 / Malaysia, Venezuela, Austria, Germany) | OL, MC, NC, S, E | 69 | 3 years |

Source: Table 4, page 32 of ISE report and List of Studies section of submission.

¹ OL=Open Label, S=Safety, E=Efficacy, R=Randomized, MC=Multicenter, NC=Noncomparative, PK/PD=Pharmacodynamic/Pharmacokinetic, C=Comparative

* This is the total number of centers for the study. The number of centers in the database for this submission may be less.

Implanon consists of a coaxial rod of ethylene vinyl acetate (EVA) copolymer core containing 68 mg etonogestrel (ENG) surrounded by a skin of EVA copolymer. After upper arm insertion, ENG is slowly released through the rate-controlling skin with an ENG initial release rate of 67 µg/day and decreasing to 25-30 µg/day at the end of the third year. Implanon must be removed by the end of the third year and may either be replaced by a new Implanon or another form of contraceptive method, if continued contraceptive protection is desired.

This submission is a complete response to an approvable letter dated June 14, 2005, whose major issues were related to data quality and insufficient number of 28-day cycles collected during the first year of treatment (at least ten thousand 28-day cycles are required). A meeting with the Division of Reproductive and Urologic Drug Products was held on August 11, 2005 to discuss these issues and the Sponsor's proposals for addressing them. A Sponsor proposal to audit clinical sites (Studies 069001, 34505, 34507, 34525, and E1729) and include additional studies/sites (Studies 34502, 34510, 34511, 34512, 34515 and 34522) to the clinical database was acceptable to the Division with the understanding that acceptability of the clinical data would be contingent upon the findings of the Sponsor site audits, the findings from the Agency's own site inspections, and upon the adequacy of the submitted clinical data. The overall audit results were reviewed with the Division on November 22, 2005 and the Division agreed to accept the updated efficacy database.

The Sponsor's proposed indication is:

Implanon (etonogestrel implant) is indicated for women for the prevention of pregnancy.

2.2 Data Sources

The study reports and additional information for this submission are available in electronic format. The SAS data sets are complete and well documented. These items are located in the Electronic Document Room at \\Cdsub1\N21529\N_000 under various submission dates ranging from 1-16-2006 to 5-15-2006 and 9-30-03 (the first submission date for the NDA).

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Table 2.1 presents an overview of all studies used in this integrated efficacy evaluation. Subjects were healthy females who were sexually active and of childbearing potential between the ages of 18 and 40 years. The subjects had normal menstrual cycles and were not to be currently pregnant or breastfeeding, except for studies 34525 and E-1729 which included breastfeeding women. In all studies, the use of condoms was not recorded, except for Study 34502 at the scheduled 3-month visits. The treatment duration was defined as the number of days between date of implant insertion and date of removal. For those subjects who were lost to follow-up, the date of their last actual assessment was used. The extent of Implanon exposure was expressed as total number of 28-day cycles. Subjects were followed after completion of the study or early withdrawal for the occurrence of pregnancy.

The efficacy database includes 923 non-breastfeeding women treated for 1-5 years with Implanon in 11 clinical studies. The 16 breastfeeding women, who were allowed to participate in Studies 34525 (n=2) and E-1729 (n=14) were excluded from the efficacy analysis because breastfeeding women are at a lower risk for pregnancy.

The primary objectives of this study are to demonstrate the efficacy and safety of Implanon contraceptive implant. The Pearl Index for the group of treated subjects 18-35 years of age is the primary efficacy variable. The Pearl Index is calculated using all on treatment pregnancies and all cycles in the group of treated subjects 18-35 years of age. There was no exclusion of any cycles where condoms were used. The Pearl Index is defined as follows:

$$\text{Pearl Index} = 100 \times (\text{number of pregnancies}) \times (13 \text{ cycles/year}) \div (\text{total number of 28-day cycles})$$

No formal Pearl Index threshold to meet was planned. All subjects' data for total exposure up to the time of loss, pregnancy, or completion of study was used in the efficacy analysis. Also, an error in calculation of the total number of 28-day cycles for Study E1729 was conveyed to the Sponsor who subsequently revised their results in the May 15, 2006 submission.

3.1.1 Overall Descriptive Statistics

There were 923 treated subjects who were not breastfeeding at the time of screening and 833 (309 in the U.S. study and 524 in the non-U.S. studies) of these treated subjects were 18 to 35 years of age, the primary efficacy group of interest. For all 11 studies, of the treated subjects aged 18-35 years, the mean age ranged from 26 to 32.3 years with the majority of subjects less than 36 years of age (range of 65% to 94.5%). In the U.S. study, the majority (>70%) of subjects are Caucasian.

3.1.2 Results

Tables 3.1 and 3.2 present yearly and 3-year cumulative Pearl Indices for all treated subjects 18-35 years of age for when no pregnancies occur on-treatment and when 6 pregnancies occur within 14 days of implant removal, respectively. Of these 6 pregnancies, 2 occurred in the U.S. study and 4 occurred in the non-U.S. studies. The Reviewer concurs with the Sponsor's results. When no on-treatment pregnancies occur, the cumulative 3-year Pearl Index for Implanon is 0 (95% C.I. from 0 to 0.23). When 6 pregnancies occur within 14 days of implant removal, the cumulative 3-year Pearl Index for Implanon is 0.38 (95% C.I. from 0.14 to 0.82).

Table 3.1
Pearl Index Calculation of Treatment Failure Rates for No On-Treatment Pregnancies:
All Cycles – All Treated Subjects 18-35 Years of Age

| Treatment Period | N | Number of On-Treatment Pregnancies | Number of Cycles | Pearl Index | 95% Confidence Interval* |
|----------------------------------|-----|------------------------------------|------------------|-------------|--------------------------|
| Year 1 (Day 1 – 365) | 833 | 0 | 9816 | 0 | (0, 0.49) |
| Year 2 (Day 366 – 750) | 671 | 0 | 7766 | 0 | (0, 0.62) |
| Year 3 (Day 731 – 1095) | 482 | 0 | 3066 | 0 | (0, 1.57) |
| Cumulative 3 Year (Day 1 – 1095) | 833 | 0 | 20648 | 0 | (0, 0.23) |

Source: Tables 13 and 14 on pages 13 and 15 of May 15, 2006 submission.

Table 3.2
Pearl Index Calculation of Treatment Failure Rates for 6 Pregnancies Occurring Within 14 Days of Implant Removal:
All Cycles – All Treated Subjects 18-35 Years of Age

| Treatment Period | N | Number of On-Treatment Pregnancies | Number of Cycles | Pearl Index | 95% Confidence Interval* |
|----------------------------------|-----|------------------------------------|------------------|-------------|--------------------------|
| Year 1 (Day 1 – 365) | 833 | 2 | 9816 | 0.27 | (0.03, 0.96) |
| Year 2 (Day 366 – 750) | 671 | 2 | 7766 | 0.34 | (0.04, 1.21) |
| Year 3 (Day 731 – 1095) | 482 | 2 | 3066 | 0.85 | (0.10, 3.07) |
| Cumulative 3 Year (Day 1 – 1095) | 833 | 6 | 20648 | 0.38 | (0.14, 0.82) |

Source: Tables 13A and 14A on pages 14 and 17 of May 15, 2006 submission.

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. For additional information, reference the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

There are no subgroup populations of interest in this submission.

5. CONCLUSIONS

From a statistical standpoint, the Sponsor has provided several adequate clinical studies that resulted in a cumulative 3-year Pearl Index of 0.38 (95% C.I. from 0.14 to 0.82) for Implanon contraceptive implant for use in the prevention of pregnancy.

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Mahboob Sobhan
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Memorandum for the Record

NDA 21-529

Sponsor: Organon

Drug Name: Implanon

Indication: Contraception

Stamp Date: December 14, 2004

Subject: Statistical review not required

This submission is a complete response to the Division's October 29, 2004 approvable letter. The submission addressed GCP and inspection issues, safety updates, labeling, and foreign registration history. No new clinical trials were performed. A Biometrics Division review is not necessary.

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Addendum to Statistical Review

NDA: 21-529

Name of drug: Implanon (etonogestrel implant), 68 mg Subdermal

Applicant: Organon USA Inc.

Indication: Oral contraceptive for the prevention of pregnancy

Project manager: Karen Anderson (HFD-580)

Date: user fee 10/29/2004

Clinical Team: Barbara Wesley, M.D., Scott Monroe, M.D. (HFD-580)

Reviewer: Moh-Jee Ng, M.S.

Biometrics Team Leader: Mike Welch, Ph.D.

The statistical review was completed and submitted into Division Files System on July 13, 2004. The medical team leader requested additional analyses for women who completed 3 years based on the combined non-U.S. studies.

The upper bounds of the 95% confidence intervals for the Pearl Indices for women who completed 3 years based on the combined non-U.S. studies are summarized in the following table.

Reviewer's analysis for women who completed 3 years based on risk of getting pregnancy in third year only

| | # of women | Total cycle of exposures | # of pregnancy | Pearl Index | Upper bound of the 95% CI * |
|----------------|------------|--------------------------|----------------|-------------|-----------------------------|
| Total | 195 | 2536 | 0 | 0 | 1.87 |
| ≤ 35 years old | 164 | 2123 | 0 | 0 | 2.23 |
| > 35 years old | 31 | 403 | 0 | 0 | 11.23 |

* Confidence intervals are two sided

Tables 1 and 5 in the original statistical review are revised so that the life-table results are given in terms of percentages. Furthermore, the 95% CI for the pearl index for total U.S. and Non-U.S. studies is corrected to (0.06, 0.6) (see the highlighted entries in both tables). The CI's for the life table pregnancy rates are also corrected to reflect a zero lower bound when appropriate.

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Table 1
Reviewer's analyses for women who completed up to 2 years of treatment

| Study | # of women | Total cycle of exposures (Women-years) | # of Pregnancies | Pearl Index (95% CI) | Life-Table Pregnancy Rate (95% CI) |
|---|------------|--|------------------|-----------------------------------|------------------------------------|
| U.S. Study | | | | | |
| 069001 | 330 | 6,105.9 (469.7) | 2 | 0.42 (0.05, 1.5) | 0.7% (0%, 2%) |
| Non-U.S. Studies | | | | | |
| 34505 | 100 | 2,358.8 (181.5) | 0 | 0.00 (0, 2.0) | .* |
| 34507 † | 617 | 13,196.8 (1015.1) | 1 | 0.01 (0, 0.5) | 0.2% (0%, 0.5%) |
| 34507 CDN | 52 | 1,032.6 (79.4) | 1 | 1.26 (0.03, 6.72) | 2% (0%, 7%) |
| Non-U.S. Studies Combined | 769 | 16,587.8 (1,276.0) | 2 | 0.16 (0.02, 0.57) | 0.3% (0%, 0.7%) |
| U.S. & Non-U.S. Studies Combined | | | | | |
| Total | 1,099 | 22,694.7 (1,745.7) | 4 | 0.23 0.06 (0.00, 0.30) | 0.4% (0.01%, 0.8%) |

Source: SAS data

*: no assessment of life-table pregnancy rate due to 0 pregnancies

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Table 5
Reviewer's analyses for women who completed up to 2 years of treatment

| Study | # of women | Total cycle of exposures (Women-years) | # of Pregnancies | Pearl Index (95% CI) | Life-Table Pregnancy Rate (95% CI) |
|---|------------|--|------------------|----------------------|------------------------------------|
| U.S. Study | | | | | |
| 069001 | | | | | |
| Total | 330 | 6,105.9 (469.7) | 2 | 0.42 (0.05, 1.50) | 0.7% (0%, 2%) |
| ≤ 35 year old | 307 | 5,698.4 (438.4) | 2 | 0.68 (0.06, 1.61) | 0.7% (0%, 2%) |
| > 35 year old | 23 | 407.3 (31.3) | 0 | 0.0 (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 (2 years) † | 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 | 0.0 (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 | 0.0 (0, 48.6) | - |
| 3 Non-U.S. studies Combined | | | | | |
| Total | 769 | 16,587.8 (1,276.0) | 2 | 0.16 (0.02, 0.57) | 0.3% (0%, 0.7%) |
| ≤ 35 year old | 640 | 13,660.9 (1,050.8) | 2 | 0.19 (0.02, 0.68) | 0.4% (0%, 0.8%) |
| > 35 year old | 129 | 2,927.4 (225.2) | 0 | 0.0 (0, 1.62) | - |
| U.S. and Non-U.S. Studies Combined | | | | | |
| Total | 1,099 | 22,694.7 (1,745.7) | 4 | 0.23 (0.16, 0.60) | 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 | 0.0 (0, 1.42) | - |

Source: SAS data

*: no assessment of life-table pregnancy rate due to 0 pregnancies

†: 2 centers (B_004 and F_041) excluded from study 34507: 18 women which provided 27.8 woman-years of exposure (362.2 cycles) had been removed from total of exposures non-US studies
grey color marked the change had been made

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Moh-Jee Ng
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Mike Welch
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Concur with review.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-529/N000

Drug Name: Implanon (etonogestrel implant), 68 mg Subdermal

Indication(s): Oral contraceptive for the prevention of pregnancy

Applicant: Organon USA Inc.

Date(s): Received 9/30/03; user fee 7/30/04

Documents Review: Study reports and the data submitted to Electronic Document Room:
\CDSESUB\N21529\N_000\2003-9-30
\CDSESUB\N21529\N_000\2004-3-10

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Moh-Jee Ng, M.S. (HFD-715)

Concurring Reviewers: Michael Welch, Ph.D. (HFD-715)

Medical Division: Division of Reproduction and Urological Drug Products

Clinical Team: Barbara Wesley, M.D., Phill Price, MD., Theresa Van der Vlugt, MD
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Clinical Team Leader: Scott Monroe, M.D. (HFD-580)

Project Manager: Karen Anderson (HFD-580)

Keywords: NDA review, clinical studies

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1. Executive Summary of Statistical Findings

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 (see Table 1). The Pearl indices per 100 women-years 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, 0.2)], 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 0.007 [95% CI: (-0.003, 0.02)], and for Non-U.S. studies are 0.002 [95% CI: (-0.002, 0.005)], and 0.02 [95% CI: (-0.02, 0.07)] for studies 34507 and 34507 CDN, respectively.

Table 1
Reviewer's analyses for women who completed 2 years of treatment

| Study | # of women | Total cycle of exposures (Women-years) | # of Pregnancies | Pearl Index (95% CI) | Life-Table Pregnancy Rate (95% CI) |
|---|------------|--|------------------|----------------------|------------------------------------|
| U.S. Study | | | | | |
| 069001 | 330 | 6,105.9 (469.7) | 2 | 0.42 (0.05, 1.5) | 0.007 (-0.003, 0.02) |
| Non-U.S. Studies | | | | | |
| 34505 | 100 | 2,358.8 (181.5) | 0 | 0.00 (0, 2.0) | .* |
| 34507 † | 617 | 13,196.8 (1015.1) | 1 | 0.01 (0, 0.5) | 0.002 (-0.002, 0.005) |
| 34507 CDN | 52 | 1,032.6 (79.4) | 1 | 1.26 (0.03, 6.72) | 0.02 (-0.02, 0.07) |
| Non-U.S. Studies Combined | 769 | 16,587.8 (1,276.0) | 2 | 0.16 (0.02, 0.57) | 0.003 (-0.001, 0.007) |
| U.S. & Non-U.S. Studies Combined | | | | | |
| Total | 1,099 | 22,694.7 (1,745.7) | 4 | 0.23 (0.006, 0.06) | 0.004 (0.00008, 0.008) |

Source: SAS data

*: no assessment of life-table pregnancy rate due to 0 pregnancies

†: 2 centers (B_004 and F_041) excluded from study 34507: 18 women which provided 27.8 woman-years of exposure (362.2 cycles) had been removed from total of exposures non-U.S. studies

2. Overview of Clinical Studies

Implanon™ is a progestagen-only contraceptive. It is a single rod, non-biodegradable, etonogestrel (ENG, 3-ketodesogestrel) releasing the implant with the specific aim to inhibit ovulation for three years. It is intended for women who are not able to tolerate estrogen, and who seek a long-term, yet reversible, contraceptive.

The sponsor presented 4 studies to evaluate safety and contraceptive efficacy with Implanon™ for 2-4 years of treatment. All studies were open-label, non-comparative and enrolled healthy sexually active women of childbearing potential 18 to 40 years old. Data are available for 2 years of exposure for studies 069001 and 34507 CDN, 3 years of exposure for study 34507, and 4 years of exposure for study 34505. Two other studies, 34506 and 34520, conducted in Indonesian sites were withdrawn by the sponsor (see amendment submitted on May 3, 2004) regarding improprieties that had occurred during the conduct of clinical studies.

For the 4 submitted studies a total of 1,117 women were exposed to Implanon™: 330 women in the U.S. Study with 475 woman-years of use equivalent to 6,186 cycles of exposure, and 787 women in the Non-U.S. studies with 1,579 woman-years of use equivalent to 20,601 cycles of exposure. Table 2 summarizes these 4 studies.

Table 2
Summary of the studies

| | # of sites (Location) | Duration of treatment (Number of women) | | | Extent of exposure | |
|-------------------------|--------------------------|--|------------|-----------|--------------------|--------------|
| | | 0-2 Years | 2-3 Years | 3-4 Years | Cycles | Woman-years |
| U.S. Study | | | | | | |
| 069001 | | 330 | -* | - | 6,186 | 475 |
| Non-U.S. Studies | | | | | | |
| 34505 | 1 (Thailand) | 100 | 68 | 51 | 3,863 | 296 |
| 34507 | 21 (Europe & Chile) | 635 | 147 | - | 15,653 | 1,200 |
| 45507 CDN | 1 (Canada) | 52 | - | - | 1,085 | 83 |
| Non-U.S. studies | | 787 | 215 | 51 | 20,601 | 1,579 |

Source: Table 14 (Integrated summary of efficacy), amendment submitted on May 3, 2004, page 65/103

*: No data available

In the U.S. Study, women aged range from 18 to 40 years of age, with most women between 21-30 years old, and the mean body mass index (BMI) was 23.6 kg/m². In the Non-U.S. studies, women age ranged from 18 to 42 years with means of 26.3, 29.1, and 24.0 years for Studies 34505, 34507 and 34507 CDN, respectively. The mean Body Mass Indices were 21.7, 22.7, and 22.8, for Studies 34505, 34507 and 34507 CDN, respectively.

3. Study Design

3.1 U.S. Study

Study 069001 is a multi-center, open-label, non-comparative, efficacy and safety study of Implanon™ in women who chose to use the contraceptive implant for the prevention of pregnancy. There were 330 women enrolled for 2 years for a total of 475 woman-years which is equivalent to 6,186 cycles of exposure (see Table 2).

3.2 Non-U.S. Studies

The 3 Non-U.S. studies are open-label, non-comparative, efficacy and safety study of Implanon™ in women who chose to use the contraceptive implant for the prevention of pregnancy.

Study 34505 enrolled 100 women for 2 years. The study was then extended up to 4 years of treatment and a total of 296 woman-years of use equivalent to 3,863 cycles of exposure (see Table 2).

Study 34507 enrolled 635 women for 2 years. The study was then extended to 3 years, for a total of 1,200 woman-years (15,653 cycles) of exposure (see Table 2). The sponsor reported in an amendment (May 3, 2004) that 2 centers (B_004 and F_041) did not sufficiently comply with GCP standards. These 2 centers which enrolled 18 women with 27.8 woman-years of exposure (362.2 cycles) have been excluded from this review.

Study 34507 CDN enrolled 52 women for 2 years for a total of 83 woman-years which is equivalent to 1,085 cycles of exposure (see Table 2).

3.3 Statistical and Analytical Plans

Contraception effectiveness was based on the occurrence of pregnancies in the All-Women-Treated Group (ASTG). ASTG includes all women who are implanted with Implanon™ but excludes the above mentioned 18 women noncompliant with GCP standards. Contraceptive efficacy was determined by Pearl Indices and Life-Table Pregnancy Rate analyses. The endpoints of interest for both analyses are 2 years cumulative treatment, between the second and third year cumulative treatment, and 3 years cumulative treatments.

The Pearl Index (per 100 women-years) is defined as the number of pregnancies times 1300 divided by the total number of exposure cycles. The Life-Table Pregnancy Rate used SAS procedure Lifetest to estimate the probability of pregnancies in a fixed time period for in-treatment pregnancy women.

3.4 Data Sources

The documents and SAS data sets were submitted electronically and were on server location at \\cdsesub1\N21529\N_000\2003-9-30.

4. Study Results

4.1 Subject Enrollment, Randomization and Disposition

Table 3 summarizes the number of randomized women and the disposition of treated women. A total of 161 women (49%) discontinued from study 069001 and the primary reason for study discontinuation is adverse experience (23%). Study 34507 has the percentage of women (17.3%) with bleeding irregularities.

Table 3
Subject disposition

| | 69001 | 34505 | 34507 | 34507 CDN |
|-----------------------------------|-----------|----------|-------------|-----------|
| Number of women randomized | 330 | 100 | 636 | 52 |
| Discontinued: | 161 (49%) | 32 (32%) | 209 (33%) | 19 (37%) |
| Adverse experience | 76 (23%) | 5 (5%) | 59 (9.3%) | 5 (9.6%) |
| Amenorrhoea | .* | 1 (1%) | 11 (1.7%) | - |
| Bleeding irregularities | 43 (13%) | 6 (6%) | 110 (17.3%) | 7 (13.5%) |
| 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%) |

Source: Protocol 069001 (Table 4), Protocol 34505 (Table 5), Protocol 34507 (Table 6), & Protocol 34507 CDN (Table 6)

*: No data available

4.2 Sponsor's Efficacy Results and Conclusions

Pregnancies were categorized as those that occurred pre-treatment (prior to implant insertion), in-treatment (with implant in place), and post-treatment (after removal of implant). If pregnancy was confirmed, the implant was to be removed and the date of conception was to be sought from the subject. The sponsor reported that no in-treatment pregnancies occurred in any of the 4 studies.

There were 4 pre-treatment pregnancies for study 34507, and 2, 6, 11, and 24 post-treatment pregnancies for studies 34507 CDN, 34505, 069001 and 34507, respectively (see Table 4). The sponsor concluded that for the combined 4 studies with 1,117 women who were treated with Implanon™ for a total of 26,787 cycles of exposure (2,054 woman-years), the Pearl Index was 0 [95% CI: (0, 0.18)]. The sponsor claimed that all 4 studies demonstrated that Implanon™ provides good contraceptive reliability, as there were no in-treatment pregnancies during a total of 26,787 cycles of exposure.

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Table 4
Summary sponsor's efficacy endpoints

| Study | Total # of women | Total cycle of exposures | Total exposures in women-year | Pre-Treatment pregnancy | In-Treatment pregnancy | 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 | | | | | | | |
| | 1,117 | 26,787 | 2,054 | 4 | 0 | 43 | 0 (0, 0.18) |

*: two-sided 95% confidence intervals computed by reviewer.

4.3 Reviewer's Efficacy Results

The medical reviewer requested this reviewer to include post-treatment pregnancies conceived within 14 days after discontinuation of study drug. There were 4 additional post-treatment pregnancies (see Table 8 in Appendix). Efficacy is based on the Pearl Index (PI) and Life Table Pregnancy Rate with 95% confidence intervals (CIs). This reviewer used SAS Proc Lifetest procedure to estimate the pregnancy rate. The efficacy results are reported as follows: 2 years cumulative treatment, between the second and third year cumulative treatment, and 3 years cumulative treatment.

4.3.1 Efficacy Results for women who completed 2 years of treatment

Table 5 summarizes efficacy results for women who completed 2 years cumulative treatment. This summary consists of data for all study women up to day 730. This reviewer included 2 pregnancies in the U.S. study and 2 pregnancies in the Non-U.S. studies. The Pearl Indices per 100 women-years for the U.S. study is 0.42 [95% CI: (0.05, 1.5)], and the Non-U.S. studies are 0 [95% CI: (0, 0.2)], 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 0.007 [95% CI: (-0.003, 0.02)], and for Non-U.S. studies are 0.002 [95% CI: (-0.002, 0.005)], and 0.02 [95% CI: (-0.02, 0.07)] for studies 34507 and 34507 CDN, respectively

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Table 5
Reviewer's analyses for women who completed 2 years of treatment

| Study | # of women | Total cycle of exposures (Women-years) | # of Pregnancies | Pearl Index (95% CI) | Life-Table Pregnancy Rate (95% CI) |
|---|------------|--|------------------|----------------------|------------------------------------|
| U.S. Study | | | | | |
| 069001 | | | | | |
| Total | 330 | 6,105.9 (469.7) | 2 | 0.42 (0.05, 1.50) | 0.007 (-0.003, 0.02) |
| ≤ 35 year old | 307 | 5,698.4 (438.4) | 2 | 0.68 (0.06, 1.61) | 0.007 (-0.003, 0.02) |
| > 35 year old | 23 | 407.3 (31.3) | 0 | 0.0 (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 (2 years) † | 617 | 13,196.8 (1012.2) | 1 | 0.01 (0, 0.5) | 0.002 (-0.002, 0.005) |
| ≤ 35 year old | 497 | 10,495.8 (807.4) | 1 | 0.12 (0, 0.006, 0.7) | 0.002 (-0.002, 0.007) |
| > 35 year old | 120 | 2,700.9 (207.8) | 0 | 0.0 (0, 1.75) | - |
| 34507 CDN | | | | | |
| Total | 52 | 1,032.6 (83.5) | 1 | 1.26 (0.03, 6.72) | 0.02 (-0.02, 0.07) |
| ≤ 35 year old | 51 | 1,006.6 (77.4) | 1 | 1.29 (0.03, 6.88) | 0.02 (-0.02, 0.07) |
| > 35 year old | 1 | 26.1 (2.0) | 0 | 0.0 (0, 48.6) | - |
| 3 Non-U.S. studies Combined | | | | | |
| Total | 769 | 16,587.8 (1,276.0) | 2 | 0.16 (0.02, 0.57) | 0.003 (-0.001, 0.007) |
| ≤ 35 year old | 640 | 13,660.9 (1,050.8) | 2 | 0.19 (0.02, 0.68) | 0.004 (-0.001, 0.008) |
| > 35 year old | 129 | 2,927.4 (225.2) | 0 | 0.0 (0, 1.62) | - |
| U.S. and Non-U.S. Studies Combined | | | | | |
| Total | 1,099 | 22,694.7 (1,745.7) | 4 | 0.23 (0.006, 0.06) | 0.004 (0.00008, 0.008) |
| ≤ 35 year old | 947 | 19,360.0 (1489.2) | 4 | 0.27 (0.08, 0.69) | 0.005 (0.0001, 0.009) |
| > 35 year old | 152 | 3,334.6 (256.5) | 0 | 0.0 (0, 1.42) | |

Source: SAS data

*: no assessment of life-table pregnancy rate due to 0 pregnancies

†: 2 centers (B_004 and F_041) excluded from study 34507: 18 women which provided 27.8 woman-years of exposure (362.2 cycles) had been removed from total of exposures non-US studies

4.3.2 Efficacy Results between the second and third year cumulative treatment

Table 6 summarizes non-U.S. studies classified by Implanon™ exposure between the second and third year of treatment. This summary data considers all women with total treatment exposure from 731 up to 1081 days.

There were no pregnancies for studies 34505 and 34507. For the combined non-U.S. studies, there are 426 women with 218.8 woman-years equivalent to 2,844.4 cycles of exposure. The Pearl index per 100 women-years is 0 [95% CI: (0, 1.7)].

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Table 6
Reviewer's analyses for women between the second and third year cumulative treatment

| 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 (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) |

Source: SAS data

*: 2 centers (B_004 and F_041) excluded from study 34507

4.3.3 Efficacy Results for women who completed 3 years of treatment

Table 7 summarizes the non-U.S. studies for those women who completed 3 years of treatment. These data consist of all women with total treatment exposures up to 1460 days. The total numbers of women exposed for 3 years of treatment were 195 instead of 197 as listed from the sponsor.

There were no pregnancies for studies 34505 and 34507. For combined non-U.S. studies, there are 195 women with 586.2 woman-years which is equivalent to 7,620.2 cycles of exposure. The Pearl index per 100 women-years is 0 [95% CI: (0, 0.62)].

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Table 7
Reviewer's analyses for women who completed 3 years of treatment

| Study | # of women | Total cycle of exposures (Women-years) | # of Pregnancies | Pearl Index (95% CI) |
|----------------------------------|------------|---|---------------------|-------------------------|
| Non-U.S. Studies | | | | |
| 34505 | | | | |
| Total | 59 | 2,306.8 (177.5) | 0 | 0 (0, 2.01) |
| ≤ 35 year old | 52 | 2033.2 (156.4) | 0 | 0 (0, 2.28) |
| > 35 year old | 7 | 273.6 (21.1) | 0 | 0 (0, 13.6) |
| 34507 | | | | |
| Total * | 136 | 5,313.4 (408.7) | 0 | 0 (0, 0.89) |
| ≤ 35 year old | 112 | 4,375.9 (336.6) | 0 | 0 (0, 1.08) |
| > 35 year old | 24 | 937.5 (72.1) | 0 | 0 (0, 4.74) |
| Non-U.S. Studies Combined | | | | |
| Total | 195 | 7,620.2 (586.2) | 0 | 0 (0, 0.62) |
| ≤ 35 year old | 164 | 6,409.1 (493.0) | 0 | 0 (0, 0.74) |
| > 35 year old | 31 | 1,211.1 (93.2) | 0 | 0 (0, 3.73) |

Source: SAS data

*: 2 centers (B_004 and F_041) excluded from study 34507

4.4 Conclusions

The effectiveness of Implanon™ in the prevention of pregnancy has been demonstrated for women who completed 2 years of treatment. 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. The Pearl Indices per 100 women-years for the U.S. study is 0.42 [95% CI: (0.05, 1.5)], and the Non-U.S. studies are 0 [95% CI: (0, 0.2)], 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 0.007 [95% CI; (-0.003, 0.02)], and for Non-U.S. studies are 0.002 [95% CI: (-0.002, 0.005)], and 0.02 [95% CI: (-0.02, 0.07)] for studies 34507 and 34507 CDN, respectively.

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5 Appendices

Table 8
Pregnancies conceived within 14 days after discontinuation of study drug

| Study | Subject # | Age | BMI | Weight kg | Height cm | Treatment Duration –days Cycle) | Estimated day of conception* |
|----------|-----------|-----|-----|--------------|--------------|------------------------------------|---------------------------------|
| 069001 | 05014 | 27 | 24 | 69.5 | 170.2 | 172 (7) | 7 |
| | 10017 | 19 | 25 | 58.1 | 152.4 | 100 (4) | 6 |
| 34507 | 00550 | 21 | 29 | 78.0 | 164.0 | 198 (8) | 14 |
| 34507CDN | 00864 | 23 | 20 | 54.0 | 165.0 | 232 (9) | 7 |

*: Days after Implant removal

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