Original research article

Safety and efficacy of Implanon™, a single-rod implantable contraceptive containing etonogestrel

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Received 14 October 2004; revised 9 November 2004; accepted 11 November 2004

Abstract

Objectives: The safety and efficacy of a single-rod implantable contraceptive containing etonogestrel (Implanon™) were investigated in a multicenter clinical trial.

Study Design: Sexually active American women (N=330) with apparently normal menstrual cycles used the implant for up to 2 years. All subjects recorded bleeding and/or spotting daily in a diary. Safety was assessed through adverse experiences (AEs), laboratory tests and physical and gynecologic examinations.

Results: Total exposure was 474 woman-years (6186 cycles), and 68% of subjects had at least 1 year of exposure. No pregnancies occurred. The most common bleeding pattern observed throughout the study was infrequent bleeding, defined as less than three episodes of bleeding in a reference period (excluding amenorrhea). The least common pattern was frequent bleeding, defined as more than five episodes of bleeding in a reference period. Infrequent, prolonged and frequent bleeding patterns were most common early in the study and declined thereafter. During the 3-month Reference Periods 2–8 (Months 4–24), the incidence of amenorrhea ranged from 14% to 20%. Forty-three subjects (13%) withdrew from the study because of bleeding pattern changes and 76 subjects (23%) discontinued because of other AEs. Other common AEs leading to discontinuation, besides bleeding irregularities, were emotional lability (6.1%), weight increase (3.3%), depression (2.4%) and acne (1.5%). Use of Implanon (etonogestrel subdermal implant, referred to herein as ENG implant) for up to 2 years had no clinically significant effects on laboratory parameters, physical and pelvic examinations, vital signs or body mass index. The average length of time required for ENG implant insertion and that for removal were 0.5 and 3.5 min, respectively, and all the procedures were uncomplicated. The return to normal menstrual cycles and fertility was rapid after removal.

Conclusions: Implanon is a safe, highly effective and rapidly reversible new method of contraception.

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Keywords: Implanon; Etonogestrel subdermal implant; ENG implant; 3-ketodesogestrel; Contraceptive implant; Contraceptive efficacy; Safety; Side effects; Bleeding

1. Introduction

Implanon™ (manufactured for Organon USA Inc., West Orange, NJ, by N.V. Organon, Oss, The Netherlands) is a single-rod, nonbiodegradable implantable contraceptive that contains the progestin etonogestrel. It has been used widely throughout the world (Europe, Australia and Indonesia), providing contraceptive protection for up to 3 years when inserted subdermally [1–3]. Etonogestrel, the active metabolite of desogestrel, is a progestin with a well-established safety and efficacy profile [2] that is also used in a contraceptive etonogestrel/ethinyl estradiol vaginal ring...
NuvaRing®, Organon USA Inc.). Early dose-finding studies showed that a release rate of 25–30 µg/day of etonogestrel is required to suppress ovulation [4,5]. The etonogestrel in Implanon is released at an initial rate of approximately 60–70 µg/day, which slowly decreases over time to about 30 µg/day [6]. This rate of release results in sufficiently high plasma levels of the progestin to inhibit ovulation and provide effective contraception for up to 3 years [7].

Previous studies with the etonogestrel subdermal implant, referred to herein as ENG implant, suggested that it was easy to insert and remove [8,9] and that it was effective in preventing pregnancy [2]. Bleeding pattern changes, usually amenorrhea or infrequent bleeding, occurred in a high proportion of women in all clinical studies [10]. Adverse events that have been reported (including weight gain, mood swings/depression, headache, acne and decreased libido) are known to occur with progestin-only contraceptives [11–13]. We present in this paper the results of a large multicenter study designed to assess the safety and efficacy of the ENG implant in American women who used the implant for up to 2 years.

2. Materials and methods

2.1. Subjects

Healthy, sexually active female volunteers between the ages of 18 and 40 years were eligible to participate in this study if they were within 80% to 130% of their ideal body weight and had apparently normal menstrual cycles. A subject was excluded from participation for any of the following reasons: use of an injectable hormonal method of contraception within the preceding 6 months or other hormonal contraceptives within the preceding month; removal of an implantable contraceptive within the preceding 2 months; delivery, abortion or miscarriage within 1 month prior to study entry; at age 35 years or older with a history of smoking; currently pregnant or lactating; history of ectopic pregnancies; presence or a history of major gynecologic disorders; disturbance of liver function; hyperlipoproteinemia; hypertension; or a cervical Papanicolaou (Pap) smear of Class III, IV or V at screening. Subjects were told not to use sex steroids, hydantoins, barbiturates, primidone, carbamazepine, rifampin or griseofulvin during the study. Contraceptive drugs or devices other than the study medication could not be used, except that the use of condoms by the subject or her partner for prophylaxis of sexually transmitted diseases was permitted. The study plan was approved by local institutional review boards, and each subject signed an informed consent form after the purpose and conduct of the study were explained to her.

2.2. Treatment

The ENG implant, 4 cm in length and 2 mm in diameter, was used in this open-label clinical trial. The single rod consists of an ethylene vinylacetate (EVA) copolymer core, containing 68 mg of etonogestrel, surrounded by a rate-limiting EVA copolymer membrane. The ENG implant was inserted subdermally in the medial aspect of a subject’s upper nondominant arm, 6–8 cm above the elbow in the groove between the biceps and triceps (sulcus bicipitalis medialis), using a specially designed preloaded disposable applicator (Fig. 1). The ENG implant was to remain in place for the duration of the study. For removal of the ENG
implant, a small amount of local anesthetic was applied under the implant, a 2- to 3-mm incision was made over the distal tip of the rod and the implant was gently pushed toward the incision until the tip was visible. The sheath surrounding the implant was incised and the bare rod was then grasped with fingers or forceps and removed. If the implant could not be pushed into the incision, closed forceps were inserted to gently dissect the tissues around the implant and free it for removal. It has been found that a fibrous capsule generally forms around contraceptive implants, which in some cases must be either sharply or bluntly dissected in order to free the rod and allow for removal.

2.3. Assessments

The screening assessment included recording of medical, gynecologic and drug histories; physical and gynecologic examinations; serum β-hCG and urine pregnancy tests; and routine blood and urine laboratory tests. Blood chemistry and enzyme analyses included sodium, potassium, chloride, phosphorus, calcium, glucose, BUN, uric acid, creatinine, alkaline phosphatase, total bilirubin, SGOT (AST), SGPT (ALT), SGGT, total protein, LDH, total cholesterol and triglycerides. Hematology assessments included hemoglobin, hematocrit, RBC, WBC and differentials and platelet (absolute) count. In addition, dipstick urinalysis was conducted to determine pH, protein, ketones, glucose and the presence of white blood cells.

If a subject met all inclusion and exclusion criteria, she returned to the clinic between Days 1 and 5 after beginning her next menses to have the ENG implant inserted. At the time of insertion, each subject was given diary cards where she could record the presence of uterine bleeding or spotting on a daily basis. Each subject returned to the clinic at 3-month intervals (including 3 months after the implant was removed) for review of daily diaries, recording of concomitant medications and reporting of adverse experiences (AEs). If a diary card showed that no uterine bleeding or only spotting had occurred in the 45 days preceding a clinic visit, a serum pregnancy test was performed. The subject concerned was to return to the clinic immediately for removal of the ENG implant if pregnancy was confirmed.

Measurements of vital signs, body weight and routine blood and urine laboratory tests (12-h fasting samples) were performed periodically during the 2-year study [at screening and at Visit Months 6, 12, 18 and 24 (or at end of study)]. Physical and gynecologic examinations were repeated at 12 and 24 months (or at the last visit if the subject did not complete 24 months of treatment). A subgroup of 20 subjects had ophthalmologic evaluations at screening and at 12 and 24 months (or at the last visit). The ophthalmologic evaluations included ocular complaints, visual acuity, refraction, external examination, slit lamp examination, lens examination and ophthalmoscopy.

The times required for insertion and removal (excluding administration of anesthetics) were recorded. An observer timed the insertion procedure from the time at which the tip of the needle of the applicator was placed into the skin until the needle was removed. An observer timed the removal procedure from the time when the incision was made until the ENG implant was removed.

2.4. Statistical methods

Since this study was an open-label single-treatment study to assess safety, efficacy and bleeding pattern data, no comparative statistical analysis was undertaken. The All-
Subjects-Treated Group was defined as all subjects who had the ENG implant inserted. The reasons for discontinuation were evaluated using the competing risk method [14]. This method allowed for the estimation of rates for each specific type of adverse event (e.g., discontinuation due to bleeding pattern changes, other medical problems, protocol violations or other reasons).

Uterine bleeding data were examined using a Reference Period Analysis [15,16]. For this analysis, each subject’s diary data were divided into consecutive periods of 90 days each (called reference periods). A subject had to have contributed a minimum of one reference period of 90 consecutive days of diary information to be included in the analysis.

3. Results

3.1. Subject characteristics

Three hundred thirty subjects from the United States participated in the study (Table 1). Most subjects were younger than 35 years. Prior to the start of the study, 37% of subjects had never been pregnant, 23% had one previous pregnancy, 23% had two previous pregnancies and the rest of the subjects had three or more pregnancies. The mean length of the menstrual cycle (28.4 days) and the mean duration of bleeding (4.5 days) were considered normal at screening. The most common methods of contraception prior to study entry were nonsteroidal contraceptives (foam, condom, suppositories or diaphragm).

3.2. Extent of exposure

A total of 330 subjects used the ENG implant for a total of 474 woman-years (365.25 days/year), equivalent to 6186 cycles (28 days/cycle). The average exposure was 530 days (19 cycles). Two hundred twenty-six subjects (68%) were exposed to study medication for at least 1 year and 169 subjects (51%) completed the entire 2-year study period.

A total of 161 subjects (49%) did not complete the entire 2-year study period (Fig. 2). The most common reasons for discontinuation were bleeding pattern changes ($n=43; 13.0\%$) and other types of AEs ($n=76; 23.0\%$). One subject (0.3%) was withdrawn because of an intercurrent illness, 4 subjects (1.2%) were classified by the investigator as protocol violators, 8 (2.4%) were unwilling to continue (reasons not divulged) and 29 (8.8%) were withdrawn for other reasons. The rate of discontinuation due to AEs was highest during the first 8 months of the study and declined thereafter.

3.3. Efficacy

No subject became pregnant while the ENG implant was in place. Posttreatment information provided by subjects showed that 46 subjects were not using any contraceptive method following ENG implant removal. Of these 46 women, 11 subjects became pregnant between 1 and 18.5 weeks after removal of the implant. The conception date in all 11 cases was after the date of ENG implant removal based on results of ultrasound and/or blood tests for $\beta$-hCG.

![Fig. 2. Disposition of subjects in the study.](image-url)
3.4. Implant insertion and removal

The mean time required to insert the ENG implant was 0.5 min (range, 0.05–15 min) and the mean time required to remove the implant was 3.5 min (range, 0.2–60 min). No insertion site complications were reported in relation to either insertion or removal in most subjects. Implant removal was difficult in only two subjects (1%), one who required three attempts to locate the implant and one whose implant had broken into two pieces during the removal attempt. In the latter case, a 1-cm piece of the implant broke off during the removal, allowing only partial removal. The remainder of the ENG implant was removed on the second attempt, which required 4 min.

3.5. Uterine bleeding patterns

Table 2 and Fig. 3 summarize uterine bleeding patterns by reference period and display the incidence of clinically important bleeding patterns, respectively. A total of 43 subjects (13%) discontinued as a result of bleeding irregularities as their primary AE. The number of subjects who discontinued as a result of bleeding irregularities was highest in the first 8 months of the study and declined thereafter. As shown in Table 2, the mean number of days with bleeding or spotting, number of bleeding–spotting episodes, length of bleeding–spotting episodes and length of bleeding-free intervals were all highest during Reference Period 1 (Months 1–3). During the remainder of the study, the mean number of bleeding–spotting episodes was fairly constant, approximately three per reference period. The mean number of days with bleeding or spotting and the length of bleeding–spotting episodes decreased consistently over time. Likewise, the percentage of subjects with prolonged bleeding episodes and that of those with frequent bleeding episodes were greatest during Reference Period 1 (36% and 14%, respectively) and then decreased during the subsequent reference periods (14% and 7%, respectively, in Reference Period 8). Because the ENG implant was inserted during a bleeding episode, the percentage of subjects with amenorrhea was very low in Reference Period 1 (2%) but ranged from 14% to 20% in Reference Periods 2–8.

3.6. Adverse experiences

Two hundred eighty-two subjects (86%) reported one or more treatment-emergent AEs during the 2-year study. Table 3 displays all the AEs that were reported by 10% or more of the subjects in the study. The most commonly reported AEs were headache, vaginitis, acne, dysmenorrhea, emotional lability, upper respiratory tract infection, weight increase, depression and urinary tract infection. Most of the reported AEs were rated mild or moderate. In addition, the most common AEs leading to discontinuation (apart from bleeding irregularities) were emotional lability, weight increase, depression and acne. A total of 10 subjects reported serious AEs; two of these serious AEs were considered by the investigator to be possibly related to the study drug (one ruptured ovarian follicle and one acute exacerbation of depression).
3.7. Condition of implant site over time

No abnormalities at the implant site were noted by investigators during any of the scheduled visits for the great majority of subjects (>97%). No expulsion, hematoma or swelling occurred at the implant site in any subject during the entire study period (up to 2 years of use). Pain and redness at the insertion site were transient and intermittent in nature. Redness at the insertion site was observed in the same subject at Visit Months 12, 15 and 18. Pain was occasionally reported on the implant acceptability form. Minor pain at the site was intermittent and limited to a small number (<2.5%) of subjects. Minor pain was experienced by three subjects each at Visit Months 3, 6 and 21, by two each at Visit Months 9 and 15 and by five at Visit Month 12. None of the participants complained of pain at Visit Months 18 and 24. There was only one subject who experienced pain both at Visit Months 9 and 12; the rest of the subjects experienced pain only once during each 3-month period.

3.8. Acne

Three hundred fifteen subjects provided baseline and postbaseline acne information. About the same percentage of subjects had acne at the baseline and postbaseline observations: 26.7% had it at baseline and 23.8% had it at postbaseline. The shift from baseline to the last assessment in the occurrence of acne showed that 51 subjects (16%) reported decreased acne, 221 (70%) reported no change and 43 (14%) reported increased acne. Of those subjects who did not have acne at baseline (n=231), 195 (84%) subjects reported no change, whereas 36 (16%) reported increased acne (Fig. 4). Of those subjects who had acne at baseline (n=84), 51 (61%) reported decreased acne, 26 (31%) reported no change and only 7 (8%) reported increased acne (Fig. 5).

3.9. Dysmenorrhea

Three hundred fifteen subjects provided baseline and postbaseline dysmenorrhea information. The percentage of subjects with dysmenorrhea at baseline was almost three times that observed at postbaseline: 59% had it at baseline and 21% had it at postbaseline. An analysis of the shift from baseline to the last assessment showed that 151 (48%) subjects reported decreased dysmenorrhea, 139 (44%) reported no change and only 25 (8%) reported an increase in dysmenorrhea. Of those subjects who had dysmenorrhea at baseline (n=187), 151 (81%) reported decreased dysmenorrhea, 26 (14%) reported no change and only 10 (5%) reported increased dysmenorrhea (Fig. 6).

Table 3
Summary of most common AEs

<table>
<thead>
<tr>
<th>AE</th>
<th>Subjects, total [n (%)]</th>
<th>Subjects, related to study medication [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>78 (23.6)</td>
<td>42 (12.7)</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>56 (17.0)</td>
<td>8 (2.4)</td>
</tr>
<tr>
<td>Acne</td>
<td>55 (16.7)</td>
<td>48 (14.5)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>50 (15.2)</td>
<td>32 (9.7)</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>48 (14.5)</td>
<td>47 (14.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>44 (13.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Weight increase</td>
<td>42 (12.7)</td>
<td>40 (12.1)</td>
</tr>
<tr>
<td>Depression</td>
<td>33 (10.0)</td>
<td>24 (7.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>33 (10.0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Adverse experiences that occurred in 10% or more of the subjects.

b Considered to be definitely, probably or possibly related to the study medication by the investigator.
3.10. Gynecologic examination

All subjects had a cervical Pap smear Class I or II at baseline and at the final evaluation with the exception of one subject. Four subjects had Class III Pap smear results at the 1-year evaluation. A subsequent evaluation revealed normal results (Class I) for two of the four subjects. The third subject, whose 1-year evaluation showed a low-grade squamous intraepithelial lesion, was withdrawn from the study at that time because of the dysplasia, which was judged by the investigator to be unrelated to the study drug. The fourth subject had atypical cells but no sign of malignancy at the 2-year evaluation. No subjects had Class IV or V results.

Most subjects had normal pelvic examinations at the last measurement (85%). The abnormal pelvic examination findings in most cases reflected the presence of mild vaginitis and associated cervical inflammation. Breast examinations revealed no notable changes in nipple discharge or contour and no abnormalities in overlying skin. In fact, there was an improvement in breast nodularity as more subjects had decreases from baseline to the last measurement and no subject had increased nodularity either at baseline or at the last measurement. Four subjects had breast masses at final evaluation, which were not present at baseline examination (one of which was diagnosed as carcinoma considered by the investigator as unlikely to be related to the study drug).

3.11. Other safety parameters

Changes in mean values from baseline to Visits 12, 24 and the last measurement for most laboratory parameters (SGOT/AST, SGPT/ALT, GGT, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, creatinine, glucose, phosphorus, sodium, potassium, uric acid and total protein) were not clinically significant. The only notable change in laboratory test results, observed at least once during the 2-year study, was a decrease in triglycerides and total cholesterol, observed in 33% and 21% of the subjects, respectively. Mean percent change from baseline to the final evaluation for these parameters was −16% and −4%, respectively. Mean LDH levels did not change during the study.

The mean systolic as well as the diastolic blood pressure showed a decrease from baseline at all time points; however, these changes did not meet predefined criteria for clinical significance and were not clinically meaningful. The changes in heart rate and body mass index were also not clinically meaningful. The mean increase in body mass index from baseline to the last measurement was 0.7 kg/m². There were no clinically significant changes in physical examination results. Ophthalmologic examinations revealed no clinically significant findings in the subset of 20 subjects who underwent gross external examinations, slit lamp examinations and ophthalmoscopy.

3.12. Posttreatment evaluation

Posttreatment information was available for 282 (85%) of the 330 subjects in the study. Two hundred forty-eight (88%) of the 282 subjects who were evaluated 3 months after ENG implant removal reported that their menses had returned to normal. There were 279 subjects who provided information concerning the use of contraceptives after ENG implant removal; of these, 108 subjects (39%) were using hormonal contraceptives (oral, implanted or injectable), 125 (45%) were using nonhormonal contraceptives and the remaining 46 (17%) were not using contraceptives. Of these 46 women who were not using any contraceptive method following implant removal, a total of 11 women became pregnant between 7 and 131 days following the removal of Implanon.

4. Discussion

This study provides clear evidence of the safety and efficacy of the single-rod implantable contraceptive containing etonogestrel, Implanon. The study was sufficient in size and duration of treatment to allow these conclusions to be drawn. The 330 women who participated in the study had a total exposure of 6186 cycles (equivalent to 474 woman-years of use). Most of the subjects (68%) remained in the study for at least 1 year.

There were no pregnancies while ENG implant was being used, confirming the high efficacy rates reported in other studies [2,7,17]. The return to normal menstrual cycles (88% of subjects) and to fertility (as indicated by posttreatment pregnancies) following removal of the ENG implant was rapid. Previous studies indicated that etonogestrel does not accumulate in the body [6] and that ovulation resumes promptly in more than 90% of subjects within 3 weeks of removal [2,7]. Insertion and removal of the ENG implant in this study were usually fast and uncomplicated and on average took less than 1 and 4 min, respectively.

Uterine bleeding pattern changes were common, as expected with a progestin-only contraceptive [1]. The incidence of clinically important bleeding patterns such as prolonged and frequent bleeding was highest during the first 3 months of the study. The most common bleeding pattern observed throughout the study was infrequent bleeding and the least common was frequent bleeding. The incidence of amenorrhea ranged from 14% to 20% in Reference Periods 2–8 (Months 4–24). Bleeding pattern changes led to premature discontinuation of treatment in 43 subjects (13%). The rate of withdrawal for this reason was highest during the first 8 months. In order to improve acceptance and continued use of the implant, counseling prior to insertion of the implant should include such topics as advantages, disadvantages and the management of side effects, with a strong emphasis on the expected changes in bleeding patterns [18].

A total of 119 subjects (36%) did not complete the study as a result of AEs; 43 subjects (13%) discontinued as a result of bleeding irregularities and 76 subjects (23%) discontinued as a result of other AEs. The most commonly reported AEs, observed in 10% to 24% of subjects, were
headache, vaginitis, acne, dysmenorrhea, emotional lability, upper respiratory tract infection, weight increase, depression and urinary tract infection. Many of these are known side effects of hormonal contraception and of progestin contraceptive methods, in particular [1,11,12]. In addition, most subjects, whether they reported having acne at baseline or not, reported either decreased acne at endpoint or no change in their acne condition. Similarly, most subjects reported either decreased dysmenorrhea or no change at endpoint, with less than 10% of subjects reporting an increase in their dysmenorrhea at endpoint.

Use of the ENG implant for up to 2 years had no clinically meaningful effects on laboratory parameters, physical and pelvic examinations, vital signs or body mass index. Only one subject (0.3%) had a Class III Pap smear at the end of treatment. All other subjects had Class I or II results both at baseline and at the final evaluation. Similarly, most studies report no clinically meaningful changes in laboratory parameters in women using progestin-only oral contraceptives or the six-capsule levonogestrel implant system (Norplant, Wyeth, Philadelphia, PA, USA) [11].

The advantages of the ENG implant (Implanon) over other contraceptive methods include excellent safety and efficacy, rapid onset and long duration of action and rapid return to fertility after removal of the implant. Furthermore, the subdermal route of administration of the active progestin etonogestrel eliminates the hepatic first-pass effect, allowing lower overall doses to be used and avoiding the high steroid peak plasma levels associated with oral administration. The results of this study suggest that Implanon provides these advantages in addition to the added advantages of easy insertion and removal.

Acknowledgments

This study was sponsored by Organon Pharmaceuticals USA Inc., Roseland, NJ. Writing and editorial support were provided by Lena S. Shapiro, PhD.

Appendix A. The Implanon™ US Study Group

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