

PN-ACA-590

93971

PHASE II-A PHARMACOKINETIC EVALUATION
OF BIODEGRADABLE NORETHINDRONE PELLET IMPLANTS

Study: 890
Centers: 908/952

FINAL REPORT
February 6, 1996

Family Health International
Research Triangle Park, NC 27709

A

FHI Staff Responsible for Document

Document title: Phase II-A Pharmacokinetic Evaluation of Biodegradable Norethindrone Pellet Implants

Date issued: February 6, 1996

This report was prepared by the following FHI staff based on listings, tables, and analyses generated by the Biostatistics Division.

Project Manager and Clinician: Elizabeth Raymond. 2/21/96
Elizabeth Raymond, Date
Associate Medical Director

The report was reviewed and approved by the following:

Director, Biostatistics: Rosalie Dominik 2/22/96
Rosalie Dominik, Director Date
Biostatistics

Director, Clinical Trials: Laneta G. Dorflinger 2/26/96
Laneta Dorflinger, Director Date
Clinical Trials

Director, Regulatory Affairs: Diane Campen 2-29-96
Diane Campen, Director, Date
Regulatory Affairs

Senior Vice President: Alan Corbin 2/29/96
Alan Corbin, Date
Senior Vice President,
Research and Development

B

ACKNOWLEDGEMENTS

FHI would like to acknowledge the following individuals for their work on this study:

Eastern Virginia Medical Center

David F. Archer, MD, Principal Investigator
Freedolph D. Anderson, MD, Investigator
Jay M. Baker, MD, Clinician
Susan P. Barr, MSN, FNP, Clinician
Theresa Abercrombie, BSN, RN, Study Coordinator
Lynn Marie Eigelsbach, MSN, RN, Study Coordinator
Barbara Ross, BSN, RN, Study Coordinator
Rebecca Bennett, Laboratory Assistant

Cornell University Medical Center

Mukul Singh, MD, Principal Investigator
Brij Saxena, PhD, Investigator
William J. Ledger, MD, Investigator

Hormone Assay Laboratory, Jones Institute for Reproductive Medicine

Robert F. Williams, PhD, Core Laboratory Director
Michelle Billeter, Research Assistant, Interim Manager
Barbara Atkinson, Manager
Mary Beth Southern, Manager
Deborah Leete, Research Assistant
Suzanne Westbrook, Research Assistant
Estella Jones, Research Assistant

EXECUTIVE SUMMARY

This study evaluated the contraceptive efficacy, pharmacokinetics, pharmacologic effects, and safety of two formulations of Annuelle® subcutaneous biodegradable norethindrone (NET)/cholesterol pellets: a 4-pellet system containing 174 mg NET, and a 5-pellet system containing 266.5 mg NET. The study included 39 women who were followed for up to 39 months after pellet insertion.

No pregnancies were observed in a total of 293 woman-months of use in the 4-pellet group and 375 woman-months in the 5-pellet group. The safety profile exhibited by both formulations was excellent. No serious adverse events were reported that were considered to be related to the study product. As with other long-acting progestin contraceptives, the main side effect was bleeding abnormalities, which occurred in most participants and persisted in half for at least two years. However, only two participants discontinued for this reason. Pellet insertion and removal were, in general, technically simple and uncomplicated procedures.

Analysis of mean serum NET levels in both groups combined showed an initial burst in the first week post-insertion followed by a steady decline over the next three years. Mean levels were higher in the 5-pellet group than in the 4-pellet group. NET levels varied substantially between women at any one time point. Life table analyses showed that the median time to initially attain a NET level of 0.3 ng/ml, which was presumed to be the minimum contraceptive level, was about 18 months in the 4-pellet group and 28.5 months in the 5-pellet group. Progesterone measurements indicated that ovulation was not consistently suppressed by either pellet system.

This study is the first in which complete absorption of available NET from any NET pellet formulation in situ has been observed. Sustained undetectable serum NET levels were documented in two women in this study, both in the 4-pellet group during the third year of their participation in the study. However, the pellet manufacturer felt that a product that took three years or longer to be absorbed would not be widely acceptable to women. Therefore, the study was stopped, with plans to design a lower-dose system or one with a different geometry that would absorb more rapidly. The Annuelle® pellet system shows potential as a safe, effective contraceptive. It has a distinct advantage over injectable contraceptive agents, since it can be removed if problems arise or if return of fertility is desired.

TABLE OF CONTENTS

I. INTRODUCTION	5
II. OBJECTIVES	6
III. INVESTIGATIONAL PLAN	7
A. Study Design	7
B. Study Product	7
C. Study Sites	7
D. Sample size	8
E. Study duration	8
F. Admission criteria	8
G. Study procedures	9
H. Laboratory analyses	11
IV. ANALYSIS METHODS	12
A. Analysis population	12
B. Baseline analyses	12
C. Follow-up and discontinuation analyses	12
D. Contraceptive efficacy analyses	12
E. Serum NET analyses	12
F. Serum progesterone and estradiol analyses	13
G. Bleeding analyses	13
H. Analyses of clinical observations and other laboratory measurements	13
I. Insertion and removal analyses	13
J. Adverse events analyses	13
V. RESULTS	14
A. Analysis population	14
B. Admission violations and deviations	14
C. Baseline characteristics	14
D. Follow-up Duration	15
E. Discontinuation	15
F. Coital frequency	16
G. Alternate contraceptive use	16
H. Contraceptive efficacy	16
I. Serum NET levels	17
J. Serum progesterone and estradiol levels	19
K. Bleeding analyses	20
L. Analyses of other laboratory measurements and clinical observations	21
M. Insertion and removal analyses	22
N. Adverse events analyses	24
O. Brief case histories	25

VI. DISCUSSION	28
VII. REFERENCES	31
APPENDIX I Summary of Study Procedures	32
APPENDIX II Analysis Methods	33
APPENDIX III Analytical Laboratory Information	44
APPENDIX IV Protocol & Amendments	46
APPENDIX V Case Report Forms	47
APPENDIX VI Tables & Figures	48

I. INTRODUCTION

Annuelle® is an investigational contraceptive implant system consisting of bioabsorbable norethindrone (NET) pellets. The pellets, which are about the size of a grain of rice, are designed to be implanted under the skin of a woman's arm. Although the pellets are formulated to fully biodegrade in situ, they can also be removed with minor surgery under local anesthesia.

Annuelle® has been under development for more than 15 years. The goal of the development process has been to make a product that will provide effective contraception for a predictable period of time (e.g., one year) and that will be completely absorbed shortly thereafter. Two small studies, published in 1979 and 1984 (1,2) examined serum NET levels, ovulation, and safety parameters among nine participants using two different handmade pellet systems. In 1984, results of a larger study (3) that used a 2-pellet handmade system containing a total of 69 mg NET were published. This multicenter study included 50 participants at five centers for up to 200 days. Although the participants in this study were instructed to use alternate contraception, three became pregnant. A second study of a 3-pellet and a 4-pellet handmade system involving 81 women followed for up to 180 days at three centers was reported in 1985 (4). In this study, Pearl pregnancy rates were reported as two pregnancies during 282 woman-months for the 3-pellet system (103 mg NET) and zero pregnancies during 170 woman-months for the 4-pellet system (138 mg NET). None of the participants in any of the studies had major complications, and reported adverse events were consistent with the known effects of other progestin-only contraceptives. Pellet insertion and removal also proved to be technically simple and uncomplicated.

Since the pellets used in these studies were handmade, large-scale, consistent production and marketing were not feasible. A decision was then made to pursue an automated manufacturing process to ensure a more uniform product for future studies.

ENDOCON, Inc., (South Walpole, MA), the manufacturer of the NET pellet product, developed two patented production processes. ENDOCON, Inc. trademarked the product under the name Annuelle®. A Phase I study (5) conducted by Family Health International in 1988 assessed three different pellet systems manufactured by these processes. Based on the Phase I results, a Phase IIA trial was initiated by FHI in 1991, and this report describes the results. This trial was designed to evaluate the efficacy and safety of two new Annuelle® formulations: a 4-pellet system containing 174 mg NET and a 5-pellet system containing 266.5 mg NET.

II. OBJECTIVES

The objectives of this analysis were to evaluate the one-year contraceptive efficacy and to measure serum NET concentrations after one of two formulations of Annuelle® implants were inserted. The effects each formulation had on ovulation, serum estradiol and progesterone levels, bleeding patterns, and participant safety over three years also were assessed.

III. INVESTIGATIONAL PLAN

A. Study Design

This was an open-label, parallel group study of two formulations of Annuelle® implants. Thirty-nine healthy women of reproductive age were enrolled at two sites and randomly assigned to receive one of the two formulations. The participants were followed for up to 39 months. No additional contraception was to be used during the first 12 months after pellet insertion, unless serum NET levels dropped below a presumed minimum contraceptive efficacy level of 0.3 ng/ml. Data were collected on:

- accidental pregnancies
- serum NET, progesterone, and estradiol levels
- bleeding patterns
- insertion and removal problems
- safety of the two formulations, including adverse events and effects on weight, blood pressure, and serum laboratory values.

The study was conducted under IND 17452.

B. Study Product

In both Annuelle® formulations, the pellets were cylindrical and were composed of 85% NET and 15% cholesterol. The 4-pellet system consisted of four pellets each 2.75 mm in diameter and 8 mm long. Although the system was designed to contain a total dose of 168 mg NET, the actual average dose on chemical analysis was 174 mg. The 5-pellet system consisted of five pellets each 3.0 mm in diameter and 8 mm long. Designed to contain a total dose of 253 mg, on analysis the system contained an actual average total dose of 266.5 mg. Each individual system was dispensed to the investigators prepackaged in a sterile, specially designed trochar. The pellets were implanted in a single line under the skin of the forearm or the upper arm.

C. Study Sites

Two centers participated in this study:

Center 908: Eastern Virginia Medical Center, Norfolk, Virginia
David Archer, MD - Principal Investigator

Center 952: Cornell Medical Center, New York City, New York
Mukul Singh, MD - Principal Investigator

Before study initiation, an Investigator's Brochure which included information about the study product was prepared and distributed to each investigator.

D. Sample size

Twenty participants were to be enrolled in each treatment group based on the following rationale. A mean serum NET concentration less than 0.3 ng/ml at the end of Month 12 was considered to indicate insufficient contraceptive efficacy to support continued product development, while a mean of 0.5 ng/ml or greater was considered to indicate that further testing was warranted. (These values were based on a consensus of the study sponsors and product manufacturer since data to firmly establish ineffective and effective contraceptive levels of NET were not available.) Sixteen women in each treatment group would be required to complete 12 months of study to test the null hypothesis that the mean NET concentration is less than or equal to 0.3 ng/ml versus the alternative hypothesis that the mean NET concentration is greater than or equal to 0.5 ng/ml with $\alpha = .05$ (one-sided) and power of 0.8, assuming a standard deviation of 0.3 ng/ml (3). The anticipated dropout rate during the study's first year was 20%; therefore, 20 women would be required at enrollment to result in 16 women at the end of 12 months.

E. Study duration

The study protocol (Appendix IV) specified that each participant would remain in the study for 24 months. This period was extended by a protocol amendment (Appendix IV) which allowed additional time for NET levels to fall below the detection limit of the assay. When it subsequently became clear that neither formulation produced the desired pattern of NET release, the study was terminated even though most remaining participants still had detectable NET levels. Participant enrollment at both sites began in September 1991 and recruitment was completed in April 1992. The study was terminated at both sites in October 1994, and the final closeout occurred in December 1994.

F. Admission criteria

A full list of the exclusion criteria is in the study protocol and Amendments 1 and 3 (Appendix IV). In summary, each participant had to:

- be between 18 and 35 years of age
- be sexually active with regular coitus
- have a negative pregnancy test
- weigh 95 - 170 pounds, and deviate no more than 15 percent from ideal weight
- have regular menstrual periods (25-35 days per cycle)
- have a normal physical examination and laboratory screening within 35 days before admission, including serum chemistries, hematology, and urinalysis, unless in the opinion of the investigator laboratory abnormalities would not jeopardize either the participant's safety or the study quality
- have a normal Pap smear
- have no evidence of infertility or previous sterilization

- have not used any hormonal contraceptive during the menstrual cycle prior to admission
- be without specified conditions that were felt to be potential contraindications to the use of the NET product.

The study protocol also specified a number of additional requirements. These included:

- admission must occur between Days 3 and 6 of menses.

G. Study procedures

A chart summarizing the study procedures is presented in Appendix I. Data were collected using uniform case report forms at both sites (Appendix V).

1. Preadmission visit: Potential participants were recruited at each site from the clinic's regular clientele and by advertising. The investigator at Center 952 advertised in the newspaper and the investigator at Center 908 advertised in *Portfolio* magazine. A preadmission visit occurred one menstrual cycle before pellet insertion and 3-7 days after menses onset. At this visit, the study was explained to the potential participant and informed consent was obtained. A prescreening interview was conducted to determine if the participant met all admission criteria. An examination was then performed, and the screening laboratory tests were completed. Participants were asked to begin keeping daily bleeding diaries, on which they noted either no bleeding, spotting (no sanitary protection needed), or bleeding. During the subsequent month, serum estradiol and progesterone levels were to be drawn twice per week.

2. Admission visit: The admission visit was scheduled to occur between Days 3 and 6 of the next menses. At this visit, the potential participant was reevaluated to ensure that all admission criteria were met. A urine pregnancy test was performed. Baseline data were recorded. The participant was randomly assigned to one of the pellet groups, and the pellets were inserted.

All participants were instructed to use no contraception other than Annuelle® through the first 12 months of the study, unless the serum NET level dropped to 0.3 ng/ml or below. At Month 13, or sooner if the NET level dropped to 0.3 ng/ml or below, all participants were advised to use alternate nonsteroidal contraception. Steroidal contraceptives were discouraged because steroids, specifically NET and levonorgestrel, cross-react with the NET assay. Participants were not discontinued, however, if they chose to use a steroidal contraceptive, or if they chose not to use any backup contraception.

3. Participant follow-up: At quarterly clinic visits participants were interviewed about coital activity, medical problems (adverse events) and concomitant medications. Pulse, blood pressure, and weight also were measured. Follow-up data were routinely recorded only through Month 24 and at discontinuation, however. After Month 24, data were recorded only

if a problem occurred. Daily bleeding diaries also were assessed at these visits through the first 24 months after pellet insertion. Pelvic and breast examinations were performed semiannually through 24 months and at discontinuation. When the participant could not make a clinic visit, an attempt was made to collect as much information as possible by telephone or letter.

Serum NET levels were measured 24 hours and 1 week after pellet insertion, and monthly thereafter. Urine pregnancy tests were performed monthly until discontinuation, although results were only recorded quarterly through Month 24 and at discontinuation. Blood samples to measure hematology, chemistry, and lipid parameters (cholesterol, triglycerides, HDL, and LDL) were drawn every 6 months through Month 24 after pellet insertion. A urinalysis was performed at admission and at Month 24 or discontinuation, whichever came first.

Progesterone and estradiol levels were to be drawn twice a week for one month following the 9-month visit and following each quarterly visit thereafter until discontinuation. Estradiols, however, were not assayed after May 1994 because a preliminary look at the data up to that point indicated no clinically significant effect of the pellets on estradiol levels. Pap smears were performed at 12 and 24 months, and at discontinuation. All laboratory tests were performed as described in Appendix III.

4. Discontinuation: The reason that each participant discontinued from the study was coded as one of the following:

- death
- pregnancy
- desire for pregnancy
- menstrual problems
- other medical problems
- other personal problems
- end of study (either the serum NET level was below the limit of detection in the NET assay on two consecutive measurements, or the sponsor stopped the study)
- protocol violation
- unable to contact participant (missed two consecutive quarterly follow-up visits, and attempts to contact her were unsuccessful)

At discontinuation, pellet removal was offered to all participants. Those who declined or for whom complete pellet removal was not technically possible were fully informed of the potential consequences of leaving the pellets in place. When the study was terminated, investigators were instructed to try to contact former participants who still had pellets in place and again offer pellet removal at that time. After pellet removal, NET levels were to be measured to document that the removal had been complete.

Some participants who discontinued from the study for one of the above reasons continued to be followed by the investigators after the date of discontinuation. Data collected after discontinuation were included in the analysis where indicated in the Results section.

H. Laboratory analyses

A description of the laboratory analyses and methods may be found in Appendix III.

IV. ANALYSIS METHODS

A detailed analysis plan may be found in Appendix II. A summary follows.

A. Analysis population

Data from all study participants, including those admitted in violation of admission criteria or other study procedures, were included in all analyses. Data were analyzed separately for each treatment group, and no statistical comparisons were made between groups. Data obtained on or after pellet removal were excluded from analyses except where indicated below.

B. Baseline analyses

The number and percent of participants with admission violations were calculated, and the reasons for these violations were summarized. Categorical data and certain categorized quantitative data were summarized as numbers and percents in frequency tables. For all quantitative data, the mean and standard deviation, median, minimum, and maximum were calculated. Data on demographic characteristics, reproductive history, recent contraceptive use and menstrual history, medical history, results of physical examinations, Pap smears, and laboratory tests were summarized.

C. Follow-up and discontinuation analyses

Follow-up rates were calculated for each quarterly follow-up visit. Reported average coital frequency in the intervals between visits was summarized. The month in which each participant began using backup contraception was listed. The timing and reasons for discontinuation from the study were tabulated.

D. Contraceptive efficacy analyses

No pregnancies were reported during the study in either treatment group. To provide context for these results, the number of woman-months in which no alternate contraception was used was calculated for each group.

E. Serum NET analyses

The mean, standard deviation, median, minimum, and maximum NET levels were calculated for each scheduled NET measurement timepoint. Mean NET levels and box plots were plotted by time for each group as a whole and stratified by baseline weight below or above the median baseline weight for each group. The number and percent of participants who ever had a serum NET concentration below 0.3 ng/ml were calculated from the 1-month through the 12-month followup visits. Life tables were prepared indicating the time to reach the first NET value of 0.3 ng/ml in each group. Hypothesis tests were performed for each group to test the null hypothesis that the mean NET concentration at the end of Month 12 was ≤ 0.3 ng/ml.

F. Serum progesterone and estradiol analyses

To assess ovulation, the number and percent of participants whose maximum progesterone level was >3 ng/ml and > 5 ng/ml among those with at least 4 measurements for each timepoint were calculated at admission, about nine months after admission and about every three months thereafter. Summary statistics were calculated to describe estradiol levels at the same timepoints through 18 months postinsertion.

G. Bleeding analyses

Bleeding diary cards kept by participants from admission through Month 24 postinsertion were analyzed for each 90-day reference period to calculate the proportion of participants who had the following defined bleeding patterns termed "clinically significant": amenorrhea, prolonged bleeding, frequent bleeding, infrequent bleeding, irregular bleeding, or any of these patterns.

H. Analyses of clinical observations and other laboratory measurements

Changes in weight, blood pressure, and lipids over time were calculated and plotted. Changes in blood glucose over time were also calculated. The percent change between the values of each of these tests at preadmission and at each semiannual visit were tested separately for each group to determine whether the changes were statistically significant. The number and percent of participants with any out-of-range laboratory value and with elevated blood pressure or pulse were calculated.

I. Insertion and removal analyses

Problems related to insertion and removal were reported. For removals, the median duration of the procedure and the number and median length of the incisions were calculated.

J. Adverse events analyses

Information about all adverse events (AEs) reported by participants during the study was recorded by the investigators. Each AE was evaluated for seriousness, severity, relationship to the study product, and expectedness. An event was coded as serious if it required hospitalization, or if it was fatal, life threatening, permanently disabling, cancer, or a study-product overdose. Severity and relatedness to the study product were coded according to the investigator's judgment. An event was coded as unexpected if it was related to the product but was not mentioned in the Investigators Brochure. The number and percent of participants who ever had any adverse event (AE) in each treatment group, who ever had any AE in a body system, and who ever had each specific condition were calculated. Separate tables were also provided for those AEs that were reported by the investigator as probably related to the study product, possibly related to the study product, and serious and/or unexpected.

V. RESULTS

A. Analysis population

Thirty-nine women were admitted to the study, 19 into the 4-pellet group and 20 into the 5-pellet group. The distribution of participants at the two study centers is presented in Table 1. Although the study design called for 20 participants at each center, only 19 participants were admitted at Center 952 because of slow enrollment. All participants had the randomly assigned pellet system implanted.

B. Admission violations and deviations

Five participants in the 4-pellet group (26.3%) and 8 in the 5-pellet group (40%) were admitted to the study with conditions that violated explicit study inclusion or exclusion criteria or other protocol requirements (Tables 2.1 and 2.2). The most common violation in both groups combined was no documentation of normal hematology, chemistry, or urinalysis test results within 35 days before admission (5 participants). Four participants were up to two years older than the specified age range of 18-35 years. Ten participants did not have documented negative serum NET levels within one week before admission, but such levels were not clearly required by the protocol. None of the admission violations are likely to have significantly affected the outcome of the study.

C. Baseline characteristics

Tables 3-5 show the baseline demographic characteristics and reproductive history of the study participants. In both groups, the ages of the participants were distributed across the full age range specified by the protocol (18-35 years). More than 70% in each group were white, and fewer than one-third were smokers. The majority (about 70% in each group) had demonstrated fertility (i.e., previous pregnancy). More than 20% in each group had live-born children and at least 15% had been pregnant during the year before admission. The most commonly used methods of birth control in the month before admission in both groups combined were condoms.

Tables 6 and 7 show the characteristics of the participants' menstrual cycles before admission. Few participants had moderate or severe dysmenorrhea, intermenstrual pain, or intermenstrual bleeding in the cycle before admission. On average over the previous three cycles, most participants bled 3-6 days with moderate flow. Cycle lengths were 25-35 days (as specified by study inclusion criteria) in all but one participant.

Ten participants in the 4-pellet group (53%) and 14 (70%) in the 5-pellet group reported a history of medical or surgical conditions at admission (Tables 8.1-8.3). Among these were a variety of gynecological infections and sexually transmitted diseases, which had affected four participants in each group. One participant had a history of ovarian cysts. Four participants were taking medications at admission, none of which would be expected to affect the study

results. All participants had normal vital signs, weight, and Pap smears at admission. One participant had a vaginal discharge, the etiology of which was not determined.

D. Follow-up Duration

Table 9 shows the number and percent of participants in each group with pellets in situ who had at least one follow-up contact within each scheduled three-month visit window through Month 24. Through 15 months, the follow-up rate for participants whose pellets had not been removed was high (>80%) in each group. After that time, the follow-up rate began to drop in the 4-pellet group, although it remained >80% in the 5-pellet group. Follow-up rates after 24 months are not presented because follow-up visits were not reported after that time unless a problem was noted.

E. Discontinuation

Table 10.1 shows the timing of discontinuations in each group for each reason, and Table 10.2 presents more detailed information about each discontinuation. Most discontinuations occurred more than two years after enrollment, particularly in the 5-pellet group. The most common reason for discontinuation in both groups combined was because the study ended (38% - 15/39). "Other personal reasons," which includes a desire for pregnancy, was the second most common set of reasons for discontinuation (33% - 13/39). No discontinuations for death, pregnancy, or protocol violations occurred in either group.

Three discontinuations occurred for medical reasons other than menstrual problems.

- PON 908/3 (4-pellet group), who was admitted to the study in 9/91, developed complications of systemic lupus erythematosus at 19 months (4/93) and discontinued from the study at 22 months (6/93).
- PON 908/1 (5-pellet group) discontinued at five months due to headaches.
- PON 952/16 (5-pellet group) was discontinued at 27 months at the request of the study sponsor and pellet manufacturer because of breast hyperplasia.

Of these three medical problems, only the headaches were thought to have a possible or probable relationship to the study product. Brief case histories of each of these participants are presented in **Section O. Brief case histories**. One additional participant discontinued because of breast pain, which was coded as a personal reason since it was not considered a medical indication for pellet removal although it was considered possibly related to the pellets. Although bleeding abnormalities were very common among participants in this study (**Section K. Bleeding Analyses**), only two participants (PONs 908/6 and 908/7) discontinued due to menstrual problems. Six participants (15%) were lost to follow-up.

F. Coital frequency

Throughout the first year of the study, most participants reported intercourse at least twice a week on average (Table 11.1). Very few reported intercourse less than once a week, which suggests that coital frequency was high enough to put participants at risk of pregnancy while the efficacy of the product was evaluated.

G. Alternate contraceptive use

Participants were instructed to begin using alternate methods of contraception at Month 13 or when their serum NET levels dropped below 0.3 ng/ml, whichever was earlier. No participant began use before month 13, although several had levels below 0.3 ng/ml earlier than that time (**Section I serum NET levels**). Because of the manner in which data were collected, the exact date of initiation of alternative contraception could not be calculated for every participant; in some cases, only a range of dates was known (see Appendix II.F). Tables 11.2 and 11.3 show the study month (or range of months) at which backup contraceptives were initiated. Of the 33 participants in both groups combined who continued in the study past 12 months, at least 21 (64%) did not begin using another contraceptive method at 13 months. Of these, 4 began another method at 14 months; one discontinued at 17 months without ever using another method; and the other 16 continued in the study for at least two years with no other method. The remaining 12 continuing participants (36%) were all using an alternate method by 17 months. The reasons that so many women did not follow protocol instructions to use alternate contraception were not collected.

Steroidal contraceptives were chosen by eight participants (28% of those who used additional contraception).

H. Contraceptive efficacy

No participant became pregnant during the study. During the first 12 months, which was for the period during which efficacy was to be assessed, there were 189 woman-months in the 4-pellet group and 233 woman-months in the 5-pellet group in which no alternate contraceptive was used. After 12 months, there were at least an additional 104 such woman-months in the 4-pellet group and 142 such woman-months in the 5-pellet group. Thus, the entire study included a total of at least 293 (4-pellet group) and 375 (5-pellet group) woman-months in which Annuelle® was the only contraceptive used. Although detailed coital data were not collected in each month individually, reported coital frequencies suggest that during most of the first 12 months, intercourse occurred often enough for participants to be at reasonably high risk of pregnancy (Table 11.1).

I. Serum NET levels

The mean, median, minimum and maximum NET levels at 24 hours, one week, and monthly after pellet insertion in each treatment group are presented in Tables 12.1 and 12.2. Graphs of the mean net levels in each group are presented in Figure 1. Graphs of each participant's NET levels over time are presented in Figures 2a-2d. Figure 3a and 3b show box plots of NET levels at each measurement timepoint. Box plots should be interpreted as follows: the center line is the median level, the upper and lower ends of the box represent the 75th and 25th percentiles, respectively, and the ends of the lines represent the extreme values. Figures 4a and 4b show mean NET levels over time in each group stratified by admission weight (above or below the median).

Of note from these analyses are the following findings:

1. In general, an initial burst in the NET level (valued higher than 2 ng/ml) occurred at 24 hours in both groups.
2. Levels decreased thereafter over the course of the next several weeks. By one month, the mean level was about 1 ng/ml in both groups. The mean level then declined slowly and steadily as long as the pellets remained in place.
3. In neither group did all participants have undetectable levels (< 0.112 ng/ml) at Month 38 postinsertion. Only two participants (PONs 952/1, 952/6), both in the 4-pellet group at 37 months, had two consecutive undetectable levels before pellet removal, which was the predefined criterion for study completion. Four other participants (PONs 908/3, 908/6, 908/11, 908/19) had one undetectable level, although one of these may have been misreported (908/6, see below in this section).
4. Mean NET levels were consistently higher in the 5-pellet group than in the 4-pellet group, although no statistical comparisons were made between the two groups.
5. The NET levels in each individual participant did not decline in a smooth curve; frequently the value in one month was higher than the value the previous month.
6. Wide variation existed between individuals in NET levels at each timepoint.
7. Heavier women appeared to have lower mean NET levels than lighter women, although no statistical comparisons were made.
8. Several participants had atypical release patterns of NET:

PON 908/7 (5-pellet group): A very high NET level was reported at 5 months after pellet insertion. (This single value entirely accounts for the apparent burst

at 5 months in the mean graph for the 5-pellet group). The specimen was assayed twice, and both times the value was > 3.587 ng/ml.

PON 952/13 (4-pellet group): A similar spike in NET level occurred at 1 month.

PON 908/10 (4-pellet group): After the initial burst at 24 hours, the NET level dropped to an unusually low value (0.263 ng/ml) at 1 week, and then rose slowly over the next 5 months, before beginning its slow decline.

PON 952/6 (4-pellet group): The NET level became undetectable at 23 months. It remained undetectable or extremely low for four consecutive months. Then it rose again to clearly detectable levels for the next nine months. Finally, the participant had two consecutive undetectable levels. Since technically the criteria for discontinuation were not met, she was retained in the study and ultimately discontinued because of study termination. No explanation was found for this "rebound" in NET levels; in particular, the participant denied using other steroids during the rebound period.

Although mean NET levels were consistently higher than 0.3 ng/ml through the first 12 months postinsertion (Table 12.1-12.2), five participants had serum NET levels below 0.3 ng/ml during the first 12 months in the study (Tables 13.1-13.2). None of these participants began using backup contraception at the time of the low NET level. However, in three of these participants (952/18, 908/12, 952/14), the low NET level was obtained during Months 11 or 12, and may not have been reported to the investigator until Month 12, and in one participant (908/6), the specimen is believed to have been drawn after pellet removal. (There was some concern that the value of 0.112 ng/ml recorded on Day 91 for PON 908/6 may have been erroneous. She had her pellets removed on Day 92, at which time a level of 0.848 ng/ml was recorded. It is possible that the specimens from Days 91 and 92 were accidentally switched in the laboratory, since both were assayed the same day, but this could not be confirmed.) However, in one participant (952/6), the low level was first obtained in Month 6, occurred repeatedly through the entire first year of the study and persisted until her discontinuation at 36 months. This participant's failure to use alternate contraception during the first year was clearly a protocol violation. Notably, although she continued to rely only on Annuelle[®] for birth control through at least Month 24 and her reported coital frequency was at least once a week during the first year, she did not conceive.

Life-table analyses of the time to first reach a NET level less than 0.3 ng/ml in each treatment group are presented in Table 13.3. Although little data exist regarding the correlation between serum NET levels and contraceptive efficacy, it was presumed that 0.3 ng/ml was the minimum level consistent with effective contraception. The median time to reach this level was 18 months in the 4-pellet group and 28 months in the 5-pellet group. It should be noted that because of the instability of the NET level decline in individual

participants, in some women the NET level may have risen again after the first level below 0.3 ng/ml.

Hypothesis testing (one-sample t-tests) indicated that the mean NET levels in the 4-pellet and 5-pellet groups were significantly greater than 0.3 ng/ml at 12 months ($p \leq 0.05$ for both groups). However, because the NET levels were not normally distributed in the 5-pellet group (Shapiro Wilk tests showed $p < 0.05$), the t-test of the mean level was not felt to be the most appropriate for these data. Therefore, a non-parametric approach was also used. For each group, the upper 95% exact binomial confidence limit was calculated for the proportion of participants with levels ≤ 0.3 ng/ml at 12 months. If the median NET value at month 12 were ≤ 0.3 ng/ml, then 50% or more of the participants would have been expected to have NET values ≤ 0.3 ng/ml. Thus, if the upper 95% confidence limit of the percent were less than 50%, then the null hypothesis that the median value is ≤ 0.3 ng/ml would be rejected ($p < 0.05$). The results of these tests were as follows:

Treatment Group	% of participants with NET levels ≤ 0.3 ng/ml at 12 months (n/total)	upper 95% confidence limit
4-pellet group	18.2% (2/11)	47.0%
5-pellet group	6.7% (1/15)	27.9%

These results indicate that the median NET value at Month 12 was significantly greater than 0.3 ng/ml in both treatment groups.

J. Serum progesterone and estradiol levels

a. Progesterone levels

Serum progesterone levels were measured at several points during the study to evaluate how the pellets affected ovulation. There is not general agreement as to what level of progesterone indicates that ovulation has occurred. Therefore, two sets of analyses were performed using two different criteria:

- maximum value greater than 3 ng/ml
- maximum value greater than 5 ng/ml

Table 14.1 shows the number and percent of participants in each treatment group with maximum progesterone levels exceeding these two levels in the month before admission (baseline) and at each scheduled quarterly follow-up time during the study. Table 14.2 lists each occurrence of a level > 3 ng/ml. Participants were included in these tables only if they had 4 or more measurements corresponding to a scheduled measurement time period. This rule ensured that each woman in the analysis had sufficient specimens to reliably diagnose

lack of ovulation if all values were ≤ 3 (or ≤ 5) ng/ml. However, some women who ovulated but who had fewer than 4 measurements at that timepoint may have been excluded from analyses.

In the 4-pellet group, all participants were ovulatory at baseline by the 3 ng/ml criterion and all but one by the 5 ng/ml criterion. By 9 months, the percentage of participants with ovulatory cycles declined substantially to 22% (2/9), but then by 21 months, all remaining participants (2/2) were ovulatory again. In the 5-pellet group, only 79% (15/19) of participants were ovulatory at baseline, and most participants who returned for progesterone measurements were anovulatory at each measurement time thereafter. Although no statistical comparisons were performed between groups, it appears that the 5-pellet system had a more substantial suppressive effect on ovulation in magnitude and duration than the 4-pellet system. It is interesting to note that two of the participants (PONs 952/9 and 952/19) who were not ovulatory at baseline were ovulatory at the 12-month measurement. Also, participants who were ovulatory at one measurement were not continuously ovulatory at each measurement thereafter, suggesting that the inhibitory effect of the pellets was not constant even within a particular woman.

b. Estradiol levels

As with progesterone levels, only participants with at least 4 measurements corresponding to a particular month were included in analyses. Although no statistical comparisons were made, all follow-up summary values of estradiol were lower in the 5-pellet group than in the 4-pellet group at each postinsertion measurement even though baseline mean levels were higher in the former group (Table 15). In the 4-pellet group, estradiol levels (mean, median, minimum, and maximum) generally rose after admission and remained higher than baseline through Month 18 postinsertion. By contrast, in the 5-pellet group, these values were generally lower than baseline through Month 18 postinsertion. These findings suggest greater suppression of follicular development in the 5-pellet group than in the 4-pellet group.

For this analysis, an estradiol level below 40 pg/ml was considered abnormally low. Table 16.1 shows the number and percent of participants with minimum and maximum estradiol levels below this level at each measurement point. No participant in either group had all estradiol levels below 40 pg/ml during any single month sampling period. In the 4-pellet group, at most 50% of women who returned for measurements at each month had at least one level below 40 pg/ml, whereas in the 5-pellet group, most of the participants had at least one low level at each month after insertion. Table 16.2 lists each minimum level ≤ 40 pg/ml measured in each time interval during the study. Several participants in the 5-pellet group had low estradiol levels during multiple sampling months.

K. Bleeding analyses

The results of the bleeding analyses are presented in Table 17 and Figures 5a and 5b. More than 80% of the participants in each pellet group had clinically significant bleeding patterns

during the first three months postinsertion. This percentage dropped over time, so that by about 2 years (the 8th 90-day reference period), roughly half the participants in each group had clinically significant patterns. Although no statistical comparison was done, no substantial difference appears between the two groups in the proportion of participants with any clinically important pattern. The predominant abnormal patterns were frequent, irregular, and prolonged bleeding; infrequent bleeding and amenorrhea did occur, but less often. These last 2 patterns were more common in the 5-pellet group than in the 4-pellet group in each reference period. None of the participants became even moderately anemic (hemoglobin <11 g/dl) during the study (**Section L. Analysis of other laboratory measurements and clinical observations**).

L. Analyses of other laboratory measurements and clinical observations

Table 18 and Figures 6a and 6b show the changes in lipid levels over the first 24 months after pellet insertion. In both groups combined, total cholesterol, LDL, and triglyceride levels dropped substantially in the first 6 months, and then remained fairly stable; while HDL levels remained fairly constant. Thus, the ratio of HDL to total cholesterol increased over the first year, so that by 24 months, the ratio was 23% higher than at baseline in the 4-pellet group and 17% higher in the 5-pellet group. Most of the changes described above were statistically significant ($p < 0.05$).

Glucose levels did not change significantly or substantially over time through 24 months (Table 19).

Tables 20.1-20.7 present the out-of-range laboratory values. Except for lipid levels, the only pattern of abnormal values of any laboratory test performed during the study was mildly elevated serum chloride in more than 10% of participants in the 5-pellet group at each measurement time. Five of the nine participants who had elevations during follow-up also had elevated values at baseline. Therefore, it is unlikely that the chloride abnormalities are due to the pellets. As noted, no participant had frank anemia (Hgb <11 g/dl) during the study.

Changes in systolic and diastolic blood pressure over time are presented in Table 21 and Figures 7a and 7b, and changes in weight over time are presented in Table 22 and Figures 8a and 8b. No statistically or clinically significant change in either parameter occurred through Month 24 postinsertion. Only one participant (PON 908/2) had abnormally high blood pressure at any time during the study (systolic more than 155 or diastolic greater than 95). This participant had five such elevated readings, and was diagnosed with hypertension (AE listings). Her admission blood pressure was normal (110/80). Only one participant was recorded as ever having a pulse higher than 100 during the study (PON 908/18 at Month 24).

Four participants (PONs 908/7, 908/10, 908/16 and 908/18) had abnormal Pap smears during the study. No participant had an abnormal breast exam, although PON 952/16 was discontinued from the study because of an abnormality discovered during a screening mammogram (**Section O. Brief case histories**)

M. Insertion and removal analyses

The study protocol did not specify the exact site of pellet insertion in the participants' arms. At Center 952, 18 of 19 insertions were performed in the forearm and 1 of 19 in the upper arm; at Center 908, 19 of 20 were performed in the upper arm and 1 of 20 in the forearm. The insertion procedure was done under local anesthesia in all participants. A slight stimulation of the ulnar nerve in PON 908/6 was the only reported complication; it resolved without treatment. In another case (PON 908/7), a technical defect was noted with the insertion trochar before insertion. The obturator was partially out of the trochar and the first pellet was in the bevel. A new trochar was used and the insertion was accomplished without difficulty.

By the time of this analysis, about half (21/39) of the study participants had their pellets removed (Table 23.1). Three postdiscontinuation removals occurred after the study was terminated in late 1994 when attempts were made to contact all former participants and again offer them pellet removal. Four (PON 908/3, 908/19, 952/1, 952/6) of the remaining 18 participants who did not undergo removal have had at least one undetectable serum NET level, suggesting that all available NET has been completely absorbed. All were in the 4-pellet group. Five participants with retained pellets are lost to follow-up (PONs 908/5, 908/19, 952/3, 952/12 and 952/15), and the other nine have declined pellet removal.

Pellet removal was a relatively minor procedure in both pellet groups. One incision was required in 62% (13/21) of all removals. Half the participants in the 5-pellet group (6/12), and 22% (2/9) in the 4-pellet group required two or three incisions (Table 23.2). The median incision length for both pellet groups combined was 8 mm (Table 23.3), and the procedure ranged from 5 to 90 minutes with a median of 25 minutes in both groups combined (Table 23.4). Removals were performed under local anesthesia, usually 1% lidocaine; a range of 1-9 ml was required. In eight participants (38%) the physician reported minor difficulties with the procedure. Related medical and surgical complications associated with removal were experienced by seven participants (33%). The table below summarizes the removal difficulties and medical complications. Multiple problems were reported for some participants.

PELLET REMOVAL DIFFICULTIES AND RELATED PROBLEMS	Number of Participants
<i>Problems with Locating Pellets</i>	
Pellets close together	1
Pellets decreased in size or partially absorbed	4
Obscured by scar tissue	1
<i>Problems Grasping or Dissecting Pellets</i>	
Pellets difficult to grasp due to scar tissue or adhesions	5
Pellets fractured	1

PELLET REMOVAL DIFFICULTIES AND RELATED PROBLEMS	Number of Participants
Capsule not well developed	1
<i>Related Medical or Surgical Problems</i>	
Buttonhole injuries	2
Vasovagal reaction	1
Pain/Discomfort/Nausea	4

According to the investigator's report, the superficial location of the pellets contributed to one of the buttonhole injuries noted in the table. No therapy was required to treat any of these conditions.

All but two participants (PONs 908/10 and 908/11), both in the 4-pellet group, had the same number of pellets removed as were inserted. Participants 908/10 and 908/11 were 38 and 35 months from insertion, respectively, at the time of removal, and the pellets were barely palpable or nonpalpable. PON 908/10 had three pellets removed, and PON 908/11 had one pellet removed. Both participants had undetectable serum NET levels on the day of removal and at least once thereafter, suggesting that the NET had been absorbed from the pellets before the procedure and that any remaining pellets were not releasing substantial amounts of NET.

The pellets were reported as fully encapsulated at the time of removal in all but one participant, PON 908/8, whose removal occurred 8 months postinsertion. In one participant, PON 908/7, two pellets were noted to be fractured in situ; her pellets were inserted 35 months prior. In seven participants, 10 pellets were fractured during the removal procedure. These seven participants included all four whose removal was performed within the first year after insertion. In these cases the broken pellets may have been a result of the physician's inexperience performing the removal procedure. The other three removals were performed at 26, 28, and 39 months postinsertion.

Investigators were instructed to obtain serum for NET measurements after removal until the level was undetectable to document that the removal had been complete. Among the 21 participants with removals, NET levels were first noted to be undetectable at the following times:

TIME WHEN NET LEVEL DOCUMENTED AS UNDETECTABLE	Number of Participants
On or before day of pellet removal	4
Within two weeks after pellet removal*	7
More than two weeks after pellet removal	4
Never documented as undetectable	6

* Includes two participants whose NET levels were undetectable within one day.

Of the 6 participants whose levels were never documented as undetectable, 5 did not have levels measured after removal, and in the other the level at the last measurement on the day of removal (0.117 ng/ml) was near the minimum detection limit of the assay (0.112 ng/ml).

This table should not be interpreted to imply that NET levels frequently remain elevated for days to weeks after removal, because in some participants, the earliest post-removal level was not obtained until some time after the procedure. Except for one participant (PON 908/18) who was taking oral contraceptives containing norgestrel at the time of removal, the longest time that NET was actually documented to remain detectable in serum after removal was 4 days. (PON 908/18 had detectable NET levels for more than two months postremoval, but since norgestrel cross reacts with NET in the NET assay, these measurements are considered unreliable.)

One participant (908/1) had a notable rise in serum NET one day after removal. This participant's level was 0.649 ng/ml on the day of removal, 2.903 ng/ml the next day, and then was undetectable at the next measurement two weeks later.

N. Adverse events analyses

Eleven participants (four in the 4-pellet group, seven in the 5-pellet group) had AEs that were felt by the investigator to be probably related to the study product (Tables 24.1-24.3). Most occurred in the first three months of the study, and none was reported as serious. The most common related events were various menstrual disturbances, which were reported in 11 participants. Sexual dysfunction (decreased libido), acne, and an ovarian cyst each were reported in one participant. The sexual dysfunction (PON 908/6) was reported as severe.

Twenty participants (10 in each group) had AEs felt to be possibly related to the study product (Tables 25.1-25.3). These occurred sporadically throughout the study period, and none was reported as serious. Again, menstrual disturbances were the most common; acne, alopecia, ovarian cyst, edema, night sweats, hypertension, headache, abdominal or adnexal pain, brief depressive reaction, other neurotic disorders (irritability and tension), other disorders of the uterus (uterine cramps), and mastalgia also occurred. Two of the possibly related adverse events were reported as severe: headaches (PON 908/1) and adnexal pain (PON 908/10) [Section O. Brief case histories].

Two participants had AEs defined as serious (Tables 26.1-26.3). PON 908/3 developed neurologic and infectious complications of systemic lupus erythematosus, which resulted in her discontinuation from the study, and PON 908/18 developed severe cervical dysplasia. Neither problem was felt to be probably or possibly related to the pellets. These two participants are discussed in **Section O. Brief case histories**.

Seven participants had AEs classified as unexpected (Tables 26.1-26.3). These included abdominal pain, adnexal pain, dysmenorrhea, menorrhagia, ovarian cyst, edema, night sweats, tooth abscess, mastalgia, carcinoma in situ of the cervix (severe dysplasia), and abnormal Pap

smear. Abdominal pain and menorrhagia were incorrectly classified as unexpected, since these conditions were listed in the Investigators' Brochure as possible side effects of the pellets. Three conditions (tooth abscess, severe dysplasia, and abnormal pap) should also not have been coded as unexpected because these conditions were not related to the study product.

Overall, 15 participants in the 4-pellet group and 17 in the 5-pellet group had an AE at some time during the study (Table 27.1-27.3). Conditions that occurred in five or more participants included dysmenorrhea and other menstrual disorders, acne, and flu. (Comparing these results to the results of the bleeding analysis clearly shows that only a minority of the menstrual disturbances were actually reported as AEs.) Four participants had ovarian cysts. Two of these (PONs 952/8 and 908/10) are discussed in **Section O. Brief case histories**; in the other two participants (PONs 908/13 and 908/18), the cysts were felt to be follicular cysts, which both resolved within two months with pellets in situ. PON 908/13 was treated with Toradol for cyst-related pain; PON 908/18 required no treatment.

At the time of this analysis, 17 AEs, none serious or unexpected, were listed as unresolved. The investigators at both sites were asked to follow up all of these problems after study closeout (Table 28). All except 3 of the participants who remained lost to follow-up at this attempt had had their pellets removed (908/5, 952/8, 952/10).

O. Brief case histories

Summaries of clinically relevant cases or events follow.

4-pellet group

PON 908/3 was enrolled in the study in 9/91. She had an episode of flu in 12/92. In 4/93, she was hospitalized for one month with a flare of systemic lupus erythematosus, complicated by cerebritis, small vessel vasculitis, peripheral neuropathy, vestibular neuronitis, mycoplasma pneumonia, oral thrush, and anemia. At that time she admitted to a long history of lupus, which was unknown to the investigators at study admission. In 6/93, two months after discharge from the hospital, she was discontinued from the study due to the lupus, but refused pellet removal.

PON 908/10 was admitted to the study in 12/91. In 9/92, she reported severe right adnexal pain considered probably unrelated to the study product. An ultrasound in 11/92 showed two cystic masses in the left pelvis. The initial presumptive diagnosis was dermoid ovarian cyst. Atypia and HPV on Pap smear also was noted at this time. Surgery for the cysts was contemplated, but serial ultrasounds showed that the cystic masses were decreasing in size. Her pain was treated with Anaprox. In 2/93, the participant underwent colposcopically directed cervical biopsies because of her abnormal Pap smear. The biopsies showed flat condyloma and endocervical lesions. The participant had NORPLANT[®] implants inserted in 2/93, and subsequently moved to Florida. She was thereafter lost to follow-up and was discontinued from the study in

10/93. She returned to the clinic in 1/95 for pellet removal. Three of the original 4 pellets were removed. Removal and pellet dissection were slightly complicated due to scar tissue and nausea. At the time of removal, the cysts and cervical lesions were reported to have resolved, apparently without treatment, on 5/31/93.

5-pellet group

PON 908/1 was admitted to the study in 9/91. She reported the onset of severe headaches six days postinsertion, and then developed severe chest pain in 10/91. The chest pain was considered unrelated to the pellets. An ECG was performed and was normal. The chest pain resolved several weeks later without treatment. The pellets were removed in 1/92 because of the headaches, which then resolved 5 days postremoval.

PON 908/5 was admitted to the study in 9/91. Four months later, in 1/92, she developed depression, which was treated with fluoxetine hydrochloride (Prozac) and resolved by 3/92. The depression recurred in 10/92, associated with irritability. No medication was administered for this episode of depression. The symptoms were mild and resolved in 4/93. She was discontinued from the study (lost to follow-up) in 11/93; her pellets were not removed.

PON 908/7 was admitted to the study in 9/91. Reported AEs included breast tenderness, and in 4/92, mild swelling of the hands and feet that was considered possibly related to the study product. The edema resolved in 8/92 without treatment, but returned in 9/92. Her pellets were removed at her request in 8/94 because of menstrual problems (amenorrhea). Because she did not return for follow-up after removal, she was not discontinued until 11/94. A pap smear at that time showed mild dysplasia. A colposcopy with biopsies done in 1/95 was normal.

PON 908/16 was admitted to the study in 3/92. Various AEs were reported including facial trauma due to spousal assault, a perineal infection, and a urinary tract infection. A Pap smear in 10/93 indicated mild dysplasia. An endocervical biopsy and a Pap smear were done in 4/94. The biopsy was normal, but the Pap smear showed CIN I. A repeat Pap smear in 11/94 was normal. The participant discontinued in 11/94 at the end of the study and her pellets were removed.

PON 908/18 was admitted to the study in 2/92. She had several nonserious AEs over the subsequent 15 months (including menstrual cramps, menorrhagia, mild chest pain, ovarian cyst, flu, tooth abscess, bronchitis, and headache.) In 6/93, a Pap smear showed CIN I. Colposcopically directed biopsies in 7/93 showed severe dysplasia. Laser ablation was performed in 9/93. In 2/94, the participant discontinued from the study for "other personal reasons" (she did not wish to continue in the study past the original 24 months) and her pellets were removed. Her Pap smear at that time was normal.

PON 952/8 was admitted to the study in 11/91. During the first year postinsertion, she reported multiple episodes of abnormal vaginal bleeding. In 10/92, she developed an ovarian cyst, which ruptured and resolved within one month without treatment. Two years later, in 10/94, she developed another ovarian cyst, which again resolved without treatment. Neither ovarian cyst was considered serious or severe. The second cyst was considered by the investigator to be probably related to the study product. The pellets were not removed when she discontinued in 10/94.

PON 952/16 was admitted to the study in 4/92. In 8/93, a screening mammogram was performed, which was abnormal. Breast biopsy was performed at an outside hospital, and was reported as showing fibrocystic disease with florid ductal hyperplasia, sclerosing adenosis, and rupture of cysts with marked chronic inflammatory reaction. The case was reviewed by the oncology board at the study investigator's hospital, which rediagnosed the condition as papillary apocrine hyperplasia. They concluded that this may have been an undiagnosed preexisting condition, which was unrelated to the study product. Although the study sponsor and the product manufacturer agreed that the condition was unrelated, they recommended that the pellets be removed. Removal was performed and she was discontinued in 6/94.

VI. DISCUSSION

Annuelle® is the latest in a series of subcutaneous, biodegradable norethindrone pellet formulations that have been developed and tested since the late 1970s for their contraceptive efficacy and general safety. This study evaluated the contraceptive efficacy, pharmacokinetics, physiologic effects, and safety of this product: a 4-pellet system containing 174 mg NET, and a 5-pellet system containing 266.5 mg NET. The study included 39 women who were followed for up to 39 months after pellet insertion.

The contraceptive efficacy of both formulations appeared promising, with no pregnancies observed in a total of 293 woman-months of use in the 4-pellet group and 375 woman-months in the 5-pellet group. The protective effect was observed for two years in the 16 study participants who remained in the study at Month 24 and did not begin using backup contraception before that time. The contraceptive efficacy of both formulations appears to be an improvement over that observed in a study (4) of two earlier lower-dose pellet formulations, one a 3-pellet system containing 103 mg NET and the other a 4-pellet system containing 138 mg NET. In that study, women using the 3-pellet system had two pregnancies in 282 woman-months, and women using the 4-pellet system had no pregnancies in 170 woman-months.

The safety profile exhibited by both formulations was excellent. No serious adverse events were reported that were felt to be related to the study product. As with other long-acting progestin contraceptives, the main side effect was bleeding abnormalities, which occurred in most participants and persisted in half for at least two years. However, AE analyses indicated that few participants actually complained of abnormal bleeding, and only two participants discontinued for this reason. This indicates that abnormal bleeding was not especially troublesome to the women in this study. Most other problems were minor as well. Acne, a known androgenic effect of progestins, occurred in several participants. Ovarian cysts were detected in four participants; none required any treatment, and whether this figure represents an elevated incidence compared to the general population is unknown.

Analysis of mean serum NET levels in both groups combined showed an initial burst in the first day postinsertion followed by a steady, sustained decline over the next three years. This pattern is similar to that observed in studies of some earlier pellet formulations (1,2,5), but not in others. Two studies (3,4) of lower-dose systems showed sustained constant serum NET levels over 6-9 months postinsertion with no initial burst. The reason for the differences between these studies is not clear.

Not unexpectedly, mean NET levels in the 5-pellet group were consistently higher than in the 4-pellet group. However, levels varied substantially between women at any one timepoint, and the slope of decline in each individual's level over time was not smooth. Unexpected spikes in NET level were noted in two participants, and a rebound phenomenon (a rise in serum NET after several months of nearly undetectable levels) was observed in one other. Heavier women had lower levels than thinner women. These findings may be a result of variations in

blood volume or drug metabolism between women and over time, or they may indicate that the NET absorption rate from the pellets is not constant. Similar variability in levels has been described in all studies of previous NET formulations (1-5), and studies of hormone levels released from other progestin contraceptives also have shown substantial variation among individuals (6).

This study was designed with the presumption that a NET level higher than 0.3 ng/ml should provide protection from pregnancy. However, the relationship between contraceptive efficacy and serum NET levels is poorly established in the literature. In a study of NET microspheres (7), one pregnancy was reported in a woman whose serum NET levels were 0.36-0.57 ng/ml, and in another study of earlier NET pellet formulations (4), three pregnancies occurred despite mean levels of 0.54 ± 0.12 ng/ml. Thus, the minimum effective level for contraception might be higher than presumed in this study. More likely, the minimum effective level may vary among individuals or populations of women; such variation was observed in several studies that examined the relationship between NET levels and ovulation (2,6,8). It has also been suggested that the rate of decline of NET levels may be as important a determinant of ovulation or fertility as the absolute level itself (7). These observations suggest that future studies of the contraceptive efficacy of NET pellet formulations should not use NET levels as a sensitive proxy for contraceptive effect.

This study is the first in which complete absorption of available NET from any NET pellet formulation in situ has been observed. Sustained undetectable serum NET levels were documented in two women in this study, both in the 4-pellet group during the third year of their participation in the study, and it is presumed that if the study had continued, additional similar cases would have been observed. However, the pellet manufacturer felt that a product that required three years or longer for NET to be absorbed would not be widely acceptable to women. Therefore, the study was stopped, with plans to design a lower-dose system or one with a different geometry that would be absorbed more rapidly.

Measurements of progesterone levels in the study participants indicated that ovulation was not consistently suppressed by either formulation tested. In the 5-pellet group, at least 21% (3/14) of participants ovulated at 12 months, and the percentage was even higher (3/17) in the 4-pellet group. This finding is consistent with our understanding of the mechanism of action of progestin-only contraceptive agents, which are believed to act by a variety of mechanisms including ovarian suppression and changes in the cervical mucus and the endometrium.

Both formulations appeared to have a beneficial effect on lipid levels, manifested by decreases in total cholesterol, LDL, and triglycerides. Although HDL was not substantially affected, the increase in the ratio of HDL to total cholesterol persisted through Month 24. Since the analysis made no adjustment for the multiple tests performed, however, this result must be confirmed with further research.

Both pellet insertion and removal were relatively simple procedures without significant complications. Removal took a median of 25 minutes, which is approximately the same as for

NORPLANT® Implants (9). After pellet removal, serum NET levels usually became undetectable in less than two weeks, although a transient rise in level was noted in one participant on the day after removal. In two participants, both about three years postinsertion, not all the pellets inserted could be removed. This was presumably due to pellet absorption, and is consistent with the fact that serum NET levels were undetectable before and after the removal procedure.

The Annuelle® pellet system shows potential as a safe, effective contraceptive. It has a distinct advantage over injectable contraceptive agents, since it can be removed if problems arise or if return of fertility is desired. Further testing to ensure predictable biodegradability of this contraceptive could be one key to its success. Regular counselling during product use could make bleeding irregularities more acceptable. If a suitable formulation can be developed to make this a one- to two-year product, Annuelle® could fill an important niche in the contraceptive marketplace.

VII. REFERENCES

1. Odland V, Moo-Young AJ, Gupta GN, Weiner E, Johansson EDB. Subdermal norethindrone pellets - a method for contraception? *Contraception*. 1979;19:639-648.
2. Joshi UM, Joshi JV, Donde, UM, Sankoli GM, Virkar KD, Saxena, BN. Phase I comparative clinical trial with subdermal implants - bioabsorbable levonorgestrel or norethisterone pellet fused with cholesterol. *Contraception*. 1985;31:71-82.
3. Program for Applied Research on Fertility Regulation. Multicenter clinical trial of implanted norethindrone pellets for long-acting contraception in women. *Contraception*. 1984;30:239-252.
4. Program for Applied Research on Fertility Regulation. Phase II clinical study of implanted norethindrone pellets for long-term contraception in women. *Adv. Contracept*. 1985;1:295-304.
5. Archer D, Jones LD, Grubb GS. Annuelle[®] biodegradable norethindrone subdermal implants: results of a phase I pharmacokinetic trial of manufactured implants. 1992; Family Health International: internal report (nonpublished).
6. Fotherby K. Pharmacokinetics and metabolism of progestins in humans. In: Goldzieher JW, Fotherby K, editors. *Pharmacology of the contraceptive steroids*. New York: Raven Press, 1993.
7. Grubb GS, Goldsmith A, Welch, JD, Rivera R, Cole L. A comparative evaluation of the safety and contraceptive effectiveness of 65 mg and 100 mg of 90-day norethindrone (NET) injectable microspheres: a multicenter study. *Fertil and Steril* 1989;51:803-810.
8. Weiner E and Johansson EDB. Plasma levels of norethindrone after I.M. Injection of 200 mg. norethindrone enanthate. *Contraception*. 1975;11:419-425.
9. World Health Organization. *Norplant[®] contraceptive subdermal implants: Managerial and technical guidelines*. Geneva: WHO, 1990.

APPENDIX I

Summary of Study Procedures

Study period	HGB, SMAC, Lipids†	Pap smear	Urinalysis	P&E assay▪	Baseline Serum NET	Serum NET	Pregnancy test	Pellet insertion	Pulse, BP, Wt.	Pelvic, breast exam	Menstrual Calendar
Pre-Adm§	✓	✓	✓	✓			✓			✓	✓
2X wk for 4 wks				✓							
Adm visit Day 3-6 menses					✓		✓	✓	✓		✓
24 hrs post adm						✓					
1 wk						✓					
1, 2 month						✓	✓				
3-mo f/u visit						✓	✓		✓		✓
4, 5 month						✓	✓				
6 mo f/u visit	✓					✓	✓		✓	✓	✓
7, 8 month						✓	✓				
9 mo f/u visit				★		✓	✓		✓		✓
10, 11 month						✓	✓				
12-mo f/u visit	✓	✓		★		✓	✓		✓	✓	✓
13, 14 month						✓	✓				
15-mo f/u visit				★		✓	✓		✓		✓
16, 17 month						✓	✓				
18-mo f/u visit	✓			★		✓	✓		✓	✓	✓
19, 20 month						✓	✓				
21-mo f/u visit				★		✓	✓		✓		✓
22, 23 month						✓	✓				
24-mo f/u visit	✓	‡	‡	★		✓	✓		‡	‡	✓
25, 26 month						✓	✓				
27-mo f/u visit				★		✓	✓				
28, 29 month						✓	✓				
30-mo f/u visit				★		✓	✓				
31, 32 month						✓	✓				
33-mo f/u visit				★		✓	✓				
34, 35 month						✓	✓				
36-mo f/u visit				★		✓	✓				

† White blood count taken only at admission.
 ▪ Estradiol assay results are available through May 1994; Progesterone assay results are available through August 1994.
 § Pre-admission screening was required to occur no later than Day 5 of menses one cycle before admission.
 ★ After the Pre-admission visit, participants had 10 ml blood draws for P&E assays 2X/wk for 1 month following each quarterly visit.
 # Pap smear, and pelvic and breast exams performed and pulse, blood pressure, and weight measured at Discontinuation Visit as well.
 ‡ Urinalysis performed at 24 months or discontinuation, whichever came first.

APPENDIX II Analysis Methods

A. Analysis population

Data from all participants including those who did not meet inclusion or exclusion criteria or other admission procedures were included in all analyses. Data were analyzed separately for each treatment group, and no statistical comparisons were made between groups. Data obtained on or after pellet removal was excluded from all analyses except as noted below.

B. Admission violations and baseline analyses

Admission violations were defined as those admissions that violated explicit study inclusion or exclusion criteria or who deviated from other admission requirements specified in the protocol. The number and percent of participants in each treatment group with admission violations were calculated, and the reasons for the violations were summarized. Abnormal laboratory results at admission were considered violations in these calculations, although the protocol stated that abnormal values were allowed if the investigator believed that they would not jeopardize participant safety or the study results.

At admission, data on demographic characteristics, reproductive history, recent contraceptive use, recent menstrual history, and medical history were collected from each participant. Results of the baseline physical examination, Pap smear and laboratory tests also were recorded. Categorical data and certain categorized quantitative data were summarized as numbers and percents in frequency tables. For all quantitative data, the mean and standard deviation, median, minimum, and maximum were calculated.

C. Duration of follow-up analyses

The number and percent of participants in each treatment group who returned to the clinic or who were contacted by letter or telephone at each scheduled quarterly follow-up visit through Month 24 were calculated. A participant was considered to have returned for a clinic follow-up visit if she adhered to the following visit schedule:

<u>Visit</u>	<u>Days after pellet insertion</u>
3-month	61 - 121
6-month	153 - 213
9-month	244 - 304
12-month	335 - 395
15-month	426 - 486
18-month	518 - 578
21-month	609 - 669
24-month	700 - 760

Participants with multiple contacts during a single follow-up visit period were counted only once during that period. Contacts that occurred after removal were excluded from this analysis.

D. Discontinuation analyses

The number of participants who discontinued from the study for each discontinuation reason (see Section III.G.4.) were calculated by treatment group. Participants who discontinued due to "desire for pregnancy" were included with those who did so for "other personal" reasons. A list is provided that contains each participant's discontinuation reason and any known details pertaining to this reason.

E. Coital frequency analyses

Average coital frequency since the previous visit as reported by participants was coded as:

- no coitus
- less than once/week
- at least once/week, but less than twice/week
- at least twice/week
- not known (patient not available to ask)

The percent of participants in each treatment group giving each response at each follow-up visit was calculated. Missing responses were included with the "not known" category. Data were analyzed only through the first 12 months of study participation since participants were instructed to use alternate contraception after that time. Data collected at follow-up visits that occurred after removal were excluded from this analysis. If a participant had more than one visit during any follow-up period, the lowest frequency of coitus reported during that period was used.

F. Alternate contraceptive use

The study month that each participant began using any form of alternate contraception, including steroidal methods, was tabulated. Information was collected only at quarterly follow-up visits, and exact dates were collected only for steroidal methods. Therefore, in the table, the time of initiation of other methods was expressed as the earliest month (or range of months) on which an alternative method was definitively known to have been used. A participant from whom contraceptive information was not collected was considered to still be using the same method she was using the previous time information was available about her, until different information was obtained.

G. Efficacy analysis

No pregnancies in either pellet group were reported by the investigators. To provide context for these numbers, the number of woman-months during which no alternate contraception was used was calculated for each group. Each woman contributed to the woman-months analysis from the date of pellet insertion to the following date:

- the day before the earliest date she may have used alternate contraception, if she used alternate contraception;
- the day before pellet removal, if she did not use alternate contraception and the pellets were removed; or
- the day of her last recorded follow-up visit if she did not use alternate contraception and the pellets were not removed; or
- the day of the last NET specimen if she had no follow-up visit, did not use alternate contraception and the pellets were not removed.

Woman-months without alternate contraception were calculated separately for the first year postinsertion, which was the intended assessment period of contraceptive efficacy, and for the study duration. It should be noted that the number of woman-months without alternate contraception is not necessarily the same as the number of woman-months of exposure to pregnancy because coital frequency was not included in the analysis. Therefore, some months may have been included in which intercourse did not occur.

H. Serum NET level analyses

Serum NET levels were obtained at 24 hours, 1 week, and then monthly after pellet insertion until the participant discontinued from the study.

Several different analyses were performed:

1. The mean and standard deviation, median, minimum, and maximum NET levels were calculated by treatment group for each scheduled measurement timepoint.
2. Graphs of each participant's NET level over time were generated.
3. Graphs of the mean levels in each treatment group over time were produced.
4. Box plots of NET levels at each measurement timepoint (except 24 hours) were produced for each treatment group.
5. For each treatment group, a graph of NET levels over time stratified by median baseline weight in that group was produced.

6. The number and percent of participants who ever had a NET serum concentration below 0.3 ng/ml from Month 1 through Month 12 during the study are presented.
7. A life table was produced for each treatment group to show the time until a participant's NET level first fell to <0.3 ng/ml. Monthly intervals through month 33 were used for the calculations; quarterly intervals are presented. Quarterly rates are presented through Month 33.
8. For each treatment group, the null hypothesis that the mean NET serum concentration at the end of Month 12 (days 358-372) was ≤ 0.3 ng/ml was tested using a one-sample t-test (one-sided). The assumption of normality for this test was evaluated using the Shapiro-Wilk test; a p-value ≤ 0.05 was considered statistically significant for both tests. When the assumption of normality was not met, a test of the null hypothesis that the median NET value is ≤ 0.3 ng/ml was performed. An upper 95% exact binomial confidence limit was calculated for the percentage of participants with NET values ≤ 0.3 ng/ml at the end of Month 12. (The 95% upper limit is equivalent to the upper bound of a 90% confidence interval.) If the upper limit is < 0.5 (i.e., less than 50%) the null hypothesis that the median value is ≤ 0.3 ng/ml was rejected (p-value ≤ 0.05).

In performing these analyses, irregular data were handled as follows in the order indicated:

- a. Net values below the detection limit of the assay (<0.112 ng/ml) obtained before admission on the day of admission, and one day after admission were excluded from all NET analyses.
- b. For graphs and calculations requiring assignment of values to a specific timepoint, the result from the latest assay date was used if multiple results were reported (i.e., multiple results with the same specimen date). If two or more values were reported for the latest assay date, then they were averaged together if none of the values were reported as inequalities (i.e., undetectable values or values above the assay detection limit). However, if some of these values were exact values and others were inequalities, only the exact values were averaged.
- c. For all graphs and calculations, levels <0.112 ng/ml were considered to be half the minimum detectable value (i.e., 0.056 ng/ml). For all graphs except the mean NET levels over time, levels reported above 2.25 ng/ml were considered to be equal to 2.25 ng/ml.
- d. For graphs and calculations requiring assignment of values to a specific timepoint, if multiple results were reported for a single participant in the same time period (e.g., more than one result that fit the definition of a "one-month" value), all the values reported for that time period were averaged together, with the following exception. Any value exceeding twice the average of the two preceding and two

following values was considered outside the accepted range. Values outside this range were excluded from the analysis when multiple values were reported during the same time period. All results obtained before pellet removal were considered to determine what value was outside the acceptable range (including results that did not fit into a specific month window). If, under these restrictions, the value under consideration did not have two values preceding it or did not have two values following it, only those values available were used in determining the acceptable range.

Statistical analyses of the NET levels included only results from specimens obtained before removal. Also, NET levels obtained when the participant was known to be using other steroidal contraceptives (such as NORPLANT Implants or oral contraceptives) were discarded, because of the known cross-reactivity of these compounds with NET in the assay.

For these analyses, NET values were assigned to the 24-hour timepoint if they were drawn on the first or second day after pellet insertion. Values were assigned to the one-week timepoint if they were drawn between 4 and 11 days after insertion, inclusive. Values were assigned to a month timepoint if they were obtained within ± 7 days of the end of each study month after pellet insertion. For example, the calculations for the one-month level included only specimens drawn between 23 and 37 days, inclusive. NET levels that were not obtained within these time restrictions (for example, a level obtained on Day 22) were not included in analyses requiring assignment of values to a specific timepoint. Each participant with available data during a given time period contributed one NET value to the analyses of that time period.

I. Serum progesterone level analyses

Serum progesterone levels were analyzed to determine if ovulation had occurred. Two different progesterone levels (3 ng/ml and 5 ng/ml) were used in separate analyses as indicators of ovulation. Higher levels were considered to signify that ovulation had occurred during that month.

The following analysis was performed. The number and percent of participants in each treatment group whose maximum progesterone level was >3 ng/ml and >5 ng/ml were calculated for each of the scheduled measurement times.

Each progesterone result was classified to correspond with a specific measurement timepoint (preadmission, and quarterly beginning at Month 9 through Month 33) as follows:

1. Results from each participant were sorted by specimen date.
2. Beginning with the second specimen date, all results from specimens obtained within 10 days of the previous specimen were grouped together in a cluster. Thus, within each cluster, each result was separated from the next by 10 days or less,

and each cluster was separated from the next by a period of 11 or more days during which no specimens had been obtained.

3. Each cluster with fewer than four observations was excluded from the analysis.
4. Each cluster was assigned to a corresponding scheduled study follow-up visit (preadmission, 9-month, 12-month, 15-month, etc.) according to the month when the middle observation (chronologically) in the cluster had been obtained. If the middle observation had been obtained during the two months prior to admission, it corresponded to pre-admission; during months 9, 10, or 11, it corresponded to the 9-month visit; during months 12, 13, or 14, it corresponded to the 12-month visit, and so on.
5. If a participant had multiple clusters within the same time period, the cluster taken closest to the time specified in the protocol was used. If two clusters occurred equidistant from the protocol designated time (e.g., a cluster at both Month 9 and Month 11), then the later cluster was used.

Within each month (cluster), the maximum progesterone level recorded was used in the analysis. Irregular data were handled in the same manner as described above for NET values (Section H. Serum NET level analyses [b.]). Data obtained on or after initiation of steroidal contraceptives were excluded.

J. Serum estradiol level analyses

Serum estradiol levels were measured at the same times as the progesterone levels. No assays were performed after May 1994.

Two analyses were performed:

1. At each of the five measurement times, the mean, median, minimum, and maximum estradiol values were determined for each participant. Within each treatment group, the mean and standard deviation of the individual participant's mean, minimum, and maximum estradiol concentrations as well as the median of the individual median estradiol concentrations for each of the five measurement times were then calculated.
2. The number and percent of participants in each treatment group whose minimum estradiol value was < 40 pg/ml and of participants whose maximum estradiol value was < 40 pg/ml were calculated for each of the five measurement times.

Irregular data were handled in the same manner as described for NET values (Section H. Serum NET level analyses [b.]).

Estradiol results were classified as corresponding to a specific measurement timepoint as described for progesterone values (**Section I. Serum progesterone level analyses**).

K. Bleeding analyses

All participants were asked to keep bleeding diary cards from the date of the preadmission visit (one menstrual cycle before pellet insertion) through the Month 24 postinsertion. For participants who discontinued before 24 months, data collection stopped the day before discontinuation or removal, whichever came first. (Because of a coding error, in one participant [PON 952/17], the data from the day of discontinuation was included in the analysis.) Data collected after participants started alternate contraception, including steroids, were included in the analysis. On each day, participants recorded either no bleeding, spotting (no sanitary protection needed) or bleeding. For these analysis, spotting was considered the same as bleeding. Only one code could be recorded on each day. The analyses of these data used the reference-period approach most recommended by WHO¹. Data obtained after removal were excluded from the analysis.

1. Reference periods: The bleeding diaries were analyzed for consecutive 90-day reference periods for the study duration (through 719 days [approximately Month 24]). Only reference periods of at least 60 consecutive days contributed to the 90-day reference period analyses. No adjustments were made when calculating the indices for reference periods less than 90 days.

2. Events for analysis: Three events of interest to the analysis were defined as:

- **bleeding/spotting episode:** any set of one or more bleeding or spotting days (either consecutive or separated by only one bleeding-free day) bounded on each end by two or more days free from bleeding or spotting.
- **bleeding/spotting-free interval:** any set of two or more consecutive bleeding-free or spotting-free days bounded by bleeding or spotting days.
- **bleeding segment:** one bleeding episode plus the immediately following bleeding-free interval.

These events are called episodes, intervals, and segments below.

3. Assignment of events to reference periods: If an event began in one reference period but ended in the subsequent reference period it was considered a truncated event. The entire length of a truncated event was counted in the reference period in which it began, with the

¹ World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction. The analysis of vaginal bleeding patterns induced by fertility regulating methods. *Contraception*. 1986;34:253-260.

following exception. An event lasting more than twice the reference period length (≥ 180 days) was assigned a length of 90 days in the analysis for the reference period in which it began and in the next reference period. If an episode or interval lasted more than three times the length of the reference period (≥ 270 days) it was assigned a length of 90 in the reference period in which it began and in the next two reference periods, and so on. If a participant began treatment during a truncated event then those data were considered part of the pretreatment period and were excluded from analysis.

Incomplete events were events that began before the first day covered by the bleeding diaries or an event that ended after the last day covered by the bleeding diaries. Episodes and intervals that were part of an incomplete bleeding segment that were less than 30 days long were excluded from the analysis. This may have resulted in a participant's last complete episode or their last incomplete interval being excluded from the analysis.

4. Missing values: Missing data for one or two consecutive days were considered to have the same bleeding pattern as the day before the missing day or days. If there were missing values on three or more days in a row, all of the participant's bleeding data from that date onward were excluded from the bleeding analysis.

5. Clinically important bleeding patterns: The percentage of participants in each reference period who had each of the following clinically important bleeding patterns was calculated:

- a. **amenorrhea:** no episodes
- b. **prolonged bleeding:** at least one episode lasting 10 days or longer
- c. **frequent bleeding:** more than four episodes
- d. **infrequent bleeding:** only one episode
- e. **irregular bleeding:** range of length of intervals exceeding 17 days

These bleeding patterns are not mutually exclusive; a single woman might have more than one pattern during a particular reference period.

L. Analyses of other laboratory measurements

Laboratory tests were performed according to the schedule presented in Appendix I. The following analyses were performed:

1. Lipids and blood glucose
 - a. Mean values for each measurement (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, HDL/total cholesterol ratio, and glucose) at pre-admission and semiannually thereafter were calculated for each treatment group.

- b. The difference between the mean values at preadmission and each semiannual visit was tested to see if there was a statistically significant change in mean levels since baseline. The assumption of normality was tested using the Shapiro-Wilk test. Comparisons were performed using a paired t-test when the assumption of normality was satisfied. The Wilcoxon signed rank test was used when the assumption of normality was rejected. A p-value $\leq .05$ was declared statistically significant.
- c. Graphs were produced showing the mean percent change over time in each group.

2. Out-of-range values for all laboratory measures

- a. The number and percent of participants to have out-of-range results in any test at each scheduled measurement point, during the first 24 months of the study or after 24 months were calculated. Any participant with multiple out-of-range values for a clinical measure in a time period was counted only once for that time period. The normal ranges used for all of these clinical measures are in Appendix III.

3. Pap smears

- a. The number and percent of participants to have a Pap smear showing any abnormality were calculated.

Data obtained on or after pellet removal and on or after participants started on other steroids were excluded from the analysis. To classify laboratory results as 6, 12, 18, or 24-month measurements, the same follow-up time periods provided in **Section C. Duration of follow-up analyses** were used. Multiple values in the same time period were handled as follows:

1. Baseline results: The value closest to 30 days before insertion was used. If two values were equally close to 30 days before insertion, then these two values were averaged.
2. Results obtained after admission: Multiple values for a given participant in the same time period were averaged, and the average value was used in the calculation of means among all participants in that time period. However, all recorded values were considered in the determination of the number of participants ever to have an out-of-range result.

M. Analyses of clinical observations

Each participant's weight, blood pressure, and pulse were measured before admission and at each quarterly follow-up visit.

The following analyses were performed for weight and blood pressure:

1. The mean value of each parameter at each scheduled measurement point and the differences between mean values before admission and at each quarterly visit

thereafter were calculated using the same procedures described above for lipids and blood glucose (Section L. Analyses of other laboratory measurements).

2. Graphs of the mean percent change over time were produced for blood pressure and weight.
3. The number of participants who had a systolic blood pressure ≤ 155 mm Hg or a diastolic pressure ≤ 95 mm Hg was calculated.

Values for these results were classified into quarterly visit windows using the follow-up time periods defined in **Section C. Duration of follow-up analyses**. Multiple values in the same time period were handled as described above for **Section L. Analyses of other laboratory measurements**. Data obtained on or after pellet removal and on or after participants started on other steroids were excluded from these analyses.

N. Insertion and removal analyses

A clinical summary of pellet insertion and removal was done. For removals, the number and percent of participants who underwent removal procedures, the duration of procedures, the number and length of required incisions, and the condition of the pellets upon removal also was summarized.

O. Adverse events analyses

Information on all adverse events (AEs) participants reported during the study with onset on or before 35 days after pellet removal was recorded as the AEs were detected by the investigators. AEs that continued over multiple follow-up visits were recorded at each visit. Each AE was evaluated for seriousness, severity, how likely it was to be related to the study product, and whether or not it was expected. Serious events were defined as any that required hospitalization or that were fatal, life threatening, permanently disabling, a product overdose or cancer. Severity was rated either mild, moderate, or severe; and relatedness was rated either not related, probably not related, possibly related, or probably related. Investigators were instructed to determine expectedness according to whether or not the condition was listed in the Investigators' Brochure. Because severity and relatedness were rated using the investigators' judgment, ratings were not always consistent for the same condition in different participants, and they may have changed as a condition progressed in a single participant. For example, "ovarian cyst" might have been considered related in one participant but not in another; it also might have been considered related when first detected, but not a month later in the same participant.

Adverse events as reported by the investigator were recoded to standardized preferred terminology using a computerized medical dictionary developed at FHI. Data on all reported AEs that occurred during the study or within 35 days after pellet removal were summarized by body system and preferred term for each treatment group. The number and percent of

participants who ever had any AE in each treatment group, who ever had any AE in a body system, and who ever had each specific condition were calculated. Separate tables were provided for those AEs that were probably related to the study product, possibly related to the study product, and serious and/or unexpected. Data listings were provided for each of these analyses by body system and preferred term for each treatment group. Each unique AE for each participant, as determined by date of onset, is presented once in these listings.

In these analyses, if a participant had more than one condition in a body system, she contributed only once to the total number of participants who ever had AEs in that body system. Similarly, if a participant reported a specific condition more than once during the study, she contributed only once to the total number of participants who ever had that condition. For example, a participant with an ovarian cyst and a urinary tract infection would be included only once in the number of participants with urogenital system problems, but would be counted once for each of the two separate conditions within that body system. Similarly, a participant who had two urinary tract infections during the study would be included only once in the number of participants who ever had a urinary tract infection. (However, both events would be included in the accompanying listing.)

For the analyses, the severity and relatedness of each AE was considered to be the highest degree of severity seriousness, or relatedness ever reported for that AE in that participant. If an AE was ever reported as unexpected, it was considered to be unexpected. The study month in which the AE occurred was determined by subtracting the insertion date from the onset date, dividing by 30.5, truncating this value, and adding one.

Some participants had ongoing AEs after discontinuing from the study. After study closeout, an attempt was made to determine the final outcome of these AEs, and the results of this effort are presented.

APPENDIX III Analytical Laboratory Information

A. Laboratory Analyses

The following laboratories were used to process study specimens:

- NET, estradiol, and progesterone analyses:

- Hormone Assay Laboratory
 - The Jones Institute for Reproductive Medicine
 - Eastern Virginia Medical School
 - 855 W. Brambleton Avenue, Suite E, Norfolk, VA 23511

- Serum lipid analyses:

- Smith Kline Beecham, File #91514, Los Angeles, CA 90074

- Serum chemistry (SMAC) hematology, the center's urine analyses

- Center 952 - Cornell University Hospital Laboratory, New York, NY
 - Center 908 - Smith Kline Beecham, Los Angeles, CA 90074

- Pap smears:

- Center 952 - Cornell University Hospital Laboratory, New York, NY
 - Center 908 - DePaul Hospital Laboratory, Norfolk, VA

- Pregnancy tests:

- performed at each clinic.

B. Steroid analyses

Serum concentrations of progesterone, estradiol, and NET were determined by radioimmunoassay. The progesterone and estradiol assays were performed with double antibody procedures commercially available from ICN Biomedicals, Inc. (Costa Mesa, CA). The intra-assay (average) and inter-assay coefficients of variation for the midrange of the assays were respectively 6% and 7% for progesterone and 8% and 11% for estradiol. The sensitivities of the assays were 0.2 ng/ml for progesterone and 10 pg/ml for estradiol. The NET determinations were performed using a single antibody procedure. The antibody (anti-NET, WHO matched reagent, lot k3627), the reference preparation (Sigma NET no. N6384, lot 33F6215), and tritiated NET were provided by the World Health Organization. Tritiated NET was also obtained from Hazleton Laboratories, Vienna, VA. For the NET assay, serum samples were extracted with diethyl ether. Specimens, controls, and reference standard were incubated overnight with the antibody and tritiated NET. The assay was terminated by the addition of a charcoal suspension. The intra-assay (average) and inter-assay coefficients of variation were 6% and 13%, respectively, for the midrange of the assay. The sensitivity of the assay was 0.112 ng/ml.

C. Laboratory normal reference values

Following are normal reference values for serum lipid, chemistry (SMAC), hematology, and urinalysis tests obtained at admission.

Laboratory test	Center 908	Center 952
<u>Lipids (mg/dl)</u>		
Total cholesterol	<200	<200
HDL	≥55	≥55
LDL	<130	<130
Triglycerides	20-150	20-150
<u>SMAC</u>		
Glucose (mg/dl)	70-115	65-115
LDH-340 (mU/ml)	0-250	110-250
SGOT-340 (AST) (mU/ml)	0-50	1.0-40.0
SGPT (mU/ml)	0-55	1.0-50.0
Alkaline phosphatase (mU/ml)	20-140	31-125
Total bilirubin (mg/dl)	0.2-1.4	0.2-1.3
Creatinine (mg/dl)	0.7-1.4	0.6-1.1
Sodium (meq/l)	135-148	134-143
Potassium (meq/l)	3.5-5.3	3.5-5.2
Chloride (meq/l)	95-110	96-107
Calcium (mg/dl)	8.5-10.6	8.6-10.0
Phosphorus (mg/dl)	2.5-4.5	2.30-4.60
Total protein (gm/dl)	6.0-8.5	6.4-8.0
Albumin (gm/dl)	3.2-5.5	3.70-4.80
<u>Hematology</u>		
Hemoglobin (g/dl)	12.0-15.6	11.9-15.8
White blood cell count (x 10 ³ /cmm)	3.8-10.1	3.9-11.4
<u>Urinalysis</u>		
Specific gravity	1.001-1.035	1.001-1.035
Protein	Negative	Negative
pH	4.6-8.0	5-8
Ketones	Negative	Negative
Glucose	Negative	Negative
Bilirubin	Negative	Negative

APPENDIX IV Protocol & Amendments

Protocol Title:

Phase II-A Pharmacokinetic Evaluation Of
Biodegradable Norethindrone Pellet Implants

Family Health International
Research Triangle Park, North Carolina 27709

Subcontract # _____

ASiml
Principal Investigator's Signature

07/19/91
Date

13 March 1991

BEST AVAILABLE DOCUMENT

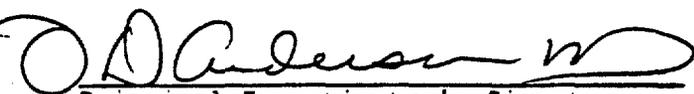
47

Protocol Title:

Phase II-A Pharmacokinetic Evaluation Of
Biodegradable Norethindrone Pellet Implants

Family Health International
Research Triangle Park, North Carolina 27709

Subcontract # _____



Principal Investigator's Signature

6/13/91

Date

13 March 1991

48

TABLE OF CONTENTS

I. Introduction1
II. Objectives1
III. Institutional Review1
IV. Informed Consent1
V. Number of Subjects2
VI. Duration of Study2
VII. Study Product2
VIII. Subject Selection Criteria2
IX. Study Plan4
X. Adverse Experiences10
XI. Data Reporting and Monitoring13
XII. Scientific Integrity13
XIII. Responsibilities of the Principal Investigator14
XIV. Data Analysis16
XV. Investigator's Agreement17

- Appendix A -- Consent Form
Appendix B -- Schedule of Study Events and Tests
Appendix C -- Admission Criteria Check List
Appendix D -- Case Record Forms:

1. Daily Bleeding Record
2. Admission Form
3. Admission Medical and Surgical Diagnoses Form
4. Insertion Form
5. Follow-up Form
6. Concomitant Medication Form
7. Adverse Experience Form
8. Removal Form
9. Discontinuation Form
10. Pregnancy Diagnosis Form
11. Pregnancy Outcome Form
12. Infant Assessment Form
13. Serum NET Results Form
14. Progesterone and Estradiol Results Form
15. Laboratory Test Results Form
16. Urine Test Results Form
17. Lipid Profile Results Form
18. User Opinion Questionnaire

- Appendix E -- Drug Inventory Control Form
Appendix F -- Weight and Frame Size Charts
Appendix G -- Specimen Processing Instructions
Appendix H -- Insertion and Removal Instructions
Appendix I -- Drug Storage Instructions
Appendix J -- Data Analysis Plan
Appendix K -- Sample Size Justification
Appendix L -- Stopping Rules
Appendix M -- Preliminary Adverse Experience Notification Form

I. INTRODUCTION

Norethindrone (NET) pellet implants are composed of norethindrone and cholesterol compressed and heated in an automated process to form pellets the size of a grain of rice. Pellets implanted subdermally are expected to release norethindrone over 12-18 months and totally biodegrade within approximately 15-20 months.

Phase I and II trials conducted in 1980-83 showed that with four pellets, made by a manual process, no pregnancies occurred in 170 women-months of use. There were no major safety problems and there were no clinically significant changes in laboratory values.

A Phase I study in 1988-89 with 4 of the manufactured pellets showed no safety problems but the blood levels of norethindrone were not great enough to sustain contraceptive effectiveness through 12 months of use. Although the pellets do not need to be removed at the end of their duration of action, these studies showed they can be removed when desired. Menstrual disturbances were a common side effect resulting from the use of NET pellets. This side effect is common to the use of all progestogen-only agents for contraception. Please refer to the NET pellet Investigator's Brochure for a complete summary of known information.

II. OBJECTIVES

This study is designed to assess the serum levels of norethindrone, progesterone and estradiol, serum chemistry effects and any adverse experiences following insertion of one of two groups of norethindrone pellet implants. The two groups differ in number of pellets inserted and in the size of the pellets. Secondly, the groups will be compared.

III. INSTITUTIONAL REVIEW

This study has received approval from the Protection of Human Subjects Committee of Family Health International (FHI). The Principal Investigator must provide FHI with written documentation that the study protocol and informed consent forms have been approved by an appropriate local ethics review committee.

IV. INFORMED CONSENT

The risks and benefits of study participation will be explained to each prospective subject by the Principal Investigator or appointed research staff. Each subject will read a copy of the Consent Form (Appendix A), which explains the reasons for the study, the way in which it will be conducted and potential risks and benefits of her participation. If the subject agrees to participate, she must acknowledge informed consent by signing the Consent Form. A copy of the Consent Form will be given to each study participant. The signed consent forms will be kept on file by the Principal Investigator for at least two years after approval of a New Drug Application submitted to the USFDA, or until such time as the Principal Investigator officially releases all study files to FHI.

V. NUMBER OF SUBJECTS

Forty volunteers will enroll in the study with 20 each at two clinics, and, at each clinic, 10 in each of the two treatment groups. (See Appendix K for sample size justification).

VI. DURATION OF STUDY

Each subject will be in the study for up to 24 months.

VII. STUDY PRODUCT

Two treatments will be evaluated: Groups D and E. (Groups A, B, and C were evaluated in an earlier study and will not be evaluated further). Group D will consist of four pellets, each 2.75 mm in diameter. Group D will contain a mean total dose of 168 mg NET. Group E will consist of five pellets, each 3.0 mm in diameter. Group E will contain a mean total dose of 253 mg NET. For both treatments each pellet will be 8 mm long, and contain 85% norethindrone and 15% cholesterol by weight. Each dose of pellets will be packed in a sterile, disposable trocar.

VIII. SUBJECT SELECTION CRITERIA

After each woman has been informed of the purpose of the study, the following admission criteria will be used to determine her eligibility to participate in the study. An Admission Criteria Check List (Appendix C) will be completed for each woman being considered for involvement in the study.

Inclusion Criteria

A woman must meet all the following criteria in order to enter the study:

1. Age 18-35 years
2. Sexually active with regular coitus
3. Weight of 95-170 lbs, with deviation no more than 15% from ideal weight (see Appendix F)
4. Regular menstrual periods (at least 25 days and no more than 35 days between starting one period and the next)
5. Normal physical examination and laboratory screening

This screening will be performed no more than 30 days prior to entry into the study.

Tests will include the following:

Blood Chemistry: fasting blood glucose, cholesterol, triglycerides, HDL and LDL, LDH, SGOT, SGPT, alkaline phosphatase, total bilirubin, creatinine, sodium, potassium, chloride, calcium, phosphorus, total protein and albumin.

Hematology: hemoglobin, total white blood cell count.

Urinalysis: routine urinalysis (Clinitest strip or equivalent).
Microscopic examination may be waived unless clinically indicated.

Abnormal lab values. A clinically significant abnormal value in any laboratory procedure must be repeated, but only if the patient continues to be considered for inclusion in the study. A second significantly abnormal value will disqualify the subject from the study unless, in the opinion of the investigator, the abnormality: 1) is consistent with the subject's condition or past medical history, 2) does not jeopardize her health, 3) is not related to any contraindication for oral contraceptives, and 4) will not compromise the study results.

Abnormal values significant for exclusion from study participation or discontinuation will be reported to the patient.

6. Normal or mildly abnormal Pap smear (Class I or IIa) at admission. This procedure may be waived if a normal Pap smear (Class I only) has been documented at the study site within 6 months prior to admission.

Subjects whose Papanicolaou smear results are returned with abnormal findings (Class IIb, III or IV) should not be included in the trial and should be referred for treatment.

7. Freely consents to participate in the study.
8. Agrees to rely exclusively upon the norethindrone implant contraceptive as her only method of contraception for the first 13 months after admission, unless advised otherwise by the investigator.
9. Negative pregnancy test (Investigators will use a test with a sensitivity of <0.4 IU HCG/ml).

Exclusion Criteria

A woman cannot enter the study if any of the following criteria exist at study initiation:

1. Known or suspected pregnancy
2. History or evidence of infertility or sterilization
3. History or evidence of thrombophlebitis or thromboembolic disorders
4. History or evidence of cerebrovascular or coronary artery disease

52

5. Frequent and severe headaches, including migraine headaches
6. Hypertension (systolic >150 mm Hg or diastolic >90 mm Hg)
7. Diabetes
8. Epilepsy
9. Active gallbladder, liver or renal disease in past 6 months
10. Benign or malignant liver tumor
11. Known or suspected breast cancer or cancer of reproductive organs
12. Undiagnosed vaginal bleeding
13. Hemoglobin <11.0 grams/dl
14. SGOT or LDH or alkaline phosphatase > 2 times the upper limit of normal
15. Total cholesterol > 240 mg/dl, or HDL < 35 mg/dl
16. Elective surgery requiring immobilization planned during study period
17. Breastfeeding a child
18. Previous hysterectomy
19. Participation in a research study involving an experimental medication in last 3 months
20. Other contraindications to the use of oral contraceptives
21. Use of rifampin, ampicillin, amoxicillin, griseofulvin, barbiturates, or phenytoin currently or within the last 30 days
22. Use of any exogenous hormonal preparation chronically or in the last 30 days
23. Use of oral contraceptives or other hormonal contraceptives during the menstrual cycle prior to pellet insertion (a spontaneous menstruation must occur 25 or more days after the pill has been discontinued before the subject can have pellets inserted)

IX. STUDY PLAN

A. Study Design

This is an open label, randomized study of two doses of NET pellet subdermal implants, conducted at two centers. Forty volunteers (twenty at

each center) will be randomly allocated to one of two treatment groups (D or E). Group D will receive 4 pellets of 2.75 mm diameter, each 8 mm long. Group E will receive 5 pellets of 3.0 mm diameter, each 8 mm long. There will be 20 subjects in each of the 2 groups. This study will measure the plasma levels of norethindrone, progesterone and estradiol in subjects prior to and following insertion of the NET pellet implant.

B. Preadmission Visit

The preadmission visit will take place one menstrual cycle prior to insertion of the pellets (the admission visit), and will occur no more than five days after onset of menses. The patient order number (PON) which identifies each subject on the case report forms will not be assigned at this visit, but will be assigned at the admission visit.

Upon giving informed consent each subject will receive a general physical and have her medical history taken. This visit constitutes the beginning of the run-in cycle (described in Section C). A pelvic and breast exam must be completed sometime during the run-in cycle, with results known prior to pellet insertion.

Pill users: Potential subjects who are using oral contraceptives will have their preadmission visit scheduled during their withdrawal bleed (following the usual 21 day active pill cycle), and will stop pill use at that time. They will be counseled regarding an appropriate non-steroid contraceptive method during the run-in cycle. The run-in cycle will last until a spontaneous menses occurs at least 25 days after the pill is stopped.

Baseline lab tests. Blood draws for baseline lab tests must be done no more than 30 days prior to the admission visit. The results of the baseline lab tests must be reviewed prior to admission. The following baseline lab tests may be done at the preadmission visit, but if it is likely the subject will not menstruate within the next 30 days the tests may be put off to a later date, when the subject returns for one of the run-in cycle progesterone and estradiol blood draws.

- 1) Papanicolaou smear (unless done within the prior six months),
- 2) hemoglobin,
- 3) white blood cell count,
- 4) SMAC,
- 5) urinalysis,
- 6) lipid panel (sent to SmithKline BioScience Laboratories).

Please note that the baseline test for serum NET concentration is to be done at the admission visit, prior to pellet insertion.

Sample procedures. Blood samples for hematology (5 ml) and SMAC (10 ml) will be drawn from fasting women (all women will fast overnight before the blood samples are drawn). After the pellets are inserted, all blood samples must be drawn from the arm contralateral to the arm with the implants.

Procedures for taking blood and urine are given in Appendix G. All test results must be reviewed by the Investigator before insertion of the NET pellet implants. The patient will be informed if any lab tests done at preadmission or during the study indicate a possible health problem.

Bleeding calendars. Women will be asked to complete bleeding calendars (Daily Bleeding Record) during each month of the study beginning with the preadmission visit.

The admission visit (for pellet insertion) should be tentatively scheduled at this time based on the expected next menses of the subject.

C. Run-in Cycle

Serum Progesterone/Estradiol levels. Starting with the preadmission visit on day 1 to 5 of the menstrual cycle, subjects will return 2 times a week to have blood samples (10 ml) drawn for progesterone (P) and estradiol (E₂) levels. There will be no fewer than 2 days and no more than 4 days between blood sampling. If any of the above preadmission labs are found to exclude the subject from the study, she will be notified and no further blood samples for P or E₂ will be drawn.

A blood sample for baseline serum NET concentration will be drawn in the week prior to insertion, at the same time as one of the samples for P and E₂.

D. Admission Visit: Insertion of Pellets

For women wishing to participate in the study, the admission visit will be scheduled between days 3 and 6 of their first menses following the run-in cycle. On the day of admission, but prior to having the pellets inserted each subject will:

- 1) be given a pregnancy test
- 2) have blood drawn for serum NET level (to be sent to CONRAD lab)

Also, before entering the study, each subject must be documented to have:

- 1) normal lab results (as specified in Item 5 of the inclusion criteria)
- 2) negative pregnancy test
- 3) Class I or IIa Pap smear
- 4) met all other study entry criteria
- 5) been provided with instructions about study participation

The insertion procedure is described in Appendix H.

Patient Order Number. Each subject will receive her study identification number, the Patient Order Number (PON), at the admission visit. Computer generated sealed envelopes will be provided with the study PONs printed in chronological order on the outside. These envelopes will reveal the treatment group assigned to each PON. The numbers will be assigned in numeric sequence. If a woman is later discontinued for any reason, her PON will not be reissued. The next woman entering the trial will be assigned the next available patient order number.

Forms to be Completed. The Admission Form, Admission Medical and Surgical Diagnoses Form, and Concomitant Medication Form (see Appendix D) will be completed at the time of insertion. The Laboratory Test Results Form, Serum NET Results Form, Progesterone and Estradiol Results Form and Urine Test Results Form will be completed for each blood or urine sample that was collected at or prior to the admission visit.

Master Log. A confidential master log of study participant names, addresses, phone numbers, clinic file numbers and study patient order numbers will be maintained by the clinic. All patient discontinuations will be noted in this log to facilitate study status review.

Follow-up appointments will be given to the woman at the time of the first insertion.

E. Follow-up Lab and Clinic Visits

Follow-up Clinic Visits. All subjects will be scheduled to return for follow-up clinic visits on a quarterly basis at 3, 6, 9, 12, 15, 18, 21 and 24 months after the insertion. Subjects will be asked to bring completed daily bleeding record forms to each visit. A pregnancy test will be administered, and pulse, blood pressure and weight will be taken at each visit. Pelvic and breast exams will be given at the 6, 12, 18 and 24 month visits.

NET Levels. Subjects will return for lab visits to have a 5 ml blood sample drawn for serum NET levels from the same arm 24 hours (1 day) later and at 1 week after insertion, then monthly thereafter for up to 24 months until NET levels drop to < 0.3 ng/ml. At that point, they will return once every three months until two NET levels are < 0.1 ng/ml. If a subject has her pellets removed, she will be requested to return for blood samples 2-4 weeks post-removal to determine serum NET levels.

Pregnancy Tests. Urine pregnancy tests will be done monthly at the visit for the NET level blood sample.

Resumption of Alternate Contraception. All subjects will begin use of a contraceptive beginning 13 months after admission. However, if serum NET levels fall below 0.3 ng/ml, regardless of time in the study, subjects should be advised to use an alternate contraceptive method. If OCs are used, the progestin component must not be norethindrone (e.g. levonorgestrel).

Hgb, SMAC and Lipids. A 15 ml blood sample will be drawn every six months at the clinic follow-up visit for hematologic, modified SMAC and lipid (triglyceride, total cholesterol, HDL and LDL) tests. The visits at which this will occur are the preadmission, 6, 12, 18 and 24 month visits. All women will fast overnight before these 15 ml samples are drawn.

Serum Progesterone/Estradiol Levels. Following the preadmission and the 9, 12, 15 and 18 month follow-up visits, women will return two times a week for one month to have blood samples (10 ml) drawn for progesterone and estradiol assays. However, subjects will not return for blood sampling once serum NET levels are documented to be at or below 0.1 ng/ml.

Urinalysis. A urinalysis will be performed at the preadmission and termination visits.

Pap Test. A Pap test will be administered at preadmission, the 12 month and the 24 month visit.

Appendix B shows the laboratory test schedule in detail.

Subject Complaints. At each quarterly clinic follow-up visit, subjects will be questioned about any perceived discomfort, as well as any other symptoms or events they experience. Subjects should not be asked about specific symptoms or events, but should be encouraged to volunteer any complaints. The reporting of all complaints, regardless of severity, will be indicated on the Follow-up Form and recorded in detail on the Adverse Experience Form (Section X. Adverse Experiences).

Medication. If the subject received any prescribed medication or therapy for any reason since the last contact, this will be indicated on the Follow-up Form and described in detail on the Concomitant Medication Form. The Concomitant Medication Form will not be sent to FHI until the patient has completed or been discontinued from the study.

Treatment for Vaginal Bleeding. If a woman is treated with hormones or surgery for bleeding, she must be discontinued from the study at the time treatment begins. In addition, the course of treatments and outcome must be fully documented.

User Opinion Questionnaires. At the 6 month, 18 month, and termination visit all subjects will be asked to complete a User Opinion Questionnaire.

F. Discontinuation from the Study

Women will be discontinued from the study and their implants removed for any of the following reasons:

- 1) they become pregnant (pregnancy will be followed and outcome reported)
- 2) the Principal Investigator feels it is in the subject's best clinical interest
- 3) treatment is necessary for vaginal bleeding
- 4) at the Principal Investigator's discretion because of poor compliance with protocol
- 5) they choose to discontinue for any reason after appropriate counseling
- 6) their serum NET concentration is <0.1 ng/ml on two measurements (at which point they will have completed the study).

If any of the reasons for initial exclusion of patients from the study occur during the course of the study, the continuation of the patient will be discussed between the investigator and FHI.

In addition, patients who are lost to follow-up will be considered discontinued from the study (see section H).

Reasons for study discontinuation must be fully documented for each woman.

A Follow-up Form, Removal Form (if applicable) and Discontinuation Form must be completed for all subjects discontinuing from the study. All exams and lab tests scheduled for the 24 month visit should be completed for all early discontinuation visits. In addition, the subject will be asked to return for blood sampling 2 to 4 weeks after implant removal to determine serum NET levels.

If pregnancy rates over the course of the study are higher than expected, the study may be terminated according to criteria described in Appendix L.

G. Removal of Pellets

The investigator will remove the pellets following the protocol provided by Endocon for handling and shipment of the pellets. A Follow-up Form, Removal Form and Discontinuation Form (Appendix D) will be completed for the subject. The subject will be given a general physical pelvic and breast exam. Blood will be drawn (10 ml) for a modified SMC and hematology profile. A routine urinalysis and a pregnancy test will be done.

The subject will be requested to return for blood samples 2-4 weeks post-removal to determine serum NET levels.

H. Lost to Follow-up

If a subject fails to return for a scheduled follow-up visit, at least three attempts must be made to contact the subject by phone to encourage her to come in to the clinic. If the subject cannot be contacted or fails to return to the clinic despite being contacted, a certified letter (explaining the risks of not returning) will be sent to her at her last known address. Subjects who cannot be contacted will be considered lost to follow-up if two consecutive quarterly follow-up visits are missed. A Discontinuation Form will be completed.

I. Laboratory Evaluation

NET, P, E₂. For the NET, P and E₂ analysis, the serum samples (5 ml) must be sent under dry ice to: Mary Beth Southern; The CONRAD Program; The Jones Institute Research Laboratories; Room A-11; Eastern Virginia Medical School; 855 W. Brambleton Ave., Suite B; Norfolk, VA 23510.

Each vial will be labeled with indelible ink indicating the center number and patient's study number, and date that blood sample was collected (Appendix G).

Results will be reported to FHI and the Investigator directly from the laboratory.

Lipids. For lipid studies, serum samples (5 ml) will be picked up at the study site by SmithKline BioScience Laboratories of Van Nuys, California (Appendix G). Results will be reported on the Lipid Profile Results Form (Appendix D).

The study center will perform the remaining laboratory tests on each blood and urine sample and report results to FHI on the appropriate forms (Appendix D).

J. Product Supplies

The clinical investigator is responsible for keeping an accurate inventory of the NET pellet implants used in this study. Each implant set will be labeled with dosage, manufacturer and package number. This number will be recorded on the Insertion Form. The NET pellet implant sets must be kept in a secure area with limited access. Instructions for storing the product are given in Appendix I.

The package number of each NET pellet implant set dispensed will be recorded on the Drug Inventory Control Form (Appendix E), identifying the subject who received it.

A dispensing record must also be kept of all pregnancy test kits supplied by FHI.

X. ADVERSE EXPERIENCES

Each woman will be advised to contact the investigator (or study coordinator) immediately if she has any medical problems during the course of this study.

All adverse experiences occurring during this study will be recorded on the Adverse Experience Form (Appendix D). Each sign or symptom reported will be graded on a 3 point scale (mild, moderate, or severe). The resolution (and date resolved) or continuation of each adverse experience will also be noted on the Adverse Experience Form.

The Investigator will discern whether or not the adverse experience is considered serious. The following reasons require classification as serious:

- 1) the event was fatal or life-threatening;
- 2) the event permanently disabled the subject;
- 3) the subject required inpatient hospitalization;
- 4) the event was the occurrence of cancer of any type;
- 5) the event was an overdose of the study product;
- 6) the event was an occurrence of a congenital anomaly in an infant conceived during the study.

The Investigator will discern whether or not the adverse experience is considered unexpected. Any event not identified in nature, severity, or frequency in the Investigator Brochure must be classified as unexpected.

The Investigator must attempt to explain each adverse experience and its relationship to the product (s) under investigation. The following criteria are to be used for determining the relationship of adverse experiences to the investigational product:

NOT RELATED. This category applies to those adverse experiences which, after careful medical consideration, are clearly felt to be due to extraneous causes (disease, environment, etc.) unrelated to the product under investigation.

PROBABLY NOT RELATED. This category applies to those adverse experiences which, after careful medical consideration, are felt unlikely to be related to the product under investigation with near certainty. An adverse experience can be considered "probably not related" if: it does not follow a reasonable temporal sequence from exposure to the product under investigation; it could readily have been a result of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; it does not reappear or worsen upon re-exposure to the product.

POSSIBLY RELATED. This category applies to those adverse experiences which, after careful medical consideration, are felt unlikely to be related to the product under investigation, although the possibility cannot be ruled out with certainty. An adverse experience can be considered "possibly related" if: it follows a reasonable temporal sequence from exposure to the product under investigation, but it could readily have been a result of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; it may or may not follow a know response pattern to the product under investigation.

PROBABLY RELATED. This category applies to those adverse experiences which, after careful medical consideration, are felt with a high degree of certainty to be related to the product under investigation. An adverse experience can be considered "probably related" if: it follows a reasonable temporal sequence from exposure to the product under investigation; it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; it disappears or decreases upon cessation of exposure or reduction in dose (there are exceptions when an adverse experience does not disappear upon cessation of exposure, yet relatedness clearly exists); it follows a know pattern of response to the suspected product under investigation.

Any 1) fatal, 2) life-threatening, 3) serious and unexpected reaction, or 4) unusual frequency of reactions, even though they may not appear to be related to the product under investigation, will be reported promptly by telephone, telex, fax or cable notification to:

Gary S. Grubb, MD
Associate Medical Director, Clinical Trials
FAMILY HEALTH INTERNATIONAL
P.O. Box 13950
Research Triangle Park, NC 27709

Telephone: 919-544-7040 (FHI office) or
[REDACTED]

or

Roberto Rivera, M.D.
Clinical Trials
FAMILY HEALTH INTERNATIONAL
P.O. Box 13950
Research Triangle Park, NC 27709

Telephone: 919-544-7040 (FHI office) or
[REDACTED]

If neither of the above persons can be reached, send notification to FHI using the following numbers:

Telex: 579442

FAX: 919-544-7261

Cable: FAMHEALTH

Preliminary reports of deaths or severe or unusual adverse experiences will be followed by detailed descriptions on the Preliminary Adverse Experience Notification Form (Appendix M) and will include copies of hospitalization summaries, pathology reports, operative reports, laboratory reports, autopsy reports and/or other documents when applicable.

For all adverse experiences, subjects will be followed until the adverse experience resolves or stabilizes.

Pregnancy. If a subject becomes pregnant, the pellet implants shall be removed as soon as possible. All pregnancies are to be reported immediately to FHI by telephone, telex, FAX or cable, and a Pregnancy Diagnosis form is to be completed and submitted immediately (Appendix D). Pregnancies will be followed to their conclusion, with outcomes of all pregnancies reported to FHI on a Pregnancy Outcome Form and on an Infant Assessment Form when applicable.

XI. DATA REPORTING AND MONITORING

Copies of all case report forms are included in Appendix D.

A complete set of forms printed on NCR paper in triplicate will be supplied to the investigator. The original and the yellow copy of each completed form will be submitted to FHI monthly for processing and analysis. The pink copy will be retained in the participant's study file, which will be kept at the clinic.

Any forms or other documentation sent to FHI should have the patient's name and other identifying information removed. Subjects will be identified at FHI solely by the combination of center number, study number, patient order number and admission form number.

Changes on Forms. It is an FDA requirement that the copy on file at FHI and on file at the center match in every detail. Therefore, no changes may be made on one that do not appear on the other. All corrections made to the forms before sending them to FHI must be made on all copies, with each correction dated and initialed by the investigator or sub-investigator (listed on the FDA 1572 form). The study coordinator may make corrections to the forms if done so before they are reviewed and signed by the investigator or sub-investigator; these changes must also be dated and initialed.

When an error is detected on a form received by FHI (e.g., an item left blank or an inconsistency between dates), a query will be written that identifies the apparent error and requests a correction or validation of the submitted information. The center will receive the white and yellow copies of the query form, with FHI retaining the pink copy for its records. The answer will be written onto the query form by an appropriate person at the center. Each query must be signed and dated by the Investigator or sub-investigator. The center will retain the yellow copy, attaching it to the case report form that was the subject of the query. The white copy of the query will then be returned to FHI. This process will enable FHI to legally make a correction to the case report form it has in-house.

Monitoring. To facilitate data coordination and quality assurance during the course of the study, an FHI clinical monitor will visit the clinic approximately every 3-6 months during the course of the study to review source documents and case report forms and help in any way with the implementation of the study. The FHI Quality Assurance Division will perform randomly selected site study audits.

XII. SCIENTIFIC INTEGRITY

Concern in the United States about the quality of biomedical and behavioral research has led to the establishment of regulations and guidelines for handling allegations of scientific misconduct. As a recipient of U.S. Government funding, FHI is obliged to develop policies and procedures that conform to these regulations. In fact, this requirement does not conflict with FHI's historic posture with regard to scientific integrity. FHI continues to exercise its discretion in working with colleagues in the United States and abroad who maintain similar respect for our profession.

The regulations do establish additional obligations on FHI with respect to the handling of such information that may come into our hands. This policy articulates the position that we will maintain should questions arise with regard to any research with which we are associated.

In addition, the regulations require that we establish procedures that we will follow in initiating an inquiry, pursuing an investigation if warranted, and, if necessary, informing a specified circle of authorities should the situation warrant it.

A copy of this policy and the attendant procedures is available in FHI and will be made available to you on request (FHI Policy No. 29 and Procedure No. 8).

XIII. RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR

Prior to Study Initiation:

1. Obtain local IRB approval to conduct the project, or inform FHI in writing, using the "Notification of Institutional Review Board Approval" form, that no local IRB is available. FHI's PHSC will then act as the local IRB.
2. Provide FHI with written documentation that the study protocol and informed consent have been approved by the local IRB. Any changes made to the protocol or to the informed consent must be approved by both the local IRB and FHI's PHSC prior to implementation.
3. Provide FHI with the membership roster of the local Institutional Review Board (IRB), including member affiliations and qualifications. Some US centers may have a general assurance number (assigned by the Department of Health and Human Services) which satisfies this requirement.
4. Sign and date the study protocol and return it to FHI. All changes or revisions to the protocol must be signed, dated and maintained with the original protocol.
5. Complete, sign and return to FHI a Statement of Investigator Form (FDA 1572).
6. Provide FHI with a Curriculum Vitae for the Principal Investigator and each Subinvestigator.
7. Supply FHI with a copy of the current license or certification for all laboratories used for the study.
8. Provide normal ranges for all laboratory tests required by the protocol.

After Study Initiation:

9. Conduct the study in strict accordance with the protocol.
10. Inform each patient of the risks and benefits of participation in the study and obtain a properly executed signed informed consent for each study participant.
11. Instruct each participant to contact the clinic if she suspects she may be pregnant, or if she experiences any serious experience during the study.
12. Report all life-threatening, fatal, or serious and unexpected adverse experiences immediately to the local IRB and FHI's PHSC by telephone, telex, FAX or cable and by submitting an Adverse Experience Form.
13. Document every adverse experience on the Adverse Experience Form and submit it to FHI.
14. Report to the local IRB as required. The local IRB must assume continued responsibility for the project and review the research on a regular basis (at least annually for FDA regulated studies). A final study summary report must be presented to the IRB following close out of the study. A letter from the local IRB must be obtained annually and sent to FHI stating continued approval of the research.
15. Send copies to FHI of all communications between the Investigator and the local IRB on issues related to this project.
16. Document and maintain adequate, accurate case reports of all participants treated with the study product as required at designated times. Sign each form, assuring the accuracy of data entered on the case report forms. Storage and custody of all records is also the responsibility of the Principal Investigator.
17. Provide FHI with original copies of all completed case report forms pertaining to the study on at least a monthly basis.
18. Make available for review by FHI staff, FDA personnel, and other authorized individuals all participant clinical records which relate to this study. Maintain records of all site visits made by the above.
19. Ensure confidentiality of all participant records which relate to the study.
20. Provide appropriate health care or referral for the study participants throughout the study.

21. Maintain a master log of study participants and establish a system to alert clinic personnel to scheduled follow-up contacts. Provide clinic personnel with a method of contacting participants who do not return for scheduled visits.
22. Complete all required laboratory tests in accordance with the protocol timetable.
23. Answer all FHI data queries in a timely fashion.
24. Supervise the use of the study product in accordance with the protocol. The investigational drug can only be administered to subjects under the principal investigator's personal supervision or under the supervision of the subinvestigator. The product may not be provided to any personnel not working under the direct supervision of the investigator or for any purpose other than conducting this study.
25. Store the study product in a secure area with limited access.
26. Maintain adequate records of the receipt and disposition of each packet of inserters and NET pellets, including dates of insertion and removal problems associated with use.
27. Store and ship all removed pellets following protocol provided by Endocon, Inc.

After the Study Concludes:

28. Return to Endocon, Inc. any unused supply of the study product following completion, discontinuation, termination or suspension of the study.
29. Retain copies for all screened and admitted patients of the case report forms and consent forms at the center for at least two years following the date a marketing application is approved for the drug or until two years after the investigation is discontinued and the FDA is notified. In any case, FHI will notify the Investigator when the two-year period commences.

XIV. DATA ANALYSIS

Data analysis will describe the pharmacokinetics of the release of norethindrone, the occurrence of ovulation indicators (progesterone and estradiol), clinical and laboratory safety measures, vaginal bleeding profile and acceptability. The two treatment groups will be evaluated separately. Secondly, the two treatments will be compared. Details of the methods of analysis are described in Appendix J.

65

XV. INVESTIGATOR'S AGREEMENT

As the Principal Investigator responsible for this study, I agree to conduct the study as described in the above protocol.

Principal Investigator's Signature

Date

Subinvestigator Signature

Date

Subinvestigator Signature

Date

Phase II-A Pharmacokinetic Evaluation of Biodegradable Norethindrone Pellet Implants

March 13, 1991

Appendix A

INFORMED CONSENT

Name of Study: Phase II-A Pharmacokinetic Evaluation of Biodegradable
Norethindrone Pellet Implants

Principal Investigator: _____

Reason for the Study

We would like you to be in a research study to find out whether a special form of norethindrone (called NET for short) in two doses works as a birth control method. This study has been approved by the ethics review committees of both Family Health International and this clinic.

NET is a drug which has been widely used in birth control pills. The NET has been put into pellets, each about the size of a grain of rice which dissolves slowly after being placed just under the skin in your upper arm. Both doses should protect against getting pregnant for 13 months and you will be assigned to get one of the doses. We will measure how much NET is in your blood during the study. Past studies of a lower dose of the pellet implants among 35 women showed it is safe.

Because we want to see what happens to the pellets after 13 months, the study will last for up to 24 months. At this clinic there will be 20 women taking part in the study. There will be 40 women in the study in total.

If you agree to be in this study you will return often to the clinic. In your first visit you will have a pelvic exam, breast exam and Pap smear, and will give a blood sample (no more than 5 teaspoons) to be sure you are healthy. You will then return twice a week over the next month to give a blood sample (about 2 teaspoons of blood will be taken each time). Then you will have 4 or 5 NET pellets placed in your arm. Every three months you will return to the clinic to answer questions about your health and to have a checkup. You will return to the clinic more often than that to give blood samples. You will be asked to keep a daily record of whether or not you had bleeding or spotting, and you will be asked how often you have sex.

Once a month you will come to the clinic to give a blood sample (no more than 1 teaspoon). Also, after your 9 month, 12 month, 15 month and 18 month checkup visit, you will be asked to come in 2 times a week for one month to give a blood sample (no more than 2 teaspoons). Over the normal course of the study not more than 1 pint of blood will be taken.

Once the NET in your blood falls below a certain low level, you will stop giving blood samples.

Each six months you will have a pelvic and breast exam. You will be told if any of the test results are not normal and would affect your health care.

If you decide to be in the study, we ask that you not use any other kind of birth control for the first 13 months of the study unless the study doctor suggests you do so. After 13 months you will decide what type of birth control you would like to use. You will not be able to use the Pill until after 13 months in the study.

Tell the clinic right away if you take antibiotics or barbiturates since they may cause the NET pellets to not work as well. Other birth control can be used in those cases, but the doctor needs to know.

Benefits and Risks

We think that the NET pellet implants will keep most women from getting pregnant. However, we cannot promise that you will not become pregnant while in the study. We will give you the NET pellets at no cost while you are in the study, and we will check your health at each return visit. What we learn from this study may help to improve the health of others.

The NET pellet does not protect against sexually transmitted diseases. Putting the NET pellets in your arm may cause some pain and bruising which may last for a few days. The small cut will be covered with a special bandage but there will be a small scar that will later fade away. There is a small risk of infection and You may feel a small amount of pain or have a bruise at the place where blood is taken. The NET pellets may change your periods, causing them to be irregular, extra heavy, extra light, or not to happen at all for awhile. You should contact your doctor if you have very heavy menstrual bleeding. Other side effects which are less likely to occur include weight gain, dizziness, abdominal discomfort, nausea and headaches.

You may ask to have the NET pellets removed at any time and you will be counseled by the clinic staff before the removal. The removal will require one or two small incisions. There may be some pain and bruising. If the NET pellets are removed, the drug will no longer be present in your blood after three days. There is a small chance that all of the pellets cannot be removed. If all cannot be removed, a low level of NET will stay in your system until the pellets dissolve (about 15-20 months).

If you should happen to become pregnant while using the NET pellets, the risk to your baby is not known. An increased risk of birth defects, including heart and limb defects, has been reported during pregnancy with the use of sex hormones like those used in birth control pills.

Other Methods of Birth Control

There are other methods of birth control available. If you decide not to be in the study, you may choose any of these other methods so long as you have no health problems that would cause us to advise against it. You may discuss these other methods with the clinic staff before deciding to be in the study.

Confidentiality

To protect your privacy, forms which are sent out of the clinic will not show your name. If the results of this study are published, your name will not be shown. However, as part of this study the staff of Family Health International and the United States Food and Drug Administration may sometimes look at your complete medical record which is kept at the clinic.

Compensation

You do not have to be in this study. You will be paid \$_____ for each blood sample you give and \$_____ for each checkup visit. You will receive the payments at the next checkup visit you go to.

If you are sick, or have a health problem because you are in this study, you will not have to pay for visits to see the study doctor. If you need more help, we will refer you to other clinics, where you may have to pay.

Right to Leave the Study

You may leave the study at any time. Also, the doctor may ask you to leave the study if he or she feels it is best for you, if you are not able to follow the study procedures or if the study is stopped. When you are no longer in the study, you will still be able to use this clinic. We will tell you if we learn of something new about the NET pellet implant that could affect your choice to be in the study. If you want to leave the study, please tell the doctor or clinic staff why you wish to leave and schedule your final study visit to have the NET pellets removed.

Contact for Questions

Please contact _____ if you have any problems or questions about this study, or about your rights while you are in the study.

If you get sick, you should phone or come back to the clinic. Also, if you think you are pregnant at any time during the study, please come back to see the doctor right away.

If you have a health problem which may be due to the study or any medical question about the study, please ask

Dr. _____ [phone number] or
Dr. _____ [phone number].

We will give you a copy of this form.

69

Height (cm)	Weight (kg)*					
	Optimal Range			Acceptable Range For This Study**		
	Small Frame	Medium Frame	Large Frame	Small Frame	Medium Frame	Large Frame
146	46-51	50-55	54-60	43-58	43-63	46-69
148	47-51	50-56	54-61	43-59	43-64	46-70
150	47-52	51-57	55-62	43-60	43-66	47-71
152	48-53	52-58	56-63	43-61	44-67	48-72
154	49-54	53-59	57-64	43-62	45-68	49-74
156	49-55	54-60	58-65	43-63	46-69	50-75
158	50-56	55-61	59-67	43-65	47-70	50-77
160	51-57	56-62	61-68	44-66	48-72	51-77
162	53-58	57-63	62-70	45-67	48-73	52-77
164	54-60	58-65	62-71	46-68	49-74	53-77
166	55-61	59-66	64-72	46-70	50-75	54-77
168	56-62	60-67	65-74	47-71	51-77	55-77
170	57-63	61-68	66-75	48-72	52-77	56-77
172	58-64	62-69	67-76	49-73	53-77	57-77
174	59-65	63-70	68-78	50-75	54-77	58-77
176	60-66	65-71	69-79	51-76	55-77	59-77
178	61-67	66-72	70-80	52-77	56-77	60-77

* All weight measurements include 1.4 kg for clothing.

Height is measured without shoes.

** Weight at admission cannot deviate more than 15% from optimal weight.

Acceptable range includes this deviation and 43 to 77 kg overall limit.

Guidelines for body frame: Body frame size is determined by elbow breadth, the measured space between the two prominent bones on either side of the elbow. This measurement should be taken while the arm is extended and the forearm is bent upwards at a 90-degree angle. The most accurate measurement can be obtained by using calipers.

The table below lists measurements for the medium frame category for women. A measurement falling below this range would constitute a small frame, a measurement higher would constitute a large frame.

Height (inches)	Elbow Breadth (inches)	Height (cm)	Elbow Breadth (cm)
57-58	2 1/4-2 1/2	146-149	5.6-6.4
59-62	2 1/4-2 1/2	150-159	5.8-6.5
63-66	2 3/8-2 5/8	160-169	5.9-6.6
67-70	2 3/8-2 5/8	170-179	6.1-6.8
71	2 1/2-2 3/4	180-181	6.2-6.9

Source of data for weight and frame charts: 1983 Metropolitan Height and Weight Tables. Statistical Bulletin 64:2-9, Jan-Jun 1983.

APPENDIX G

SPECIMEN PROCESSING INSTRUCTIONS

PROCEDURES FOR HANDLING BLOOD AND URINE SAMPLES AND TAKING BLOOD PRESSURE

NET: A 5 ml sample will be obtained, put in a red top tube and left at room temperature for one hour. It will then be centrifuged at 3000 revolutions for 20 minutes. The serum will be divided equally and put in two plastic containers, capped, immediately frozen at -20 degrees centigrade and kept frozen until one is shipped on dry ice to Mary Beth Southern, The CONRAD Program, The Jones Institute Research Laboratories; Room A-11, Eastern Virginia Medical School, 855 Brambleton Ave., Suite B; Norfolk, Virginia 23510. The other sample will remain frozen at the center.

SMAC: A 10.0 cc blood sample will be obtained from fasting women and centrifuged as soon as it clots (within 1/2 hours of drawing).

LDL/HDL: A 2.5 cc blood sample will be obtained and centrifuged as soon as it clots (within 1/2 hour of drawing. Telephone SmithKline BioScience Labs when there are more than ten samples or on a bi-weekly basis.

Hemoglobin: A 7.0 cc blood sample will be obtained. It must be refrigerated if it will be sitting for more than two hours.

Urinalysis: This test requires an uncontaminated sample of 10.0 cc of urine. A sample is contaminated if: 1) the specimen has been allowed to sit too long and develop bacterial overgrowth 2) the specimen contains vaginal discharge; i.e. is not obtained as a clean midstream voided sample.

Blood

Pressure:

1. Have patient sit at rest for at least 5 minutes.
2. With patient remaining seated, take reading.

Unacceptable values (cause for exclusion from study) are:
Systolic >150, Diastolic >90.

72

INSTRUCTIONS FOR USE OF
THE HANFMAN INJECTOR, MARK I™
(SINGLE USE DISPOSABLE MODEL)

1. Prepare the target area of the patient's skin (usually the inner surface of the upper arm). The preferred method is to clean the area carefully with povidone and/or 70% ethyl alcohol, wiping two or three times in a spiral pattern outward from the site with a fresh pledget or cotton swab. Local anesthetic may be infiltrated into the target area with a small gauge needle.
2. Remove the needle cover from the injector by pulling it forward and slightly rotating it clockwise (Fig. 1). Avoid any sudden jerking of the cover which could dislodge an implant from the needle.
3. Grasp a fold of the patient's skin with the thumb and forefinger of your free hand, being careful not to directly touch the target area (Fig 2). With firm, steady pressure, puncture the fold of skin and advance the needle until the notch on the barrel reaches the puncture site (Fig 3). CAUTION: Keep the direction of needle motion parallel to the plane of, and just under, the skin. Do not angle down into deeper tissue.
4. To deposit implant(s) (Fig 4), release the fold of skin and, keeping the barrel motionless, free the flange from the lock notch by rotating it counterclockwise (Fig. 4-A). Then, with the thumb, slide the flange backward along the barrel slot (Fig 4-B) until it stops. This motion withdraws the needle from the patient's skin, leaving the implant(s) behind.

73
Lock hub into rear lock notch by a slight counterclockwise rotation (Fig. 4-C). This prevents the needle from slipping forward, causing injury.

Withdraw the cannula and obturator from patient's skin. Maintain steady pressure on the puncture site with sterile gauze for 1-2 minutes to control bleeding. Gently palpate area beyond the puncture site to verify that the implant(s) are in proper position. Puncture site may be protected with a small sterile bandage for 12-24 hours.

DISCARD THE INJECTOR. DO NOT ATTEMPT TO RELOAD OR REUSE.

EHA

Engineering Development Associates, Inc. 13523 Argo Drive, Dayton, Maryland 21036
AN ENDOCOR COMPANY

Fig. 1



Fig. 2

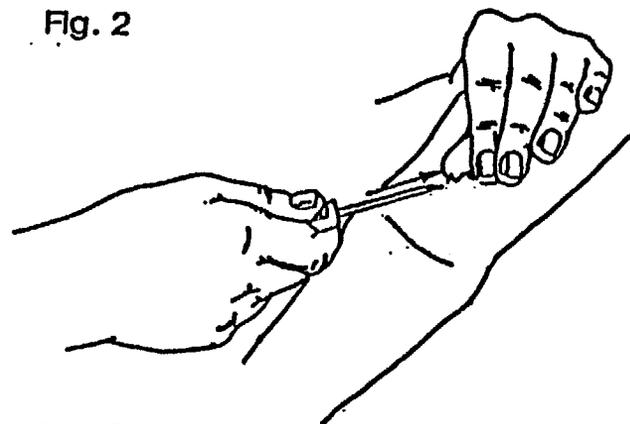


Fig. 3

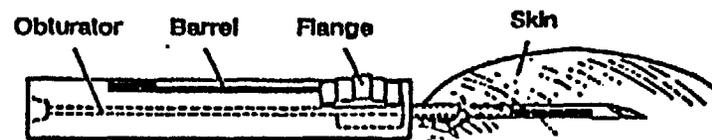
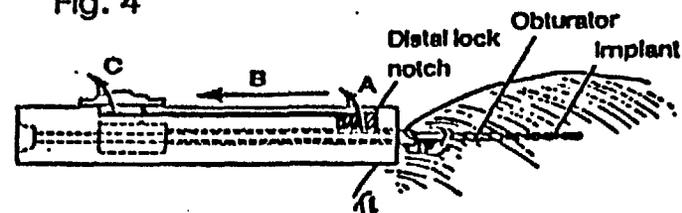


Fig. 4



APPENDIX I

DRUG STORAGE INSTRUCTIONS

The packets containing the NET pellet implants can be stored at room temperature in a normal clinical facility.

It is imperative that the implants be protected during storage from:

- A. Any water contamination
- B. Temperature above 40 degrees centigrade

The packets containing the implants should, therefore, be placed in a dry, shaded location, such as a laboratory cabinet, away from water sources (such as a sink) and away from extreme heat sources (such as a building heat unit, mechanical equipment or direct sunlight). Water and heat will cause the implant material to biodegrade.

The individual packets containing the implants should not be opened until the time of use. This will protect the implants from moisture or other contamination.

APPENDIX J

DATA ANALYSIS PLAN

STATISTICAL ANALYSIS

The objective of this study is to determine if either or both treatments result in NET serum concentrations sufficient to prevent pregnancy at the end of one year. Data for each treatment group will be analyzed separately.

Baseline demographic and clinical parameters will be summarized for each treatment group and center.

Efficacy Analysis

NET serum concentration at the end of year one is the primary efficacy variable. For each group, the null hypothesis that the mean NET serum concentration at the end of year one is less than or equal to .3 ng/ml will be tested using a one-sided t-test. A p-value $\leq .05$ will be considered statistically significant.

In addition, the number of women who ever had a NET serum concentration below .5 will be tallied for each treatment group. NET serum concentrations will be plotted by group over time. Also, mean area under the curve will be estimated for each subject using the trapezoid rule. Time to peak serum concentration and maximum NET serum concentration will be summarized for each treatment group.

A secondary indicator of efficacy is the proportion of women with progesterone levels which indicate that ovulation has been suppressed. For each group, the null hypothesis that the proportion suppressed is less than or equal to .25 will be tested using Fleming's single stage procedure for Phase II trials (Fleming, 1982). Only women with at least one progesterone measurement available for each of months 1 through 12 will be used in this analysis. A p-value $\leq .05$ will be considered statistically significant.

In addition, the proportion of women with suspected ovulation as indicated by other criteria (i.e., estradiol levels) may also be reported for each treatment group. Gross and net cumulative lifetable rates for discontinuation will be computed.

Safety Analysis

Insertion and removal problems will be described for each treatment group. For each group, adverse experiences will be presented by body system and by preferred term within a body system. The number of women with out of range clinical chemistry parameters will also be reported. Key laboratory parameters' (e.g., HDL, LDL, total cholesterol, blood pressure) will be plotted over time. Differences in key parameters from baseline to the end of the study will be tested for each treatment group separately using a paired t-test. A p-value of $\leq .05$ will be declared statistically

significant for any safety analysis.

Baseline versus last exam results will be presented for Pap smear results, breast exam findings, pelvic exam findings, and laboratory test results for each treatment group. A 90 day reference period will be used for the analysis of bleeding data. Mean number of bleeding and spotting days, mean number of bleeding episodes, and mean bleeding episode length will be summarized and plotted over time for each treatment group. Clinically important bleeding patterns will be summarized.

Interim Analyses

Interim analyses will be performed monthly but the results will only be used to terminate one or both treatment groups if an unacceptably high pregnancy rate is observed (see Appendix L). Neither treatment group will be terminated early due to an early finding of statistical significance (e.g., mean 12 month NET serum concentrations greater than .3 ng/ml or proportion ovulating greater less than .25) so a multiple comparisons adjustment to the p-value ($\alpha < .05$) considered statistically significant is not needed.

Fleming T. R. (1982) One-sample multiple testing procedure for Phase II clinical trials. Biometrics, 38, 142-151.

APPENDIX K

Sample Size Justification

The objective of this study is to determine if either or both treatments result in NET serum concentrations sufficient to prevent pregnancy at the end of one year. Efficacy for the two treatment groups will be evaluated separately. A treatment with a mean NET serum concentration of .3 ng/ml or lower at the end of month 12 would indicate insufficient efficacy. A mean of .5 ng/ml or greater would imply that the method warrants further testing. Testing the null hypothesis that the mean NET concentration is less than or equal to .3 ng/ml versus the alternative hypothesis that the mean NET concentration is greater than or equal to .5 ng/ml with $\alpha=.05$ (one-sided) and power of .8 requires that 16 women complete 12 months of study for each of the investigative treatments (assuming a standard deviation of .3 ng/ml).¹

A second indicator of efficacy is the proportion of women with progesterone levels which indicate that ovulation has been suppressed. If the proportion of women who have month 12 progesterone levels suggesting that ovulation has been suppressed is .25 or less would imply poor efficacy. A proportion of .6 or greater would imply that the method warrants further testing. Eleven women with complete month 12 data are needed to test the null hypothesis that the proportion without ovulation as indicated by progesterone levels is less than or equal to .25 against the alternative hypothesis² that the proportion is at least .6 with $\alpha=.05$ (one-sided) and power=.8.

Enrolling 20 women in each treatment groups will allow the hypotheses described above to be tested for each pellet group, assuming 80% of the women complete one year of study.

¹Machin, D. and M.J. Campbell, Statistical Tables for the Design of Clinical Trials, Blackwell Scientific Publications, Oxford, 1987, pp. 79-88.

²Machin, D. and M.J. Campbell, Statistical Tables for the Design of Clinical Trials, Blackwell Scientific Publications, Oxford, 1987, pp. 178-196.

Appendix I

Stopping Rules

Stopping rules for an excess number of pregnancies were developed using the Bayesian approach suggested by Mehta and Cain¹. This procedure involves calculating the posterior probability that an event rate is below (or above) a prespecified level given that r of n accrued patients have experienced the event. If the posterior probability is less than .03, the study is stopped. Instead of accrued patients, however, we used the number of patients with at least one three-month pregnancy test. Otherwise, posterior probabilities would be biased upward by including women who have never had a pregnancy test since enrollment in the "no event" group.

If 10% of the 20 women enrolled in one of the pellet groups become pregnant, this would correspond to a one-year cumulative life-table pregnancy rate estimate greater than or equal to 10 per 100 women for the method. If ever during the study, the probability that the true pregnancy rate is less than .10 is lower than .03 for one of the groups, the study of that method will be terminated and women already enrolled will be advised to use an additional method. Using the formula provided by Mehta and Cain, the following termination parameters were calculated. That is, the posterior probability for a group will be less than .03 if any of the situations given in the table are observed.

Number of Pregnancies Needed to Terminate Study	Number of Women With at Least 1 Follow-up Visit
1	1-2
2	3-6
3	7-11
4	12-17
5	18-20

Reference:

¹Mehta, C.R. and K.C. Cain: Charts for the early stopping of pilot studies. J Clin Oncology 2:676-683, 1984.

FAMILY HEALTH INTERNATIONAL

MEMORANDUM

TO: Dennis M. Campbell, PHSC Chairperson
FROM: Roberto Rivera, ^{RR} Director of Clinical Trials
DATE: 10 October 1990
SUBJECT: Expedited Review Request: Amendment to Proposal 869 (Proposal 869-1)

Title (revised): Phase II-A Pharmacokinetic Evaluation of Biodegradable Norethindrone Implants

The major changes to this protocol are the switch to a Phase 2 design (with the resulting enrollment of fertile women to test efficacy) and an increase in the size of the pellets under study. The decision to proceed with a Phase II study was based on the results of a Phase II study of hand made pellets in which no pregnancies occurred, and which showed serum NET levels comparable to those observed in FHI's Phase 1 trial (0.4 ng/ml).

The increase in pellet size for treatments using 4 and 5 pellets represents a 23% and 60% increase in dose, respectively, over the Phase 1 Group F treatment. The mean blood levels of norethindrone from the Phase 1 pellets were sufficiently low (0.5 ng/ml) to permit a 60% increase that would still be well below mean serum NET levels observed with the use of the NET 90-day injectable (1-2 ng/ml), NET enanthate injectable (3-8 ng/ml), or a 1 mg NET oral contraceptive pill (4-6 ng/ml). Therefore, we do not feel the increase in dose implies any risk to the patients.

Other changes to the study design reflect reductions in enrollment size and number of lab tests (listed below). Detailed changes to the protocol are described in the Study Proposal Form.

1. 40 subjects at 2 centers, rather than 99 at 3 centers
2. 4 and 5 pellets will be evaluated, rather than 6 and 8
3. 2 treatment groups instead of 3
4. Fewer blood tests for progesterone and estradiol levels

Expedited review is requested to enable investigators to initiate the review process with local IRBs.

Record of Action Taken:

Request Approved:
Request Not Approved:

Signed: Dr. Dennis M. Campbell Date: October 15, 1990
Chairperson, PHSC

OCT 16 1990

FAMILY HEALTH INTERNATIONAL

MEMORANDUM

TO: Vanessa P. Haygood, PHSC Vice-Chairperson

FROM: Roberto ^{RR}Rivera, Director of Clinical Trials

DATE: 8 February 1991

SUBJECT: Expedited Review Request:
 Proposal #869-2: Phase II-A Pharmacokinetic Evaluation
 of Biodegradable Norethindrone Pellet Implants

Investigators: Freedolph D. Anderson, MD; CONRAD Program,
 Norfolk, VA
 Mukul Singh, MD; New York Hospital, NYC

Expedited review is requested for review of the informed consent forms modified by the two centers' IRBs.

Changes from prior protocol:
 Local IRB-approved Informed Consent Form:

The two centers for this study, CONRAD and New York Hospital, have revised the FHI model informed consent form for the local IRB approval (attached). We have reviewed the local informed consent form using the 'Elements of Informed Consent Checklist' (attached). Both forms conform to the requirements for informed consent forms in FDA regulations.

Record of action taken:

Request Approved: ✓

Request Not Approved: _____

Signed: *Vanessa P. Haygood*
 Dr. Vanessa P. Haygood
 Vice-Chairperson, PHSC

Date: 2/14/91

FEB 19 1991

(Handwritten initials)

80

FAMILY HEALTH INTERNATIONAL

MEMORANDUM

TO: Dennis M. Campbell, PHSC Chairperson
 FROM: Roberto Rivera, ^{Call for file.} Director of Clinical Trials
 DATE: 3 December 1991
 SUBJECT: Expedited Review Request: Amendment to Proposal 869 (869-4)
 Title: Phase II-A Pharmacokinetic Evaluation of Biodegradable Norethindrone Pellet Implants

The major change to this protocol is the removal of the pellets from all study participants. The pellets will be removed, beginning at the end of 9 months of pellet use, from one subject per dose group each month over four months using a table of random numbers. Removals will be performed to estimate the amount of NET released through this time period by assaying the amount of drug left in the the removed pellets. All subjects will have the pellets removed prior to the end of the study per request of both the manufacturer and the FDA to ensure that no drug remains in the subject after the study is finished.

Other changes to the protocol reflect screening and preadmission time period adjustments (see below). Detailed changes to the protocol are described in the attached Study Proposal Form.

1. The length of screening is changed from 30 days to 35 days.
2. The preadmission visit is changed from 3 to 5 days to 3 to 7 days after menses onset.

Expedited review is requested because the changes do not increase the risks to study participants.

 Record of Action Taken:

Request Approved: _____

Request NOT Approved: _____

Signed: *Dennis M. Campbell* Date: Dec. 6, 1991
 Dr. Dennis M. Campbell
 Chairperson, PHSC

DEC 9 1991

82

(Call)

FAMILY HEALTH INTERNATIONAL

TO: Dennis Campbell, BD, PhD, Chairperson, PHSC

FROM: Anita Flick, MD, Associate Medical Director, Clinical Trials Division
through *[Signature]*
Carol Connell, RN, Director, Clinical Trials Division

DATE: April 30, 1993

SUBJECT: Expedited Review Request : PHSC Proposal No. 869-5, "Phase II-A
Pharmacokinetic Evaluation of Biodegradable Norethindrone Pellet Implants"

Duration of Study

In the original protocol, the study ends at 24 months. However, it has been decided that an evaluation should be made of the length of time required for NET levels to drop to the lowest detectable level (<.112 ng/ml). Because of this, it is requested that the study be extended indefinitely until all study participants have undetectable NET levels. It is estimated that NET levels will be undetectable within 36 months of insertion, hence an anticipated extension of approximately 12 months.

Procedural Changes

1. Bleeding calendars will not be filled out beyond 24 months postinsertion.
2. The protocol originally allowed the use of oral contraceptives as an alternative contraceptive method with the proviso that the progestin component not be norethindrone. It is felt that any steroid containing contraceptive could affect measurement of NET levels because of cross-reactivity in the NET assay, and therefore, should be avoided. Women will be encouraged to use non-steroidal contraceptives after 13 months in the study and discouraged from using steroidal methods. Any women who choose to use oral contraceptives will be scheduled for blood draws at the end of the pill-free week."
3. The contacts for reporting adverse experiences have been changed due to staff reassignments. Anita Flick, MD and Carol Connell, RN are now the designated contacts.

FHI

Headquarters:
P.O. Box 13950
Research Triangle Park, NC 27709 USA
Telephone: 919-544-7040
Telex: 579442 . Fax: 919-544-7261

AIDSCAP Division:
2101 Wilson Boulevard, Suite 700
Arlington, VA 22201
Telephone: 703-516-9779 . Fax: 703-516-9781
Voice Mail: 703-516-0460

[Signature]

475

FAMILY HEALTH INTERNATIONAL

Expedited Review Memo
Proposal No. 869-5
Page 2

Changes related to subject care

1. Subjects will return for lab visits on a monthly basis, rather than a quarterly basis as was stated in the original protocol, in order to have a 5 ml blood sample drawn for serum NET levels. When two NET levels are $<.112$ ng/ml, the subject will have completed the study.
2. In the original protocol, every three months the subjects return to the clinic two times a week for one month to have blood samples (10 ml) drawn for progesterone and estradiol assays. These visits will now continue beyond the 24-month visit and will last until NET levels are below .112 ng/ml.
3. Originally, the pellets were going to be removed when the subject completes the study. However, it has been determined that, due to the degeneration of the pellets over time, removal is not always possible/advisable. If the Investigator feels that it is in the best interests of the subject, or if the subject requests it, the pellets can be removed.
4. A supplement has been added to the Informed Consent which describes the procedural and medical changes listed above.

Record of Action Taken:

Request Approved:

Request NOT Approved:

Signed: Dr. Dennis M. Campbell

Dr. Dennis M. Campbell
Chairperson, PHSC

Date: May 5, 1993

476
FHI

Headquarters:
P.O. Box 13950
Research Triangle Park, NC 27709 USA
Telephone: 919-544-7040
Telex: 579442 - Fax: 919-544-7261

AIDSCAP Division:
2101 Wilson Boulevard, Suite 700
Arlington, VA 22201
Telephone: 703-516-9779 - Fax: 703-516-9781
Voice Mail: 703-516-0460

MAY 10 1993

24

APPENDIX V Case Report Forms

85

**NET Pellet Implant Study
ADMISSION MEDICAL AND SURGICAL DIAGNOSES FORM**

STUDY IDENTIFICATION

1. Center number:

--	--	--	--	--

1-4

2. Study number:

--	--	--	--	--

5-8

3. Patient order number:

--	--	--	--	--	--

9-13

4. Admission form number:

--	--	--	--	--	--	--

14-18

CONTACT DATA

5. Date of admission:

<i>day</i>		<i>month</i>		<i>year</i>	

20-25

List all pre-existing medical and surgical diagnoses present at admission visit;
include past history relevant to this study:

6. Medical or Surgical Diagnosis	7. Date of Onset (month / year)	8. Resolved Prior To Admission Visit? 0=no 1=yes	9. Current drug therapy for this condition? 0=no 1=yes If yes, complete Concomitant Medication Form	FOR FHI USE ONLY																																
_____	<table border="1"> <tr> <td></td><td></td> <td></td><td></td> </tr> <tr> <td align="center" colspan="2">26 - 29</td> <td align="center" colspan="2">30</td> </tr> </table>					26 - 29		30		<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td></td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td align="center" colspan="6">32 - 36</td> </tr> <tr> <td></td><td></td><td></td><td></td><td align="center">0</td><td align="center">3</td> </tr> <tr> <td align="center" colspan="6">79 - 80</td> </tr> </table>							32 - 36										0	3	79 - 80					
26 - 29		30																																		
32 - 36																																				
				0	3																															
79 - 80																																				
_____	<table border="1"> <tr> <td></td><td></td> <td></td><td></td> </tr> <tr> <td align="center" colspan="2">26 - 29</td> <td align="center" colspan="2">30</td> </tr> </table>					26 - 29		30		<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td></td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td align="center" colspan="6">32 - 36</td> </tr> <tr> <td></td><td></td><td></td><td></td><td align="center">0</td><td align="center">3</td> </tr> <tr> <td align="center" colspan="6">79 - 80</td> </tr> </table>							32 - 36										0	3	79 - 80					
26 - 29		30																																		
32 - 36																																				
				0	3																															
79 - 80																																				
_____	<table border="1"> <tr> <td></td><td></td> <td></td><td></td> </tr> <tr> <td align="center" colspan="2">26 - 29</td> <td align="center" colspan="2">30</td> </tr> </table>					26 - 29		30		<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td></td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td align="center" colspan="6">32 - 36</td> </tr> <tr> <td></td><td></td><td></td><td></td><td align="center">0</td><td align="center">3</td> </tr> <tr> <td align="center" colspan="6">79 - 80</td> </tr> </table>							32 - 36										0	3	79 - 80					
26 - 29		30																																		
32 - 36																																				
				0	3																															
79 - 80																																				
_____	<table border="1"> <tr> <td></td><td></td> <td></td><td></td> </tr> <tr> <td align="center" colspan="2">26 - 29</td> <td align="center" colspan="2">30</td> </tr> </table>					26 - 29		30		<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td></td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td align="center" colspan="6">32 - 36</td> </tr> <tr> <td></td><td></td><td></td><td></td><td align="center">0</td><td align="center">3</td> </tr> <tr> <td align="center" colspan="6">79 - 80</td> </tr> </table>							32 - 36										0	3	79 - 80					
26 - 29		30																																		
32 - 36																																				
				0	3																															
79 - 80																																				
_____	<table border="1"> <tr> <td></td><td></td> <td></td><td></td> </tr> <tr> <td align="center" colspan="2">26 - 29</td> <td align="center" colspan="2">30</td> </tr> </table>					26 - 29		30		<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td></td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td align="center" colspan="6">32 - 36</td> </tr> <tr> <td></td><td></td><td></td><td></td><td align="center">0</td><td align="center">3</td> </tr> <tr> <td align="center" colspan="6">79 - 80</td> </tr> </table>							32 - 36										0	3	79 - 80					
26 - 29		30																																		
32 - 36																																				
				0	3																															
79 - 80																																				
_____	<table border="1"> <tr> <td></td><td></td> <td></td><td></td> </tr> <tr> <td align="center" colspan="2">26 - 29</td> <td align="center" colspan="2">30</td> </tr> </table>					26 - 29		30		<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td></td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td align="center" colspan="6">32 - 36</td> </tr> <tr> <td></td><td></td><td></td><td></td><td align="center">0</td><td align="center">3</td> </tr> <tr> <td align="center" colspan="6">79 - 80</td> </tr> </table>							32 - 36										0	3	79 - 80					
26 - 29		30																																		
32 - 36																																				
				0	3																															
79 - 80																																				
_____	<table border="1"> <tr> <td></td><td></td> <td></td><td></td> </tr> <tr> <td align="center" colspan="2">26 - 29</td> <td align="center" colspan="2">30</td> </tr> </table>					26 - 29		30		<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td></td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td align="center" colspan="6">32 - 36</td> </tr> <tr> <td></td><td></td><td></td><td></td><td align="center">0</td><td align="center">3</td> </tr> <tr> <td align="center" colspan="6">79 - 80</td> </tr> </table>							32 - 36										0	3	79 - 80					
26 - 29		30																																		
32 - 36																																				
				0	3																															
79 - 80																																				
_____	<table border="1"> <tr> <td></td><td></td> <td></td><td></td> </tr> <tr> <td align="center" colspan="2">26 - 29</td> <td align="center" colspan="2">30</td> </tr> </table>					26 - 29		30		<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td></td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td align="center" colspan="6">32 - 36</td> </tr> <tr> <td></td><td></td><td></td><td></td><td align="center">0</td><td align="center">3</td> </tr> <tr> <td align="center" colspan="6">79 - 80</td> </tr> </table>							32 - 36										0	3	79 - 80					
26 - 29		30																																		
32 - 36																																				
				0	3																															
79 - 80																																				

Signature of Investigator _____

Date of Signature _____

87

**FAMILY HEALTH INTERNATIONAL
NET Pellet Implant Study
FOLLOW-UP FORM**

FU

STUDY IDENTIFICATION

1. Center number:

--	--	--	--

 1-4

2. Study number:

--	--	--	--

 5-8

3. Patient order number:

--	--	--	--	--	--

 9-13

4. Admission form number:

--	--	--	--	--	--	--	--

 14-18

CONTACT DATA

5. Date of follow-up contact:

--	--

 day

--	--

 month

--	--

 year 20-25

6. Type of contact:
1= clinic visit
2= home visit
3= telephone contact
4= letter
5= other → specify:

--

 26

--	--

 27-28

7. Pregnancy test: 0= negative
1= positive, 2= not done 29

→ If positive complete Pregnancy Diagnosis Form, Notify FHI immediately

8. Patient status:
1= continuing study
2= discontinuing from study
3= discontinued at earlier date 30

9. Removal requested by patient since last visit?
0= no 1= yes 31

→ If yes and implants were not removed, note reason:

10. Implant status at this visit:
1= no implant procedure performed
2= removal only
3= repeat insertion only
4= removal and repeat insertion 32

→ If coded 2 or 4 (removal was done), complete a Removal Form

→ If coded 3 or 4 (repeat insertion was done), complete an Insertion Form

MEDICAL HISTORY AND PHYSICAL

11. Illnesses, complaints or problems since last visit (including bleeding-related):
0= no 1= yes 33

→ If yes, indicate on Adverse Experience Form

12. Medications taken since last visit?:
0= no 1= yes 34
→ If yes, indicate on Concomitant Medications Form

13. Pelvic examination:
0= not done
1= normal
2= abnormal → specify findings: 35

14. Breast examination:
0= not done
1= normal
2= abnormal → specify findings: 36

15. Blood pressure (mm Hg), Siting, 5 minute rest:

--	--	--

 systolic 37-39

--	--	--

 diastolic 40-42

16. Pulse (beats per minute):

--	--	--

 43-45

17. Weight (kg):

--	--	--

 46-48

18. Average frequency of coitus since last visit:
0= no coitus, 1= less than once/week,
2= at least once/week but less than twice/week,
3= at least twice/week, 4= not known
(patient not available to ask) 49

LABORATORY TESTS

19. Pap smear: 1= normal 2= atypia
3= dysplasia 4= malignancy
5= smear inadequate 6= not done 50

SPECIAL STUDIES

20.

--	--	--

 51-53

21.

--	--	--

 54-56

22. REMARKS

--	--

 79-80

For FHI Use Only

0 5	26-27		28-29		30-34	7 0	79-80
0 5	26-27		28-29		30-34	7 0	79-80
0 5	26-27		28-29		30-34	7 0	79-80
0 5	26-27		28-29		30-34	7 0	79-80
0 5	26-27		28-29		30-34	7 0	79-80
0 5	26-27		28-29		30-34	7 0	79-80
0 5	26-27		28-29		30-34	7 0	79-80
0 5	26-27		28-29		30-34	7 0	79-80

Signature of Investigator _____

Date of Signature _____

PLEASE AIRMAIL TO:
Family Health International
P.O. Box 13950
Research Triangle Park Branch
Durham, NC 27709
USA

99

FAMILY HEALTH INTERNATIONAL
NET Pellet Implant Study
DISCONTINUATION FORM

STUDY IDENTIFICATION

1. Center number: 1-4

2. Study number: 6-8

3. Patient order number: 9-13

4. Admission form number: 14-19

CONTACT DATA

5. Date of discontinuation: 20-25
day month year

6. Reason for discontinuation:

- 01= patient died -> Complete Adverse Experience Form and Notify FHI
- 02= unable to contact patient
- 03= patient is pregnant
- 04= patient wants to become pregnant
- 05= menstrual problems
- 06= other medical
- 07= other personal
- 08= protocol violation
- 09= end of study

26-27

-> If coded 05, 06, 07, or 08, specify primary reason here:

- > If coded 01, 05, or 06, complete an Adverse Experience Form
- > If coded 03, 04, 05, 06, 07, 08, or 09, complete a Follow-Up Form
- > If coded 03 complete a Pregnancy Diagnosis Form

7. REMARKS

78-80

Signature of investigator

Date of Signature

For FHI Use Only

07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80
07	26-27	<input type="text"/>	28-29	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	30-34	70	78-80

PLEASE AIRMAIL TO:
 Family Health International
 P.O. Box 13950
 Research Triangle Park Branch
 Durham, NC 27709
 USA

93

PREGNANCY DIAGNOSIS FORM

STUDY IDENTIFICATION

1. Center number:

--	--	--	--

 1-4

2. Study number:

--	--	--	--

 5-8

3. Patient order number:

--	--	--	--	--	--

 9-13

4. Admission form number:

--	--	--	--	--	--	--	--

 14-18

CONTACT DATA

5. Date of this contact:

--	--

 day

--	--

 month

--	--

 year 20-25

6. Study contraceptive method: _____

--	--	--	--	--	--

 26-30

PREGNANCY DATA

7. How was pregnancy diagnosed (specify test or method used): _____

--	--	--	--	--	--

 31-35
If test not used, Skip to Item 9.

8. If pregnancy test was used, specify date the specimen was collected:

--	--

 day

--	--

 month

--	--

 year 36-41

9. Estimated gestational age at this visit: (in weeks since estimated date of conception)

--	--

 42-43

10. Location of pregnancy:
 1) suspected uterine implantation
 2) confirmed uterine implantation
 3) suspected extrauterine implantation
 4) confirmed extrauterine implantation
 5) location not determined 44

11. Estimation of when pregnancy occurred:
 1) probably before admission to study
 2) probably during study 3) probably after end of study 4) estimation not done 45

Reason for this estimation: _____

--	--	--	--	--	--

 46-47

If coded 1 or 3, Skip to Item 13.

12. Reason for pregnancy:
 1) method failure 2) user failure 3) other 4) unknown 48

Reason for this determination: _____

--	--	--	--

 49-50

13. Remarks: _____

--	--	--	--

 51-52

6	6
---	---

 70-80

NOTE: The outcome of all pregnancies must be reported to FHI on the FHI Pregnancy Outcome Form.

 Investigator's Signature

 Date

PLEASE AIRMAIL TO:
 Family Health International
 P.O. Box 13950
 Research Triangle Park Branch
 Durham, NC 27709
 USA

COPY DISTRIBUTION: White and Yellow - Return to FHI
 Pink - Retained by Investigator

Clinical Trials Disk-2
 Pregnancy Diagnosis Form
 July 18, 1969

94

PREGNANCY OUTCOME FORM

STUDY IDENTIFICATION

1. Center number: 1-4
2. Study number: 5-8
3. Patient order number: 9-13
4. Admission form number: 14-19

CONTACT DATA

5. Date of pregnancy outcome: 20-25
day month year

PREGNANCY OUTCOME DATA

6. Estimated gestational age at outcome: 26-27
(in weeks since estimated date of conception)

7. Pregnancy outcome: 01) singleton live birth
 02) singleton stillbirth 03) multiple birth
 04) induced abortion ≤ 12 weeks 05) induced abortion > 12 weeks
 06) spontaneous abortion 07) septic abortion 08) tubal ectopic pregnancy
 09) extra-tubal ectopic pregnancy 10) hydatidiform mole or choriocarcinoma
 11) other 12) unknown 28-29

If coded 03) multiple birth, specify number of infants: (if 7 or more, code "7") 30
(if number not known, code "8")

If coded 11 or 12, specify details: _____

_____ 31-32

If coded 04, 05, 06, 07, 08, 09, 10, 11 or 12, Skip → to Item 14.

NOTE: If outcome resulted in a singleton live birth, singleton stillbirth, or multiple birth, complete a separate FHI Infant Assessment Form for each infant delivered.

8. Course of pregnancy: 0) normal 1) abnormal 2) unknown 33

If coded 1) abnormal, specify details: _____

_____ 34-38

9. Concomitant medication used during course of pregnancy: 0) no 1) yes 2) unknown 39

NOTE: If coded 1) yes, complete FHI Concomitant Medication Form.

10. Course of labor: 0) normal 1) abnormal 2) elective Cesarean section 3) unknown 40

If coded 1) abnormal, specify details: _____

_____ 41-45

11. Induction or augmentation of labor: 0) no 1) yes 2) unknown 46

If coded 1) yes, specify details: _____

_____ 47-51

12. Location of delivery:
 01) government hospital 02) private hospital
 03) government health clinic 04) private health clinic
 05) government family planning clinic 06) private family planning clinic
 07) at midwife's home 08) at woman's home 09) other 10) unknown 52-53

If coded 09) other, specify location: _____

13. Delivery attended by:
 01) ob/gyn physician 02) general physician
 03) resident physician 04) intern 05) nurse
 06) midwife 07) paramedic 08) other 09) unknown 54-55

If coded 08) other, specify: _____

14. Health of woman immediately following pregnancy outcome:
 0) normal 1) abnormal 2) unknown 60

If coded 1, specify details: _____

15. Re-estimation of when pregnancy occurred:
 1) probably before admission 2) probably during study
 3) probably after end of study 4) re-estimation not done 65

If estimation differs from Pregnancy Diagnosis Form, specify reason for change: _____

16. Remarks: _____

NOTE: If a serious, life threatening or unexpected medical problem occurs to the subject or the infant, including hospitalization or death, an FHI Adverse Experience Report must be completed and signed by the investigator and returned to FHI immediately.

Investigator's Signature _____

Date _____

PLEASE AIRMAIL TO:
 Family Health International
 P.O. Box 13950
 Research Triangle Park Branch
 Durham, NC 27709
 USA

PY DISTRIBUTION: White and Yellow – Return to FHI
 Pink – Retained by Investigator

Clinical Trials Disk-2
 Pregnancy Outcome Form
 July 18, 1989

95

STUDY IDENTIFICATION

- 1. Center number: 1-4
- 2. Study number: 5-8
- 3. Patient order number: 9-13
- 4. Admission form number: 14-19

ASSESSMENT DATA

- 5. Date of pregnancy outcome: 20-25
day month year
- 6. Delivery order of this infant for this pregnancy:
 1) singleton or first infant 2) second infant
 3) third infant 4) fourth infant 5) fifth infant
 6) sixth infant 7) seventh infant 26

NOTE: If coded 2, 3, 4, 5, 6 or 7, a separate FHI Infant Assessment Form must be completed for each additional infant delivered.

- 7. Type of delivery: 01) spontaneous
 02) outlet forceps 03) vacuum extraction
 04) mid or high forceps 05) forceps rotation
 06) breech (spontaneous, assisted) 07) version and extraction
 08) low cervical Cesarean section 09) classical Cesarean section
 10) destructive procedure (cranioclasty or embryotomy) 11) other 12) unknown 27-28

If coded 11) other, specify details:

29-33

- 8. Pregnancy outcome for this infant: 34
 0) live birth 1) stillbirth

If coded 1) stillbirth, specify details:

35-39

If coded 1) stillbirth, SKIP → to Item 10.

- 9. Infant post-partum condition:
 0) normal 1) congenital abnormalities 40
 2) other abnormalities 3) unknown

If coded 1 or 2, specify details:

41-45

- 10. Sex of infant: 46
 1) male 2) female 3) unknown

- 11. Birth weight in grams: 47-50
(code "9998" if unknown)

- 12. Length in centimeters (crown to heel): 51-53
(code "998" if unknown)

- 13. Remarks:

54-55

6 9 79-80

NOTE: If a serious, life threatening or unexpected medical problem occurs to the subject or the infant, including hospitalization or death, an FHI Adverse Experience Report must be completed and signed by the investigator and returned to FHI immediately.

Investigator's Signature

Date

PLEASE AIRMAIL TO:
 Family Health International
 P.O. Box 13950
 Research Triangle Park Branch
 Durham, NC 27709
 USA

COPY DISTRIBUTION: White and Yellow - Return to FHI
 Pink - Retained by Investigator

016

**FAMILY HEALTH INTERNATIONAL
NET Pellet Implant Study
LABORATORY TEST RESULTS**

LAB 21

STUDY IDENTIFICATION

1. Center number:

--	--	--	--

 1-4

2. Study number:

--	--	--	--

 5-8

3. Patient order number:

--	--	--	--	--	--

 9-13

4. Admission form number:

--	--	--	--	--	--	--	--

 14-19

CONTACT DATA

5. Date of blood sample:

--	--

day

--	--

month

--	--

year 20-25

LABORATORY RESULTS

6. Hemoglobin (g/dl):

--	--

 .

--

 26-28

7. White blood cell count/mm³

--	--	--	--	--	--	--	--

 29-34

8. SMAC

Glucose (mg/dl)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table>				36-37
LDH-340 (mU/ml)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table>				38-40
SGOT-340 (AST) (mU/ml)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table>				41-43
SGPT (mU/ml)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table>				44-46
Alkaline Phosphates (mU/ml)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table>				47-49
Bilirubin, Total (mg/dl)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td>.</td><td> </td></tr></table>		.		50-51
	.				
Creatinine (mg/dl)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td>.</td><td> </td></tr></table>		.		52-53
	.				
Sodium (meg/l)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table>				54-56
Potassium (meg/l)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td>.</td><td> </td></tr></table>		.		57-58
	.				
Chloride (meg/l)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table>				59-61
Calcium (mg/dl)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td>.</td><td> </td></tr></table>		.		62-64
	.				
Phosphorus (mg/dl)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td>.</td><td> </td></tr></table>		.		65-66
	.				
Protein, Total (gm/dl)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td>.</td><td> </td></tr></table>		.		67-69
	.				
Albumin (gm/dl)	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td>.</td><td> </td></tr></table>		.		70-72
	.				

9. REMARKS

Signature of Investigator _____

Date of Signature _____

PLEASE AIRMAIL TO:
Family Health International
P.O. Box 13950
Research Triangle Park Branch
Durham, NC 27709
USA

		73-74
2	1	79-80

97

FAMILY HEALTH INTERNATIONAL
NET Pellet Implant Study
LIPID PROFILE RESULTS

STUDY IDENTIFICATION

- 1. Center number:

--	--	--	--

 1-4
- 2. Study number:

--	--	--	--

 5-8
- 3. Patient order number:

--	--	--	--	--	--

 9-13
- 4. FHI admission form number:

--	--	--	--	--	--	--	--

 14-19

CONTACT DATA

- 5. Date of blood sample:

--	--

day

--	--

month

--	--

year 20-25

RESULTS

- 6. Triglycerides (mg/dl):

--	--	--	--

 26-29
- 7. Cholesterol (mg/dl):

--	--	--	--

 30-32
- 8. HDL (mg/dl):

--	--	--	--

 33-35
- 9. LDL (mg/dl):

--	--	--	--

 36-38

10. REMARKS

2	2

30-40
70-80

Signature of Investigator

Date of Signature

PLEASE AIRMAIL TO:
 Family Health International
 P.O. Box 13950
 Research Triangle Park Branch
 Durham, NC 27709
 USA

99



FAMILY HEALTH INTERNATIONAL NET PELLET IMPLANT STUDY DAILY BLEEDING RECORD

Center number:

Study number:

Patient order number:

FHI admission form number:

					1-4
					5-8
					9-13
					14-18

Contraceptive: _____

				20-23
--	--	--	--	-------

Date of first injection:

				24-29
day	month	year		

001

YEAR	MONTH

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
					</																										

**FAMILY HEALTH INTERNATIONAL
NET Pellet Implant Study
ADDITIONAL CONTRACEPTIVE METHOD FORM**

STUDY IDENTIFICATION

1. Center number: 1-4
2. Study number: 5-8
3. Patient order number: 9-13
4. Admission form number: 14-19

CONTACT DATA

5. Date of contact: 20-26
day month year

6. If any contraceptive method(s) other than NET pellets have been used since subject's last NET blood draw, please specify from the choices listed below: 26-27

Additional Contraceptive Method

- 00= none
- 01= foam/suppositories
- 02= sponge
- 03= condom alone
- 04= condom with spermicide
- 05= rhythm/natural family planning
- 06= withdrawal
- 07= diaphragm alone
- 08= diaphragm with spermicide
- 09= cervical cap alone
- 10= cervical cap with spermicide
- 11= NORPLANT® implants
- 12= oral contraceptives
- 13= IUD
- 14= injectables
- 15= male sterilization
- 16= female sterilization
- 17= other
- 18= combination

Specify Type(s)
(Items 12-18 Only)

Date Method Begun

(day)	month	year	
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	28-33
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	34-39
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	40-45
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	46-51
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	52-57
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	58-63
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	64-69
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	70-75

(If combination includes a hormonal method or IUD, indicate date hormones or IUD were started. If not, code date '88 88 88' in box 18)

76-80

Note: If hormonal contraceptives have been used (ie, OCs, steroid-releasing IUDs, implants, injectables) this information should also be recorded on the Concomitant Medications form.

101

FAMILY HEALTH INTERNATIONAL
Phase II-A Pharmacokinetic Evaluation of Biodegradable
Norethindrone Pellet Implants
SERUM NET RESULTS

STUDY IDENTIFICATION

- 1. Center number: 1-4
- 2. Study number: 5-8
- 3. Patient order number: 9-13
- 4. Admission form number: 14-18

CONTACT DATA

- 5. Date of blood sample: 20-25
day month year
- 6. Time of blood sample: : 26-29
hour min.
- 7. Date of assay: 30-36
day month year
- 8. NET (pg/mL): 38-41
 - <
 - >
 - X (= BD-TBR)

79-80

Print Name of Transcriber _____

Signature of Transcriber _____

Date of Signature _____

102

FAMILY HEALTH INTERNATIONAL
Phase II-A Pharmacokinetic Evaluation of Biodegradable
Norethindrone Pellet Implants
SERUM PROGESTERONE RESULTS

STUDY IDENTIFICATION

- 1. Center number: 1-4
- 2. Study number: 5-8
- 3. Patient order number: 9-13
- 4. Admission form number: 14-18

CONTACT DATA

- 5. Date of blood sample: 20-25
day month year
- 6. Time of blood sample: : 26-29
(00:00 -> 23:59) *hour min.*
- 7. Date of assay: 30-35
day month year
- 8. Progesterone (ng/mL): . 36-40
<
>
X (= BD-TBR)
- 79-80

Print Name of Transcriber

Signature of Transcriber

Date of Signature

103

FAMILY HEALTH INTERNATIONAL
Phase II-A Pharmacokinetic Evaluation of Biodegradable
Norethindrone Pellet Implants
SERUM ESTRADIOL RESULTS

STUDY IDENTIFICATION

- 1. Center number:

--	--	--	--

 1-4
- 2. Study number:

0	8	9	0
---	---	---	---

 5-8
- 3. Patient order number:

--	--	--	--	--

 9-13
- 4. Admission form number:

--	--	--	--	--	--

 14-19

CONTACT DATA

- 5. Date of blood sample:

--	--

day

--	--

month

--	--

year 20-25
- 6. Time of blood sample:
(00:00 → 23:59)

--	--

hour :

--	--

min. 26-29
- 7. Date of assay:

--	--

day

--	--

month

--	--

year 30-35
- 8. Estradiol 17-B(pg/mL):

--

--	--	--	--

 36-40
<
>
X (= BD-TBR)

4	2
---	---

 79-80

Print Name of Transcriber

Signature of Transcriber

Date of Signature

pcj

APPENDIX VI Tables & Figures

Unless otherwise specified, all table titles end in "by Treatment Received".

LIST OF TABLES

- 1 Distribution of Participants by Center and Treatment Received
- 2.1 Number and Percent of Participants with Protocol Deviations
- 2.2 List of Participants with Protocol Deviations
- 3 Age, Race, and Smoking History at Admission
- 4 Pregnancy History at Admission
- 5 Contraceptive History at Admission
- 6 Menstrual Information for Cycle Prior to Admission
- 7 Menstrual History for Three Cycles Prior to Admission
- 8.1 Medical History and Physical at Admission
- 8.2 List of Participants with Pre-existing Medical Diagnosis or Medication
- 8.3 List of Participants with Abnormal Pelvic Exam, Breast Exam, or Pap Smear Results at Admission
- 9 Number and Percent of Participants with any Follow-up Contact
- 10.1 Number of Discontinuations from Clinic Follow-up
- 10.2 List of Participants Discontinuing from Clinic Follow-up
- 11.1 Reported Average Coital Frequency Since Last Contact Through 12 Months
- 11.2 Use of Additional Contraceptive Methods, 4-Pellet
- 11.3 Use of Additional Contraceptive Methods, 5-Pellet
- 12.1 Summary of NET Values (ng/ml), 4-Pellet
- 12.2 Summary of NET Values (ng/ml), 5-Pellet
- 13.1 Number and Percent of Participants Who Ever Had a NET Concentration Below 0.3 ng/ml From the 1-month Follow-up Through the 12-month Follow-up
- 13.2 List of Participants Who Ever Had a NET Concentration Below 0.3 ng/ml from the 1-Month Follow-up Through the 12-Month Follow-up
- 13.3 Time Until First NET < .3 ng/ml
- 14.1 Number and Percent of Participants with Elevated Progesterone Levels (ng/ml)
- 14.2 List of Participants with Elevated Progesterone Levels (>3 ng/ml) by Time Period and Treatment Received
- 15 Mean of Each Participant's Mean, Minimum, and Maximum Concentration of Estradiol (pg/ml) and Median of Each Participant's Median Concentration of Estradiol (pg/ml)
- 16.1 Number and Percent of Participants with Low Estradiol Levels (pg/ml)
- 16.2 List of Participants with Minimum Estradiol Levels <40 pg/ml by Time Period and Treatment Received
- 17 Proportion of Participants with Clinically Important Bleeding Patterns by Reference Period and Treatment Received
- 18 Comparison of Lipid Profiles (mg/dl) Between Baseline and Follow-up
- 19 Comparison of Glucose (mg/dl) Between Baseline and Follow-up

- 20.1 Number and Percent of Participants with Laboratory Values Outside Laboratory Normal Reference at Baseline
- 20.2 Number and Percent of Participants with Laboratory Values Outside Laboratory Normal Reference at the 6-month Follow-up
- 20.3 Number and Percent of Participants with Laboratory Values Outside Laboratory Normal Reference at the 12-month Follow-up
- 20.4 Number and Percent of Participants with Laboratory Values Outside Laboratory Normal Reference at the 18-month Follow-up
- 20.5 Number and Percent of Participants with Laboratory Values Outside Laboratory Normal Reference at the 24-month Follow-up
- 20.6 List of Participants Who Ever Had a Laboratory Value Outside Laboratory Normal Reference Reported at Baseline Through the 24-month Follow-up
- 20.7 List of Participants Who Ever Had a Laboratory Value Outside Laboratory Normal Reference Reported After the First 24 Months (760 days) of Follow-up
- 21 Comparison of Blood Pressure (mm Hg) Between Baseline and Follow-up
- 22 Comparison of Weight (kg) Between Baseline and Follow-up
- 23.1 Number and Percent of Participants Whose Pellets Were Removed
- 23.2 Number and Percent of Incisions Required for Pellet Removal
- 23.3 Length of Incisions (mm) Required for Pellet Removal
- 23.4 Time Required (minutes) for Pellet Removal
- 24.1 Adverse Experiences Probably Related to the Study Product by Body System and Preferred Term
- 24.2 List of Participants with Adverse Experiences Probably Related to the Study Product by Body System and Preferred Term, 4-Pellet
- 24.3 List of Participants with Adverse Experiences Probably Related to the Study Product by Body System and Preferred Term, 5-Pellet
- 25.1 Adverse Experiences Possibly Related to the Study Product by Body System and Preferred Term
- 25.2 List of Participants with Adverse Experiences Possibly Related to the Study Product by Body System and Preferred Term, 4-Pellet
- 25.3 List of Participants with Adverse Experiences Possibly Related to the Study Product by Body System and Preferred Term, 5-Pellet
- 26.1 Serious and/or Unexpected Adverse Experiences by Body System and Preferred Term
- 26.2 List of Participants with Serious and/or Unexpected Adverse Experiences by Body System and Preferred Term, 4-Pellet
- 26.3 List of Participants with Serious and/or Unexpected Adverse Experiences by Body System and Preferred Term, 5-Pellet
- 27.1 All Adverse Experiences by Body System and Preferred Term
- 27.2 List of Participants with any Adverse Experience by Body System and Preferred Term, 4-Pellet
- 27.3 List of Participants with any Adverse Experience by Body System and Preferred Term, 5-Pellet
- 28 Follow-up of Adverse Events Reported as Unresolved at Participant Discontinuation

106

LIST OF FIGURES

- 1a Mean NET Levels over time
- 2a Individual NET Levels over time, 4-Pellet, Center 908
- 2b Individual NET Levels over time, 5-Pellet, Center 908
- 2c Individual NET Levels over time, 4-Pellet, Center 952
- 2d Individual NET Levels over time, 5-Pellet, Center 952
- 3a Box Plots of NET Levels over time, 4-Pellet
- 3b Box Plots of NET Levels over time, 5-Pellet
- 4a Mean NET Levels over time by Admission Weight Reference and Treatment Received, 4-Pellet
- 4b Mean NET Levels over time by Admission Weight Reference and Treatment Received, 5-Pellet
- 5a-b Frequency of Clinically Important Bleeding Patterns, 4-Pellet and 5-Pellet
- 6a-b Percent Change in Lipids over time, 4-Pellet and 5-Pellet
- 7a-b Percent Change in Blood Pressure over time, 4-Pellet and 5-Pellet
- 8a-b Percent Change in Weight over time, 4-Pellet and 5-Pellet

Table 1

Distribution of Participants by Center and Treatment Received

Center	4-Pellet		5-Pellet		Total	
	n	(%)	n	(%)	n	(%)
908	10	(52.6)	10	(50.0)	20	(51.3)
952	9	(47.4)	10	(50.0)	19	(48.7)
N	19		20		39	

Note: Percentages may not sum to 100 due to rounding.

July 21, 1995

NET Pellet Phase II-A
Study 890

108

Table 2.1
 Number and Percent of Participants
 With Protocol Deviations
 by Treatment Received

Protocol deviation	4-Pellet (N=19)		5-Pellet (N=20)	
	n	(%)	n	(%)
Abnormal pelvic exam	0	(0.0)	1	(5.0)
Adm visit not b/w day 3 - 6 of menses	0	(0.0)	2	(10.0)
Lab done more than 35 days prior to adm	2	(10.5)	3	(15.0)
Menstrual length not b/w 25-35 days	0	(0.0)	1	(5.0)
Out of age range	2	(10.5)	2	(10.0)
Total cholesterol > 240 mg/dl	1	(5.3)	0	(0.0)
Any Protocol Deviations	5	(26.3)	8	(40.0)

January 5, 1996

NET Pellet Phase II-A
 Study 890

bcl

Table 2.2

List of Participants with Protocol Deviations
by Treatment Received

Center	PON	Treatment	Selection Criteria	Comments
908	2	4-Pellet	Out of age range	age = 36
908	3	4-Pellet	Out of age range	age = 37
908	11	4-Pellet	Total cholesterol > 240 mg/dl	cholesterol = 241 mg/dl
908	17	4-Pellet	Lab done more than 35 days prior to adm	SMAC, CBC, UA at -77d; lipids at -52d
952	1	4-Pellet	Lab done more than 35 days prior to adm	SMAC, CBC, UA, lipids at -59d
908	12	5-Pellet	Lab done more than 35 days prior to adm	UA at -40d
908	12	5-Pellet	Menstrual length not b/w 25-35 days	cycle length = 37 days
908	16	5-Pellet	Out of age range	age = 36
908	18	5-Pellet	Abnormal pelvic exam	vaginal discharge
952	8	5-Pellet	Lab done more than 35 days prior to adm	SMAC, CBC, UA, lipids at -65d
952	9	5-Pellet	Lab done more than 35 days prior to adm	SMAC, CBC, UA, lipids at -41d
952	16	5-Pellet	Out of age range	age = 36
952	17	5-Pellet	Adm visit not b/w day 3-6 of menses	adm on d 7 of cycle
952	19	5-Pellet	Adm visit not b/w day 3-6 of menses	adm on d 7 of cycle

110

Table 3

Age, Race, and Smoking History at Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Age in years				
<= 20	1	(5.3)	3	(15.0)
21-25	8	(42.1)	4	(20.0)
26-30	6	(31.6)	5	(25.0)
31-35	2	(10.5)	6	(30.0)
>= 36	2	(10.5)	2	(10.0)
Total	19		20	
Mean (SD)	26.7	(5.29)	28.2	(5.91)
Median	26.0		27.5	
Min	19		19	
Max	37		36	
Race				
White	14	(73.7)	17	(85.0)
Black	2	(10.5)	2	(10.0)
Hispanic	1	(5.3)	1	(5.0)
Asian	2	(10.5)	0	(0.0)
Total	19		20	

Note: Percentages may not sum to 100 due to rounding.

July 23, 1995

NET Pellet Phase II-A
Study 890

Table 3 (Continued)

Age, Race, and Smoking History at Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Number of cigarettes smoked in a typical day				
0	13	(68.4)	16	(80.0)
1-9	2	(10.5)	1	(5.0)
10-20	4	(21.1)	3	(15.0)
Total	19		20	
Mean (SD)	3.2	(5.76)	3.2	(6.89)
Median	0.0		0.0	
Min	0		0	
Max	20		20	

Note: Percentages may not sum to 100 due to rounding.

July 23, 1995

NET Pellet Phase II-A
Study 890

112

Table 4
Pregnancy History at Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Number of live births				
0	15	(78.9)	12	(60.0)
1	2	(10.5)	6	(30.0)
2-4	2	(10.5)	2	(10.0)
Total	19		20	
Mean (SD)	0.3	(0.67)	0.6	(0.94)
Median	0.0		0.0	
Min	0		0	
Max	2		3	
Outcome of last pregnancy				
Not previously pregnant	6	(31.6)	6	(30.0)
Live birth	4	(21.1)	5	(25.0)
Induced abortion <= 12 weeks (aseptic)	9	(47.4)	9	(45.0)
Total	19		20	

Note: Percentages may not sum to 100 due to rounding.

August 15, 1995

NET Pellet Phase II-A
Study 890

113

Table 4 (Continued)
Pregnancy History at Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
<hr/>				
Number of months since ¹ last pregnancy termination				
<hr/>				
1-6	2	(15.4)	4	(28.6)
7-12	0	(0.0)	0	(0.0)
>= 13	11	(84.6)	10	(71.4)
Total	13		14	
Mean (SD)	48.2	(37.36)	52.6	(55.25)
Median	43.0		34.0	
Min	3		2	
Max	142		183	

¹ Excludes participants not previously pregnant.

Note: Percentages may not sum to 100 due to rounding.

August 15, 1995

NET Pellet Phase II-A
Study 890

Table 5
Contraceptive History at Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Main contraceptive method used in month prior to admission				
None	1	(5.3)	0	(0.0)
Condom alone	8	(42.1)	9	(45.0)
Condom with spermicide	1	(5.3)	4	(20.0)
Withdrawal	1	(5.3)	0	(0.0)
Rhythm	2	(10.5)	0	(0.0)
Diaphragm	3	(15.8)	2	(10.0)
Foam, suppositories	0	(0.0)	1	(5.0)
Sponge	1	(5.3)	2	(10.0)
Other	2	(10.5)	2	(10.0)
Total	19		20	

Note: Percentages may not sum to 100 due to rounding.

July 23, 1995

NET Pellet Phase II-A
 Study 890

115

Table 6

Menstrual Information for Cycle Prior to Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Day of menses at admission				
3-6	19	(100.0)	18	(90.0)
>= 7	0	(0.0)	2	(10.0)
Total	19		20	
Mean (SD)	4.0	(1.00)	4.8	(1.32)
Median	4.0		5.0	
Min	3		3	
Max	6		7	
Dysmenorrhea in past cycle				
None	7	(36.8)	13	(65.0)
Mild	8	(42.1)	5	(25.0)
Moderate	4	(21.1)	1	(5.0)
Severe	0	(0.0)	1	(5.0)
Total	19		20	

Note: Percentages may not sum to 100 due to rounding.

August 10, 1995

NET Pellet Phase II-A
Study 890

1/6

Table 6 (Continued)

Menstrual Information for Cycle Prior to Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Intermenstrual pelvic pain in past cycle				
None	17	(89.5)	19	(95.0)
Moderate	2	(10.5)	1	(5.0)
Total	19		20	
Intermenstrual bleeding in past cycle				
None	19	(100.0)	20	(100.0)
One or more days	0	(0.0)	0	(0.0)
Total	19		20	

Note: Percentages may not sum to 100 due to rounding.

August 10, 1995

NET Pellet Phase II-A
Study 890

117

Table 7
Menstrual History for Three Cycles
Prior to Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Average duration of menstrual flow in days				
1-2	0	(0.0)	2	(10.0)
3-6	17	(89.5)	18	(90.0)
7-10	2	(10.5)	0	(0.0)
Total	19		20	
Mean (SD)	4.8	(1.08)	4.1	(1.25)
Median	5.0		4.0	
Min	3		1	
Max	7		6	
Usual amount of menstrual flow				
Scanty	0	(0.0)	5	(25.0)
Moderate	16	(84.2)	14	(70.0)
Heavy	3	(15.8)	1	(5.0)
Total	19		20	

Note: Percentages may not sum to 100 due to rounding.

July 21, 1995

NET Pellet Phase II-A
Study 890

118

Table 7 (Continued)

Menstrual History for Three Cycles
Prior to Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Usual length of menstrual cycle in days (from day 1 of menses)				
25-29	10	(52.6)	14	(70.0)
30-35	9	(47.4)	5	(25.0)
>= 36	0	(0.0)	1	(5.0)
Total	19		20	
Mean (SD)	29.3	(2.13)	29.4	(2.21)
Median	29.0		29.0	
Min	25		27	
Max	34		37	

Note: Percentages may not sum to 100 due to rounding.

July 21, 1995

NET Pellet Phase II-A
Study 890

119

Table 8.1

Medical History and Physical at Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Any pre-existing medical or surgical diagnoses				
No	9	(47.4)	6	(30.0)
Yes	10	(52.6)	14	(70.0)
Total	19		20	
Any medications being taken				
No	18	(94.7)	17	(85.0)
Yes	1	(5.3)	3	(15.0)
Total	19		20	
Pelvic exam results				
Normal	19	(100.0)	19	(95.0)
Abnormal	0	(0.0)	1	(5.0)
Total	19		20	

Note: Percentages may not sum to 100 due to rounding.

July 21, 1995

NET Pellet Phase II-A
Study 890

120

Table 8.1 (Continued)

Medical History and Physical at Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Breast exam results				
Normal	19	(100.0)	20	(100.0)
Abnormal	0	(0.0)	0	(0.0)
Total	19		20	
Pap smear results				
Normal	19	(100.0)	20	(100.0)
Atypia	0	(0.0)	0	(0.0)
Total	19		20	
Blood pressure (mm Hg) sitting, 15 min. rest				
Systolic				
Total	19		20	
Mean (SD)	111.7	(8.95)	112.3	(10.18)
Median	112.0		120.0	
Min	92		90	
Max	122		124	

Note: Percentages may not sum to 100 due to rounding.

July 21, 1995

NET Pellet Phase II-A
Study 890

121

Table 8.1 (Continued)

Medical History and Physical at Admission
by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Diastolic				
<hr/>				
Total	19		20	
Mean (SD)	75.4	(6.08)	74.9	(6.41)
Median	78.0		79.0	
Min	62		62	
Max	84		82	
Pulse (beats per minute)				
<hr/>				
Total	19		19	
Mean (SD)	79.5	(8.32)	76.4	(7.76)
Median	80.0		80.0	
Min	64		60	
Max	100		88	
Weight (kg)				
<hr/>				
Total	19		20	
Mean (SD)	61.3	(7.76)	61.4	(8.18)
Median	60.0		58.0	
Min	51		52	
Max	74		77	

July 21, 1995

NET Pellet Phase II-A
Study 890

122

Table 8.1 (Continued)
 Medical History and Physical at Admission
 by Treatment Received

Participant Characteristic	4-Pellet		5-Pellet	
	n	(%)	n	(%)
Height (cm)				
Total	19		20	
Mean (SD)	165.4	(5.76)	165.9	(5.44)
Median	165.0		166.5	
Min	152		153	
Max	176		174	
Body mass index kg/m²				
Total	19		20	
Mean (SD)	22.4	(3.04)	22.3	(2.49)
Median	21.6		21.1	
Min	16		19	
Max	27		27	

July 21, 1995

NET Pellet Phase II-A
 Study 890

123

Table 8.2

List of Participants with Pre-existing Medical Diagnosis or Medication
by Treatment Received

Center	PCW	Treatment received	Medical or surgical diagnosis	Medication
908	2	4-Pellet	Trichomonas vaginitis Gonorrhea, genital, site NS Contusion/hematoma, site NS Tonsillectomy	
908	3	4-Pellet	Lupus erythematosus Cholecystectomy	
908	6	4-Pellet	Hypothyroidism, NOS Tonsillectomy	Other thyroid hormones and substitutes
908	8	4-Pellet	Genital herpes, NOS Human papilloma virus, site NS	
908	13	4-Pellet	Human papilloma virus, site NS	
908	19	4-Pellet	Bilateral breast reduction	
952	1	4-Pellet	Congenital deformity of knee, NOS Repair of knee, NOS	
952	7	4-Pellet	Breast implant(s)	
952	11	4-Pellet	Jaundice, NOS	
952	18	4-Pellet	Genital herpes, NOS	
908	1	5-Pellet	Anemia, NOS Cystitis, NOS Melena (visible or occult) Tonsillectomy Herniorrhaphy, NOS	Ferrous sulphate

July 21, 1995

NET Pellet Phase II-A
Study 890

124

Table 8.2 (Continued)

List of Participants with Pre-existing Medical Diagnosis or Medication
by Treatment Received

Center	POW	Treatment received	Medical or surgical diagnosis	Medication
908	4	5-Pellet	Genital herpes, NOS	
908	5	5-Pellet	Vaginitis, chlamydia Cystitis, NOS Human papilloma virus, site NS Ulcer disease, site NS Eczema, site NS	Calcium carbonate w/wo other Aluminum hydroxide (gel) Magnesium hydroxide Simethicone
908	7	5-Pellet	Hemorrhoids, NOS	
908	9	5-Pellet	Degenerative disc disease	Tolmetin (tolectin)
908	12	5-Pellet	Asthma, NOS	
908	14	5-Pellet	Genital herpes, NOS, history of Upper respiratory tract infection, NOS	
908	16	5-Pellet	Ovarian cyst, NOS Cystitis, NOS Laparoscopy for diagnostic reasons only	
908	18	5-Pellet	Human papilloma virus, site NS	
908	20	5-Pellet	Raynaud's syndrome/disease	
952	4	5-Pellet	Tonsillectomy	
952	8	5-Pellet	Tonsillectomy	
952	10	5-Pellet	Adenoidectomy	
952	14	5-Pellet	Bilateral breast reduction	

July 21, 1995

NET Pellet Phase II-A
Study 890

Table 8.3

List of Participants with Abnormal Pelvic Exam, Breast Exam, or Pap Smear Results
at Admission
by Treatment Received

Center	POW	Treatment received	Pelvic exam results	Breast exam results	Pap smear results
908	18	5-Pellet	Vaginal discharge, NOS (leukorrhea)	Normal	Normal

July 21, 1995

NET Pellet Phase II-A
Study 890

126

Table 9

Number and Percent of Participants with any Follow-up Contact
by Treatment Received

Month	4-Pellet ¹			5-Pellet ¹		
	Total	n	(%)	Total	n	(%)
3-month	19	17	89.5	20	20	100.0
6-month	17	15	88.2	19	19	100.0
9-month	16	13	81.3	19	18	94.7
12-month	16	13	81.3	19	19	100.0
15-month	16	13	81.3	19	19	100.0
18-month	15	10	66.7	19	19	100.0
21-month	15	10	66.7	18	16	88.9
24-month	15	8	53.3	18	15	83.3

¹ Total is the number of participants whose pellets have not previously been removed.

July 24, 1995

NET Pellet Phase II-A
Study 890

127

Table 10.1

Number of Discontinuations from Clinic Follow-up
by Treatment Received

4 - Pellet

Discontinuation reason	Month of Discontinuation													Total
	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	
Menstrual problems		1												1
Other medical								1						1
Other personal		1	1			2		1	1	1				7
End of study											2	2	1	5
Unable to contact patient			2					1			1		1	5
Total	0	2	3	0	0	2	0	3	1	1	3	2	2	19

5 - Pellet

Discontinuation reason	Month of Discontinuation													Total
	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	
Menstrual problems													1	1
Other medical		1							1					2
Other personal							2		3	1				6
End of study										1	1	7	1	10
Unable to contact patient									1					1
Total	0	1	0	0	0	0	2	0	5	2	1	7	2	20

August 15, 1995

NET Pellet Phase II-A
Study 890

Table 10.2

List of Participants Discontinuing from Clinic Follow-up
by Treatment Received
4 - Pellet

Center	PON	Treatment received	Date of disc.	Study Month	Reason for discontinuation	Comments
908	2	4-Pellet	18OCT93	26	Other personal	Moving out of state/country
908	3	4-Pellet	23JUN93	22	Other medical	ENCEPHALITIS (CEREBRITIS) DUE TO LUPUS
908	6	4-Pellet	20DEC91	4	Menstrual problems	MENSTRUATION, IRREGULAR
908	8	4-Pellet	22MAY92	8	Other personal	Moving out of state/country
908	10	4-Pellet	21OCT93	24	Unable to contact participant	Moving out of state/country
908	11	4-Pellet	20OCT94	35	End of Study	
908	13	4-Pellet	04MAY94	29	Other personal	Family health problems
908	15	4-Pellet	29JUN93	17	Other personal	Wants to quit due to new job demands
908	17	4-Pellet	18NOV93	22	Other personal	Moving out of state/country
908	19	4-Pellet	20OCT92	8	Unable to contact participant	
952	1	4-Pellet	16SEP94	37	End of Study	
952	3	4-Pellet	16NOV94	37	Unable to contact participant	
952	6	4-Pellet	02NOV94	36	End of Study	
952	7	4-Pellet	26MAR92	5	Other personal	BREAST PAIN (MASTALGIA)
952	11	4-Pellet	13OCT94	32	End of Study	
952	12	4-Pellet	25AUG92	7	Unable to contact participant	
952	13	4-Pellet	10OCT94	32	End of Study	
952	15	4-Pellet	01DEC94	32	Unable to contact participant	
952	18	4-Pellet	15SEP93	17	Other personal	Decreasing NET level, wants oral pill

November 21, 1995

NET Pellet Phase II-A
Study 890

129

Table 10.2 (Continued)

List of Participants Discontinuing from Clinic Follow-up
by Treatment Received
5 - Pellet

Center	PON	Treatment received	Date of disc.	Study Month	Reason for discontinuation	Comments
908	1	5-Pellet	24JAN92	5	Other medical	HEADACHE, NOS.
908	4	5-Pellet	01DEC93	27	Other personal	Participant doesn't want to cont. study
908	5	5-Pellet	30NOV93	27	Unable to contact participant	
908	7	5-Pellet	30NOV94	39	Menstrual problems	AMENORRHEA
908	9	5-Pellet	06MAY93	20	Other personal	Moving out of state/country
908	12	5-Pellet	17JUN93	19	Other personal	School/work conflicts w/clinic visits
908	14	5-Pellet	02NOV94	34	End of Study	
908	16	5-Pellet	16NOV94	34	End of Study	
908	18	5-Pellet	23FEB94	25	Other personal	Wouldn't continue past original 24 mths.
908	20	5-Pellet	13JUL94	28	End of Study	
952	2	5-Pellet	17OCT94	36	End of Study	
952	4	5-Pellet	03NOV94	37	End of Study	
952	5	5-Pellet	14OCT94	36	End of Study	
952	8	5-Pellet	31OCT94	36	End of Study	
952	9	5-Pellet	24SEP94	34	End of Study	
952	10	5-Pellet	17NOV94	36	End of Study	
952	14	5-Pellet	25NOV94	33	End of Study	
952	16	5-Pellet	26JUN94	27	Other medical	BREAST HYPERPLASIA, BENIGN
952	17	5-Pellet	26APR94	25	Other personal	Participant wants to become pregnant
952	19	5-Pellet	18AUG94	28	Other personal	Volunteering for ovum donation program

November 21, 1995

NET Pellet Phase II-A
Study 890

130

Table 11.1

Reported Average Coital Frequency Since Last Contact
Through 12 Months
by Treatment Received

Follow-up period	4-Pellet		5-Pellet	
	n	(%)	n	(%)
3 months				
No coitus	1	(5.9)	1	(5.0)
Less than once/week	1	(5.9)	1	(5.0)
At least once/week but less than twice/week	1	(5.9)	4	(20.0)
At least twice/week	14	(82.4)	14	(70.0)
¹ Total	17		20	
6 months				
No coitus	1	(6.7)	0	(0.0)
Less than once/week	0	(0.0)	0	(0.0)
At least once/week but less than twice/week	2	(13.3)	6	(31.6)
At least twice/week	12	(80.0)	13	(68.4)
¹ Total	15		19	

¹ Total is the number of women who had a contact during the follow-up period and whose pellets had not been previously removed.

Note: Percentages may not sum to 100 due to rounding.

November 20, 1995

NET Pellet Phase II-A
Study 890

Table 11.1 (Continued)

Reported Average Coital Frequency Since Last Contact
Through 12 Months
by Treatment Received

Follow-up period	4-Pellet		5-Pellet	
	n	(%)	n	(%)
<u>9 months</u>				
No coitus	0	(0.0)	0	(0.0)
Less than once/week	0	(0.0)	1	(5.6)
At least once/week but less than twice/week	3	(23.1)	4	(22.2)
At least twice/week	10	(76.9)	13	(72.2)
¹ Total	13		18	
<u>12 months</u>				
No coitus	0	(0.0)	0	(0.0)
Less than once/week	1	(7.7)	0	(0.0)
At least once/week but less than twice/week	2	(15.4)	5	(26.3)
At least twice/week	9	(69.2)	14	(73.7)
Unknown	1	(7.7)	0	(0.0)
¹ Total	13		19	

¹ Total is the number of women who had a contact during the follow-up period and whose pellets had not been previously removed.

Note: Percentages may not sum to 100 due to rounding.

November 20, 1995

NET Pellet Phase II-A
Study 890

132

Table 11.2
Use of Additional Contraceptive Methods
4 - Pellet

Center	Pon	¹ Earliest Month any additional contraceptive	Earliest month any steroidal contraceptive	Steroidal contraceptive	Study month discontinued
908	2	15 *	never used	n/a	26
908	3	15 *	never used	n/a	22
908	6	never used	never used	n/a	4
908	8	never used	never used	n/a	8
908	10	15 *	16	NORPLANT (R) implants	24
908	11	15 *	never used	n/a	35
908	13	15 *	never used	n/a	29
908	15	17 *	never used	n/a	17
908	17	14 *	19	Lo Ovrul	22
908	19	never used	never used	n/a	8
952	1	25-28 **	never used	n/a	37
952	3	25-31 **	never used	n/a	37
952	6	24-35 **	never used	n/a	36
952	7	never used	never used	n/a	5
952	11	24-32 **	never used	n/a	32
952	12	never used	never used	n/a	7
952	13	26-32 **	never used	n/a	32
952	15	never used	never used	n/a	32
952	18	never used	never used	n/a	17

¹ Participants were supposed to begin using additional contraception in Month 13. Where determinable, the exact month that use began is given. Otherwise the following is given:

- * Earliest month information on additional use collected. Use began on or before this month.
- ** Use began sometime between these months (inclusive).

August 15, 1995

Net Pellet Phase II-A
Study 890

133

Table 11.3
 Use of Additional Contraceptive Methods
 5 - Pellet

Center	Pon	¹ Earliest Month any additional contraceptive	Earliest month any steroidal contraceptive	Steroidal contraceptive	Study month discontinued
908	1	never used	never used	n/a	5
908	4	15 *	21	Lo Ovrал	27
908	5	14	14	Triphasil	27
908	7	15 *	never used	n/a	39
908	9	14	14	Triphasil	20
908	12	14 *	never used	n/a	19
908	14	14	14	Lo Ovrал	34
908	16	13	never used	n/a	34
908	18	13	13	Triphasil	25
908	20	14	14	Lo Ovrал	28
952	2	24-35 **	never used	n/a	36
952	4	24-37 **	never used	n/a	37
952	5	24-36 **	never used	n/a	36
952	8	24-35 **	never used	n/a	36
952	9	25-34 **	never used	n/a	34
952	10	25-34 **	never used	n/a	36
952	14	25-33 **	never used	n/a	33
952	16	never used	never used	n/a	27
952	17	never used	never used	n/a	25
952	19	24-28 **	never used	n/a	28

¹ Participants were supposed to begin using additional contraception in Month 13. Where determinable, the exact month that use began is given. Otherwise the following is given:

- * Earliest month information on additional use collected. Use began on or before this month.
- ** Use began sometime between these months (inclusive).

August 15, 1995

Net Pellet Phase II-A
 Study 890

134

Table 12.1
Summary of NET Values (ng/ml)
4-Pellet

Follow-up Period	Total ¹	Mean	(SD)	Median	Min	Max
24-hour	19	2.873	(0.9319)	2.704	1.784	5.331
1-week	19	1.376	(0.4252)	1.460	0.263	1.878
1-month	18	0.928	(0.4325)	0.917	0.474	2.369
2-month	13	0.850	(0.3164)	0.721	0.395	1.443
3-month	11	0.607	(0.2582)	0.632	0.056	0.936
4-month	13	0.794	(0.2186)	0.788	0.393	1.144
5-month	12	0.715	(0.2475)	0.672	0.362	1.275
6-month	13	0.619	(0.2003)	0.645	0.268	0.939
7-month	12	0.571	(0.1083)	0.579	0.334	0.710
8-month	9	0.542	(0.1507)	0.554	0.282	0.756
9-month	11	0.554	(0.1859)	0.535	0.272	0.926
10-month	9	0.461	(0.1221)	0.448	0.271	0.705
11-month	11	0.491	(0.1328)	0.501	0.307	0.711
12-month	11	0.487	(0.1748)	0.444	0.265	0.860
13-month	13	0.426	(0.1251)	0.395	0.268	0.643
14-month	9	0.401	(0.1580)	0.359	0.193	0.727
15-month	9	0.380	(0.1379)	0.314	0.218	0.619
16-month	9	0.449	(0.1546)	0.438	0.288	0.813
17-month	9	0.385	(0.1713)	0.380	0.161	0.760
18-month	4	0.337	(0.2121)	0.271	0.161	0.644
19-month	6	0.314	(0.1563)	0.250	0.153	0.522
20-month	8	0.309	(0.1293)	0.278	0.156	0.539
21-month	5	0.286	(0.1342)	0.289	0.142	0.466
22-month	7	0.279	(0.1208)	0.250	0.117	0.471
23-month	6	0.246	(0.1526)	0.207	0.056	0.431
24-month	5	0.300	(0.0618)	0.322	0.198	0.361
25-month	9	0.212	(0.0903)	0.197	0.056	0.336

¹Total is the number of participants with data at each time period who have not had pellets removed and who are not on steroidal contraceptives.

July 24, 1995

NET Pellet Phase II-A
Study 890

135

Table 12.1 (Continued)
 Summary of NET Values (ng/ml)
 4-Pellet

Follow-up Period	Total ¹	Mean	(SD)	Median	Min	Max
26-month	4	0.227	(0.1178)	0.266	0.056	0.321
27-month	5	0.225	(0.0598)	0.213	0.168	0.313
28-month	5	0.201	(0.0689)	0.179	0.160	0.323
29-month	3	0.208	(0.0541)	0.205	0.156	0.264
30-month	3	0.180	(0.0704)	0.150	0.129	0.260
31-month	3	0.178	(0.0484)	0.197	0.123	0.214
32-month	3	0.176	(0.0208)	0.168	0.161	0.200
33-month	2	0.152	(0.0007)	0.152	0.151	0.152
34-month	1	0.056	(N/A)	0.056	0.056	0.056
35-month	1	0.160	(N/A)	0.160	0.160	0.160
36-month	2	0.056	(0.0000)	0.056	0.056	0.056
37-month	2	0.056	(0.0000)	0.056	0.056	0.056
38-month	1	0.056	(N/A)	0.056	0.056	0.056

¹Total is the number of participants with data at each time period who have not had pellets removed and who are not on steroidal contraceptives.

July 24, 1995

NET Pellet Phase II-A
 Study 890

Table 12.2
Summary of NET Values (ng/ml)
5-Pellet

Follow-up Period	Total ¹	Mean	(SD)	Median	Min	Max
24-hour	20	3.311	(1.2546)	3.551	1.397	5.492
1-week	20	2.036	(0.6883)	2.081	0.713	3.141
1-month	20	1.090	(0.3883)	1.024	0.558	2.164
2-month	17	1.025	(0.3116)	0.937	0.393	1.732
3-month	18	0.920	(0.2000)	0.897	0.604	1.221
4-month	16	0.912	(0.2569)	0.803	0.643	1.261
5-month	13	1.640	(2.8348)	0.827	0.399	11.030
6-month	17	0.811	(0.2711)	0.778	0.424	1.327
7-month	14	0.723	(0.2437)	0.700	0.406	1.234
8-month	12	0.731	(0.3043)	0.642	0.420	1.466
9-month	17	0.649	(0.2032)	0.638	0.305	1.200
10-month	15	0.651	(0.2302)	0.644	0.309	1.154
11-month	17	0.642	(0.2579)	0.630	0.292	1.287
12-month	15	0.639	(0.2429)	0.564	0.293	1.088
13-month	16	0.564	(0.2013)	0.513	0.271	1.017
14-month	13	0.618	(0.2461)	0.551	0.311	1.199
15-month	13	0.589	(0.2060)	0.531	0.258	1.104
16-month	11	0.549	(0.1524)	0.586	0.263	0.805
17-month	11	0.589	(0.2251)	0.571	0.298	0.985
18-month	8	0.492	(0.2161)	0.395	0.309	0.942
19-month	12	0.458	(0.1938)	0.410	0.219	0.822
20-month	12	0.504	(0.2012)	0.417	0.245	0.889
21-month	11	0.445	(0.1650)	0.415	0.154	0.659
22-month	10	0.477	(0.2116)	0.482	0.171	0.862
23-month	7	0.502	(0.2207)	0.455	0.223	0.898
24-month	7	0.384	(0.0854)	0.326	0.310	0.516
25-month	4	0.514	(0.1703)	0.450	0.390	0.765

¹ Total is the number of participants with data at each time period who have not had pellets removed and who are not on steroidal contraceptives.

July 24, 1995

NET Pellet Phase II-A
Study 890

137

Table 12.2 (Continued)
 Summary of NET Values (ng/ml)
 5-Pellet

Follow-up Period	Total ¹	Mean	(SD)	Median	Min	Max
26-month	6	0.393	(0.0827)	0.381	0.319	0.543
27-month	7	0.347	(0.1552)	0.271	0.231	0.634
28-month	5	0.380	(0.1416)	0.298	0.271	0.598
29-month	4	0.424	(0.1040)	0.424	0.296	0.550
30-month	5	0.345	(0.1341)	0.346	0.178	0.506
31-month	4	0.316	(0.1235)	0.314	0.168	0.469
32-month	3	0.257	(0.0808)	0.249	0.181	0.342
33-month	2	0.370	(0.0962)	0.370	0.302	0.438
34-month	2	0.266	(0.0622)	0.266	0.222	0.310
35-month	3	0.158	(0.0340)	0.174	0.119	0.181
36-month	2	0.283	(0.0523)	0.283	0.246	0.320
37-month	2	0.359	(0.1570)	0.359	0.248	0.470

¹ Total is the number of participants with data at each time period who have not had pellets removed and who are not on steroidal contraceptives.

July 24, 1995

NET Pellet Phase II-A
 Study 890

Table 13.1

Number and Percent of Participants Who Ever
 Had a NET Concentration Below 0.3 ng/ml
 From the 1-month Follow-up Through the 12-month Follow-up
 By Treatment Received

	4-Pellet		5-Pellet	
	n	(%)	n	(%)
NET concentration ever below 0.3 ng/ml				
Yes	3	(16.7)	2	(10.0)
No	15	(83.3)	18	(90.0)
Total	18		20	

Note: Percentages may not sum to 100 due to rounding.

August 15, 1995

NET Pellet Phase II-A
 Study 890

139

Table 13.2

List of Participants Who Ever Had a NET Concentration
 Below 0.3 ng/ml from the 1-month Follow-up
 Through the 12-month Follow-up
 By Treatment Received

Center	PON	Treatment received	NET value (ng/ml)	Study Month
908	6	4-Pellet	< 0.112	3
952	6	4-Pellet	0.268	6
952	6	4-Pellet	0.282	9
952	6	4-Pellet	0.272	9
952	6	4-Pellet	0.265	13
952	18	4-Pellet	0.271	11
952	18	4-Pellet	0.296	12
908	12	5-Pellet	0.293	12
952	14	5-Pellet	0.292	12

August 15, 1995

NET Pellet Phase II-A
 Study 890

Table 13.3

Time Until First NET < .3 ng/ml
by Treatment Received

Time in study	4 - Pellet			5 - Pellet		
	At Risk ¹ n	Cumulative event rate per woman	(S.E.)	At Risk ¹ n	Cumulative event rate per woman	(S.E.)
3 - month	17.0	0.110	0.0732	20.0	0.000	0.0000
6 - month	15.0	0.169	0.0892	19.0	0.000	0.0000
9 - month	13.0	0.169	0.0892	19.0	0.000	0.0000
12 - month	12.0	0.233	0.1027	18.5	0.108	0.0722
15 - month	11.0	0.303	0.1146	12.0	0.108	0.0722
18 - month	7.0	0.525	0.1322	11.0	0.182	0.0972
21 - month	5.0	0.605	0.1318	10.5	0.182	0.0972
24 - month	5.0	0.684	0.1270	8.5	0.182	0.0972
27 - month	2.5	0.763	0.1173	7.0	0.285	0.1279
30 - month	2.0	0.763	0.1173	3.0	0.693	0.1446
33 - month	1.0	0.881	0.1024	3.0	0.693	0.1446

¹The number at risk in each interval is the number of participants entering the interval minus one-half of those censored during the interval. Censored participants are those who never had a NET < .3 ng/ml and whose last valid NET measurement occurred during the interval. Valid NET measurements include those that occurred prior to pellet removal or prior to the use of steroidal contraceptives.

August 16, 1995

Net Pellet Phase II-A
Study 890

Table 14.1

Number and Percent of Participants with Elevated
Progesterone Levels (ng/ml)
by Treatment Received

	Total ¹	Max >3		Max >5	
		n	(%)	n	(%)
4-Pellet					
Baseline	19	19	(100.0)	18	(94.7)
9-Month	9	2	(22.2)	2	(22.2)
12-Month	7	3	(42.9)	3	(42.9)
15-Month	4	1	(25.0)	1	(25.0)
18-Month	7	3	(42.9)	3	(42.9)
21-Month	2	2	(100.0)	2	(100.0)
24-Month	6	6	(100.0)	6	(100.0)
27-Month	5	5	(100.0)	5	(100.0)
30-Month	2	2	(100.0)	2	(100.0)
33-Month	1	1	(100.0)	1	(100.0)
5-Pellet					
Baseline	19	15	(78.9)	15	(78.9)
9-Month	14	1	(7.1)	1	(7.1)
12-Month	14	4	(28.6)	3	(21.4)
15-Month	7	3	(42.9)	3	(42.9)
18-Month	8	2	(25.0)	2	(25.0)
21-Month	2	1	(50.0)	1	(50.0)
24-Month	7	2	(28.6)	2	(28.6)
27-Month	3	0	(0.0)	0	(0.0)
30-Month	4	2	(50.0)	2	(50.0)
33-Month	1	0	(0.0)	0	(0.0)

1

Total is the number of participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

Table 14.2

List of Participants with
Elevated Progesterone Levels (>3 ng/ml)
by Time Period and Treatment Received

Center	PON	Treatment received	Max Progesterone level (ng/ml)	Study Month
Baseline				
908	2	4-Pellet	11.43	-1
908	3	4-Pellet	10.69	-1
908	6	4-Pellet	14.57	-1
908	8	4-Pellet	21.50	-1
908	10	4-Pellet	17.90	-1
908	11	4-Pellet	14.80	-1
908	13	4-Pellet	9.25	-1
908	15	4-Pellet	15.80	-1
908	17	4-Pellet	11.30	-1
908	19	4-Pellet	6.30	-1
952	1	4-Pellet	14.06	-2
952	3	4-Pellet	18.16	-1
952	6	4-Pellet	10.35	-1
952	7	4-Pellet	19.06	-1
952	11	4-Pellet	12.47	-1

1

List includes participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

October 30, 1995

NET Pellet Phase II-A
Study 890

143

Table 14.2 (Continued)

List of Participants with
Elevated Progesterone Levels (>3 ng/ml)
by Time Period and Treatment Received

Center	PON	Treatment received	Max Progesterone level (ng/ml)	Study Month
952	12	4-Pellet	17.60	-1
952	13	4-Pellet	3.14	-1
952	15	4-Pellet	6.96	-1
952	18	4-Pellet	13.92	-1
908	1	5-Pellet	7.52	-1
908	4	5-Pellet	13.98	-1
908	5	5-Pellet	9.11	-1
908	7	5-Pellet	17.70	-1
908	9	5-Pellet	12.10	-1
908	12	5-Pellet	7.65	-1
908	14	5-Pellet	6.07	-1
908	16	5-Pellet	9.56	-1
908	18	5-Pellet	7.68	-1
908	20	5-Pellet	7.08	-1
952	2	5-Pellet	27.10	-1
952	4	5-Pellet	11.36	-1
952	5	5-Pellet	12.42	-1

1

List includes participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

October 30, 1995

NET Pellet Phase II-A
Study 890

144

Table 14.2 (Continued)

List of Participants with
Elevated Progesterone Levels (>3 ng/ml)
by Time Period and Treatment Received

Center	PON	Treatment received	Max Progesterone level (ng/ml)	Study Month
952	14	5-Pellet	8.03	-1
952	16	5-Pellet	9.73	-1
9-Month				
908	10	4-Pellet	12.11	10
908	13	4-Pellet	7.56	10
908	12	5-Pellet	14.85	10
12-Month				
908	11	4-Pellet	7.58	13
908	13	4-Pellet	8.64	13
952	11	4-Pellet	8.68	12
908	12	5-Pellet	10.93	13
908	20	5-Pellet	4.54	12
952	9	5-Pellet	10.17	13
952	19	5-Pellet	5.81	12

1

List includes participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

October 30, 1995

NET Pellet Phase II-A
Study 890

145

Table 14.2 (Continued)

List of Participants with
Elevated Progesterone Levels (>3 ng/ml)
by Time Period and Treatment Received

Center	PON	Treatment received	Max Progesterone level (ng/ml)	Study Month
<u>15-Month</u>				
908	2	4-Pellet	7.53	16
908	12	5-Pellet	11.27	15
952	2	5-Pellet	13.47	17
952	9	5-Pellet	8.19	16
<u>18-Month</u>				
908	2	4-Pellet	10.05	19
908	11	4-Pellet	10.95	19
952	11	4-Pellet	8.02	19
952	2	5-Pellet	10.36	19
952	9	5-Pellet	8.47	19
<u>21-Month</u>				
908	11	4-Pellet	6.44	23

1

List includes participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

October 30, 1995

NET Pellet Phase II-A
Study 890

146

Table 14.2 (Continued)

List of Participants with
Elevated Progesterone Levels (>3 ng/ml)
by Time Period and Treatment Received

Center	PON	Treatment received	Max Progesterone level (ng/ml)	Study Month
908	13	4-Pellet	21.81	22
952	9	5-Pellet	10.23	22
24-Month				
908	2	4-Pellet	6.65	25
908	11	4-Pellet	5.68	26
908	13	4-Pellet	21.34	25
952	1	4-Pellet	16.36	25
952	3	4-Pellet	15.93	25
952	6	4-Pellet	6.09	25
952	2	5-Pellet	19.06	25
952	19	5-Pellet	8.79	25
27-Month				
908	11	4-Pellet	12.55	29
908	13	4-Pellet	5.88	28

1

List includes participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

October 30, 1995

NET Pellet Phase II-A
Study 890

147

Table 14.2 (Continued)

List of Participants with
Elevated Progesterone Levels (>3 ng/ml)
by Time Period and Treatment Received

Center	PON	Treatment received	Max Progesterone level (ng/ml)	Study Month
952	1	4-Pellet	9.79	28
952	6	4-Pellet	10.77	28
952	11	4-Pellet	7.09	28
30-Month				
908	11	4-Pellet	14.19	31
952	6	4-Pellet	8.69	31
952	2	5-Pellet	18.63	31
952	5	5-Pellet	10.13	31
33-Month				
952	1	4-Pellet	13.50	33

¹ List includes participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

148

Table 15

Mean of Each Participant's Mean, Minimum, and Maximum Concentration of Estradiol (pg/ml)
and Median of Each Participant's Median Concentration of Estradiol (pg/ml)
by Treatment Received

	1 Total	Mean Participant Mean (SD)	Mean Participant Min (SD)	Mean Participant Max (SD)	Median Participant Median
4-Pellet					
Baseline	15	112.7 34.79	47.7 21.13	205.4 72.02	92.5
9-Month	8	163.9 81.30	60.3 20.64	359.3 212.77	135.3
12-Month	7	164.1 66.07	48.1 18.26	370.0 185.86	120.5
15-Month	4	202.0 107.44	74.0 28.13	545.8 407.22	128.8
18-Month	4	227.4 59.64	47.5 15.11	549.0 100.54	162.0
5-Pellet					
Baseline	13	122.1 41.92	48.2 20.62	230.4 101.30	92.5
9-Month	14	90.3 42.81	35.1 11.33	207.6 111.06	59.3
12-Month	14	82.8 24.12	37.1 12.80	171.3 98.34	66.8
15-Month	7	128.0 72.19	35.3 6.58	302.7 224.57	96.5
18-Month	6	106.8 43.99	43.8 16.50	206.2 100.01	81.8

¹ Total is the number of participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

October 30, 1995

NET Pellet Phase II-A
Study 890

bbl

Table 16.1

Number and Percent of Participants with Low Estradiol Levels (pg/ml) by Treatment Received

	Total ¹	Min <40		Max <40	
		n	(%)	n	(%)
4-Pellet					
Baseline	15	5	(33.3)	0	(0.0)
9-Month	8	1	(12.5)	0	(0.0)
12-Month	7	1	(14.3)	0	(0.0)
15-Month	4	0	(0.0)	0	(0.0)
18-Month	4	2	(50.0)	0	(0.0)
5-Pellet					
Baseline	13	2	(15.4)	0	(0.0)
9-Month	14	9	(64.3)	0	(0.0)
12-Month	14	9	(64.3)	0	(0.0)
15-Month	7	6	(85.7)	0	(0.0)
18-Month	6	3	(50.0)	0	(0.0)

¹

Total is the number of participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

October 30, 1995

NET Pellet Phase II-A
Study 890

150

Table 16.2
List of Participants with Minimum Estradiol Levels <40 pg/ml
by Time Period and Treatment Received

Center	PON	Treatment received	Estradiol level (pg/ml)	Study Month
<u>Baseline</u>				
908	8	4-Pellet	28	-1
908	15	4-Pellet	< 16	-1
908	19	4-Pellet	33	-1
952	11	4-Pellet	28	-1
952	15	4-Pellet	36	-1
908	16	5-Pellet	< 16	-1
952	14	5-Pellet	19	-1
<u>9-Month</u>				
908	15	4-Pellet	27	10
908	4	5-Pellet	33	10
908	5	5-Pellet	30	10
908	7	5-Pellet	22	10
908	9	5-Pellet	29	10
908	12	5-Pellet	22	10

1

List includes participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

October 30, 1995

NET Pellet Phase II-A
Study 890

151

Table 16.2 (Continued)
 List of Participants with Minimum Estradiol Levels <40 pg/ml
 by Time Period and Treatment Received

Center	PON	Treatment received	Estradiol level (pg/ml)	Study Month
908	14	5-Pellet	32	10
908	16	5-Pellet	29	10
952	14	5-Pellet	22	10
952	19	5-Pellet	37	10
 12-Month				
908	11	4-Pellet	20	13
908	4	5-Pellet	34	13
908	7	5-Pellet	31	13
908	12	5-Pellet	23	13
908	14	5-Pellet	39	13
908	16	5-Pellet	25	13
908	20	5-Pellet	30	12
952	2	5-Pellet	23	13
952	14	5-Pellet	31	13
952	19	5-Pellet	39	13

1
 List includes participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

October 30, 1995

NET Pellet Phase II-A
 Study 890

152

Table 16.2 (Continued)
List of Participants with Minimum Estradiol Levels <40 pg/ml
by Time Period and Treatment Received

Center	PON	Treatment received	Estradiol level (pg/ml)	Study Month
<u>15-Month</u>				
908	4	5-Pellet	36	16
908	7	5-Pellet	38	16
908	12	5-Pellet	30	16
908	16	5-Pellet	35	16
952	2	5-Pellet	37	16
952	14	5-Pellet	25	16
<u>18-Month</u>				
908	11	4-Pellet	33	19
908	13	4-Pellet	36	19
908	4	5-Pellet	39	19
908	7	5-Pellet	35	19
908	16	5-Pellet	19	19

1

List includes participants with at least four measurements at each time period who have not had pellets removed and who are not on steroidal contraceptives.

October 30, 1995

NET Pellet Phase II-A
Study 890

153

Table 17

Proportion of Participants with Clinically
Important Bleeding Patterns by
Reference Period and Treatment Received

Treatment/Reference Period (Days)	Total ¹ N	Amenorrhea (%)	Infrequent Bleeding (%)	Frequent Bleeding (%)	Irregular Bleeding (%)	Prolonged Bleeding (%)	Clinically Important Patterns n (%)	
<u>4-Pellet</u>								
1 (0-89)	18	0.0	0.0	33.3	55.6	50.0	15	83.3
2 (90-179)	16	6.2	6.2	12.5	50.0	12.5	12	75.0
3 (180-269)	15	0.0	13.3	20.0	46.7	40.0	14	93.3
4 (270-359)	13	0.0	7.7	23.1	38.5	15.4	10	76.9
5 (360-449)	13	7.7	0.0	15.4	23.1	7.7	6	46.2
6 (450-539)	12	0.0	8.3	25.0	16.7	25.0	8	66.7
7 (540-629)	10	10.0	0.0	0.0	50.0	20.0	7	70.0
8 (630-719)	8	0.0	0.0	0.0	37.5	12.5	4	50.0
<u>5-Pellet</u>								
1 (0-89)	20	5.0	10.0	20.0	50.0	50.0	18	90.0
2 (90-179)	19	15.8	26.3	26.3	52.6	26.3	19	100.0
3 (180-269)	19	15.8	15.8	26.3	47.4	31.6	17	89.5
4 (270-359)	19	21.0	10.5	10.5	21.0	15.8	12	63.2
5 (360-449)	19	21.0	10.5	10.5	36.8	26.3	15	79.0
6 (450-539)	19	21.0	5.3	26.3	31.6	26.3	15	79.0
7 (540-629)	16	18.8	6.2	18.8	31.2	31.2	12	75.0
8 (630-719)	13	15.4	0.0	0.0	23.1	23.1	7	53.8

¹ Total is the number of participants for at least the first 60 days in the 90-day reference period.

August 15, 1995

NET Pellet Phase II-A
Study 890

Table 18
 Comparison of Lipid Profiles (mg/dl) Between
 Baseline and Follow-up
 by Treatment Received

Lipid	4-Pellet				5-Pellet			
	Total ¹	Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>Total cholesterol</u>								
Baseline	19	184.1	(31.97)		20	185.2	(22.32)	
6-month	15	164.8	(30.38)		19	161.6	(26.31)	
12-month	12	168.9	(30.57)		18	166.2	(24.21)	
18-month	8	173.2	(28.82)		13	163.5	(27.78)	
24-month	6	164.0	(27.62)		11	164.6	(25.85)	
<u>Percent change in total cholesterol</u>								
Baseline to 6-month change	15	-12.4	(10.09)	<.01	19	-12.5	(10.39)	<.01
Baseline to 12-month change	12	-13.1	(12.08)	<.01	18	-9.8	(11.77)	<.01
Baseline to 18-month change	8	-9.2	(10.10)	.04	13	-13.2	(10.15)	<.01
Baseline to 24-month change	6	-15.4	(15.81)	.06	11	-10.4	(12.40)	<.01

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the total cholesterol comparisons for the baseline to 24-month change in the 5-Pellet group. No comparisons are made between treatment groups.

August 15, 1995

Net Pellet Phase II-A
 Study 890

Table 18 (continued)

Comparison of Lipid Profiles (mg/dl) Between
Baseline and Follow-up
by Treatment Received

Lipid	Total ¹	4-Pellet			5-Pellet			p-value ²
		Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	
<u>Triglycerides</u>								
Baseline	19	92.8	(32.67)		20	100.8	(29.52)	
6-month	15	74.4	(21.80)		19	81.5	(31.08)	
12-month	12	89.9	(38.03)		18	79.4	(31.05)	
18-month	8	86.5	(33.77)		13	67.6	(22.12)	
24-month	6	93.2	(75.43)		11	67.3	(15.84)	
<u>Percent change in triglycerides:</u>								
Baseline to 6-month change	15	-19.8	(26.79)	.01	19	-12.4	(40.00)	.19
Baseline to 12-month change	12	-7.8	(41.79)	.53	18	-16.1	(37.08)	.08
Baseline to 18-month change	8	-16.1	(28.31)	.15	13	-25.1	(32.43)	.02
Baseline to 24-month change	6	-24.7	(38.22)	.17	11	-23.3	(32.75)	.04

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test. No comparisons are made between treatment groups.

August 15, 1995

Net Pellet Phase II-A
Study 890

Table 18 (continued)
 Comparison of Lipid Profiles (mg/dl) Between
 Baseline and Follow-up
 by Treatment Received

Lipid	Total ¹	4-Pellet			5-Pellet			
		Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>HDL</u>								
Baseline	19	56.5	(09.84)		20	56.6	(11.31)	
6-month	15	55.9	(11.86)		19	56.5	(11.18)	
12-month	12	55.2	(15.32)		18	58.3	(13.00)	
18-month	8	60.1	(14.18)		13	61.2	(12.81)	
24-month	6	58.8	(09.75)		11	59.3	(10.60)	
<u>Percent change in HDL:</u>								
Baseline to 6-month change	15	-0.3	(19.09)	.58	19	0.0	(10.98)	.99
Baseline to 12-month change	12	0.9	(21.37)	.89	18	4.3	(14.75)	.67
Baseline to 18-month change	8	5.2	(20.69)	.50	13	5.8	(16.85)	.24
Baseline to 24-month change	6	1.0	(17.75)	.90	11	2.2	(16.73)	.67

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the HDL comparisons for the baseline to 6-month change in the 4-Pellet group and for the baseline to 12-month change in the 5-Pellet group. No comparisons are made between treatment groups.

August 15, 1995

Net Pellet Phase II-A
 Study 890

157

Table 18 (continued)
 Comparison of Lipid Profiles (mg/dl) Between
 Baseline and Follow-up
 by Treatment Received

Lipid	4-Pellet				5-Pellet			
	Total ¹	Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>HDL to total cholesterol ratio</u>								
Baseline	19	0.32	(0.081)		20	0.31	(0.062)	
6-month	15	0.35	(0.075)		19	0.35	(0.068)	
12-month	12	0.33	(0.091)		18	0.35	(0.081)	
18-month	8	0.35	(0.086)		13	0.38	(0.098)	
24-month	6	0.37	(0.085)		11	0.37	(0.079)	
<u>Percent change in HDL to total cholesterol ratio:</u>								
Baseline to 6-month change	15	14.3	(21.15)	.02	19	15.8	(18.82)	<.01
Baseline to 12-month change	12	17.7	(27.39)	.05	18	17.1	(19.85)	<.01
Baseline to 18-month change	8	17.5	(28.02)	.12	13	24.7	(32.54)	<.01
Baseline to 24-month change	6	22.5	(31.45)	.09	11	17.1	(30.97)	.10

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the HDL to total cholesterol comparisons for the baseline to 6-month and baseline to 24-month changes in the 4-pellet group and for the baseline to 18-month change in the 5-pellet group. No comparisons are made between treatment groups.

821

Table 18 (continued)
 Comparison of Lipid Profiles (mg/dl) Between
 Baseline and Follow-up
 by Treatment Received

Lipid	Total ¹	4-Pellet			5-Pellet			
		Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>LDL</u>								
Baseline	19	108.9	(31.10)		20	108.5	(21.70)	
6-month	15	93.8	(28.35)		19	88.8	(23.18)	
12-month	12	95.8	(26.00)		18	91.9	(22.27)	
18-month	8	95.9	(26.37)		13	88.5	(27.76)	
24-month	6	88.0	(34.32)		11	91.5	(24.28)	
<u>Percent change in LDL:</u>								
Baseline to 6-month change	15	-15.7	(15.34)	<.01	19	-16.5	(19.02)	<.01
Baseline to 12-month change	12	-18.9	(16.87)	<.01	18	-13.5	(20.55)	.01
Baseline to 18-month change	8	-13.9	(16.75)	.051	13	-19.7	(20.80)	<.01
Baseline to 24-month change	6	-19.4	(30.14)	.18	11	-13.0	(20.53)	.01

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the LDL comparisons for the baseline to 24-month change in the 5-pellet group. No comparisons are made between treatment groups.

August 15, 1995

Net Pellet Phase II-A
 Study 890

159

Table 19

Comparison of Glucose (mg/dl) Between
Baseline and Follow-up
by Treatment Received

Glucose	4-Pellet				5-Pellet			
	Total ¹	Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>Glucose</u>								
Baseline	19	90.6	(09.74)		20	91.4	(08.26)	
6-month	14	88.7	(10.28)		19	93.3	(11.17)	
12-month	12	92.0	(10.51)		19	91.3	(14.63)	
18-month	8	93.0	(11.06)		13	92.4	(09.53)	
24-month	7	92.1	(06.31)		11	90.7	(12.28)	
<u>Percent change in glucose:</u>								
Baseline to 6-month change	14	-0.6	(08.81)	.82	19	2.3	(10.50)	.36
Baseline to 12-month change	12	1.2	(12.65)	.75	19	1.2	(22.61)	.25
Baseline to 18-month change	8	-0.6	(06.87)	.80	13	1.2	(09.14)	.63
Baseline to 24-month change	7	-1.7	(08.73)	.62	11	-1.6	(10.00)	.60

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the glucose comparisons for the baseline to 12-month change in the 5-Pellet group. No comparisons are made between treatment groups.

August 15, 1995

Net Pellet Phase II-A
Study 890

160

Table 20.1
 Number and Percent of Participants with ¹
 Laboratory Values Outside Laboratory Normal Reference
 at Baseline
 by Treatment Received

	4-Pellet			5-Pellet		
	Total ²	n	(%)	Total ²	n	(%)
Lipids (mg/dl)						
Total Cholesterol	19	5	(26.3)	20	5	(25.0)
HDL	19	8	(42.1)	20	10	(50.0)
LDL	19	4	(21.1)	20	3	(15.0)
Triglycerides	19	1	(5.3)	20	1	(5.0)
SMAC						
Glucose (mg/dl)	19	0	(0.0)	20	0	(0.0)
LDH-340 (mU/ml)	19	0	(0.0)	20	0	(0.0)
SGOT-340 (AST) (mU/ml)	19	0	(0.0)	20	0	(0.0)
SGPT (mU/ml)	19	0	(0.0)	20	1	(5.0)
Alkaline Phosphates (mU/ml)	19	0	(0.0)	20	1	(5.0)
Bilirubin, Total (mg/dl)	19	0	(0.0)	20	0	(0.0)
Creatinine (mg/dl)	19	1	(5.3)	20	0	(0.0)
Sodium (meq/l)	19	0	(0.0)	20	0	(0.0)
Potassium (meq/l)	19	0	(0.0)	20	2	(10.0)
Chloride (meq/l)	19	2	(10.5)	20	3	(15.0)
Calcium (mg/dl)	19	0	(0.0)	20	0	(0.0)
Phosphorus (mg/dl)	19	1	(5.3)	20	1	(5.0)
Protein, Total (gm/dl)	19	0	(0.0)	20	0	(0.0)
Albumin (gm/dl)	19	0	(0.0)	20	0	(0.0)

¹ See laboratory normal references in attached appendix.

² Total is the number of participants having the lab test at least once at baseline.

161

Table 20.1 (Continued)

Number and Percent of Participants with ¹
 Laboratory Values Outside Laboratory Normal Reference
 at Baseline
 by Treatment Received

	4-Pellet			5-Pellet		
	Total ²	n	(%)	Total ²	n	(%)
Hematology						
Hemoglobin (g/dl)	19	2	(10.5)	20	2	(10.0)
White blood cell count/cmm	19	4	(21.1)	20	3	(15.0)
Urinalysis						
Specific gravity	19	2	(10.5)	20	0	(0.0)
Protein	19	4	(21.1)	20	2	(10.0)
pH	19	0	(0.0)	20	0	(0.0)
Ketones	19	1	(5.3)	20	0	(0.0)
Glucose	19	0	(0.0)	20	0	(0.0)
Bilirubin	19	0	(0.0)	20	0	(0.0)

¹ See laboratory normal references in attached appendix.

² Total is the number of participants having the lab test at least once at baseline.

July 24, 1995

NET Pellet Phase II-A
 Study 890

162

Table 20.2

Number and Percent of Participants with ¹
 Laboratory Values Outside Laboratory Normal Reference
 at the 6-month Follow-up
 by Treatment Received

	4-Pellet			5-Pellet		
	Total ²	n	(%)	Total ²	n	(%)
Lipids (mg/dl)						
Total Cholesterol	15	1	(6.7)	19	2	(10.5)
HDL	15	8	(53.3)	19	9	(47.4)
LDL	15	2	(13.3)	19	1	(5.3)
Triglycerides	15	0	(0.0)	19	1	(5.3)
BAC						
Glucose (mg/dl)	14	0	(0.0)	19	1	(5.3)
LDH-340 (mU/ml)	14	0	(0.0)	19	0	(0.0)
SGOT-340 (AST) (mU/ml)	14	0	(0.0)	19	0	(0.0)
SGPT (mU/ml)	14	0	(0.0)	19	0	(0.0)
Alkaline Phosphates (mU/ml)	14	0	(0.0)	19	0	(0.0)
Bilirubin, Total (mg/dl)	14	0	(0.0)	19	0	(0.0)
Creatinine (mg/dl)	14	1	(7.1)	19	0	(0.0)
Sodium (meq/l)	14	0	(0.0)	19	0	(0.0)
Potassium (meq/l)	14	0	(0.0)	19	0	(0.0)
Chloride (meq/l)	14	1	(7.1)	19	4	(21.1)
Calcium (mg/dl)	14	0	(0.0)	19	0	(0.0)
Phosphorus (mg/dl)	14	1	(7.1)	19	0	(0.0)
Protein, Total (gm/dl)	14	0	(0.0)	19	0	(0.0)
Albumin (gm/dl)	14	0	(0.0)	19	0	(0.0)

¹ See laboratory normal references in attached appendix.

² Total is the number of participants having the lab test at least once at the 6-month follow-up.

July 24, 1995

NET Pellet Phase II-A
 Study 890

163

Table 20.2 (Continued)

Number and Percent of Participants with ¹
 Laboratory Values Outside Laboratory Normal Reference
 at the 6-month Follow-up
 by Treatment Received

	4-Pellet			5-Pellet		
	Total ²	n	(%)	Total ²	n	(%)
Hematology						
Hemoglobin (g/dl)	14	1	(7.1)	19	2	(10.5)
White blood cell count/cmm	14	1	(7.1)	19	1	(5.3)

¹ See laboratory normal references in attached appendix.

² Total is the number of participants having the lab test at least once at the 6-month follow-up.

July 24, 1995

NET Pellet Phase II-A
 Study 890

169

Table 20.3
 Number and Percent of Participants with ¹
 Laboratory Values Outside Laboratory Normal Reference
 at the 12-month Follow-up
 by Treatment Received

	4-Pellet			5-Pellet		
	Total ²	n	(%)	Total ²	n	(%)
Lipids (mg/dl)						
Total Cholesterol	12	1	(8.3)	18	2	(11.1)
HDL	12	7	(58.3)	18	10	(55.6)
LDL	12	1	(8.3)	18	1	(5.6)
Triglycerides	12	1	(8.3)	18	1	(5.6)
SMAC						
Glucose (mg/dl)	12	1	(8.3)	19	1	(5.3)
LDH-340 (mU/ml)	12	0	(0.0)	19	1	(5.3)
SGOT-340 (AST) (mU/ml)	12	0	(0.0)	19	0	(0.0)
SGPT (mU/ml)	12	0	(0.0)	19	0	(0.0)
Alkaline Phosphates (mU/ml)	12	0	(0.0)	19	0	(0.0)
Bilirubin, Total (mg/dl)	12	0	(0.0)	19	0	(0.0)
Creatinine (mg/dl)	12	1	(8.3)	19	0	(0.0)
Sodium (meq/l)	12	0	(0.0)	19	0	(0.0)
Potassium (meq/l)	12	0	(0.0)	19	0	(0.0)
Chloride (meq/l)	12	2	(16.7)	19	2	(10.5)
Calcium (mg/dl)	12	0	(0.0)	19	0	(0.0)
Phosphorus (mg/dl)	12	1	(8.3)	19	0	(0.0)
Protein, Total (gm/dl)	12	0	(0.0)	19	0	(0.0)
Albumin (gm/dl)	12	0	(0.0)	19	0	(0.0)

¹ See laboratory normal references in attached appendix.

² Total is the number of participants having the lab test at least once at the 12-month follow-up.

182

Table 20.3 (Continued)

Number and Percent of Participants with
Laboratory Values Outside Laboratory Normal Reference
at the 12-month Follow-up
by Treatment Received

	4-Pellet ²			5-Pellet ²		
	Total	n	(%)	Total	n	(%)
Hematology						
Hemoglobin (g/dl)	12	1	(8.3)	19	2	(10.5)
White blood cell count/cmm	8	0	(0.0)	11	1	(9.1)

¹ See laboratory normal references in attached appendix.

² Total is the number of participants having the lab test at least once at the 12-month follow-up.

July 24, 1995

NET Pellet Phase II-A
Study 890

166

Table 20.4

Number and Percent of Participants with
Laboratory Values Outside Laboratory Normal Reference
at the 18-month Follow-up
by Treatment Received

	4-Pellet ²			5-Pellet ²		
	Total	n	(%)	Total	n	(%)
Lipids (mg/dl)						
Total Cholesterol	8	1	(12.5)	13	2	(15.4)
HDL	8	3	(37.5)	13	5	(38.5)
LDL	8	0	(0.0)	13	1	(7.7)
Triglycerides	8	1	(12.5)	13	0	(0.0)
SMAC						
Glucose (mg/dl)	8	1	(12.5)	13	0	(0.0)
LDH-340 (mU/ml)	8	0	(0.0)	13	0	(0.0)
SGOT-340 (AST) (mU/ml)	8	0	(0.0)	13	0	(0.0)
SGPT (mU/ml)	8	0	(0.0)	13	0	(0.0)
Alkaline Phosphates (mU/ml)	8	0	(0.0)	13	0	(0.0)
Bilirubin, Total (mg/dl)	8	0	(0.0)	13	0	(0.0)
Creatinine (mg/dl)	8	1	(12.5)	13	0	(0.0)
Sodium (meq/l)	8	0	(0.0)	13	0	(0.0)
Potassium (meq/l)	8	0	(0.0)	13	1	(7.7)
Chloride (meq/l)	8	0	(0.0)	13	2	(15.4)
Calcium (mg/dl)	8	0	(0.0)	13	0	(0.0)
Phosphorus (mg/dl)	8	1	(12.5)	13	2	(15.4)
Protein, Total (gm/dl)	8	0	(0.0)	13	1	(7.7)
Albumin (gm/dl)	8	0	(0.0)	13	0	(0.0)

¹ See laboratory normal references in attached appendix.

² Total is the number of participants having the lab test at least once at the 18-month follow-up.

July 24, 1995

NET Pellet Phase II-A
Study 890

167

Table 20.4 (Continued)
 Number and Percent of Participants with ¹
 Laboratory Values Outside Laboratory Normal Reference
 at the 18-month Follow-up
 by Treatment Received

	4-Pellet			5-Pellet		
	Total ²	n	(%)	Total ²	n	(%)
Hematology						
Hemoglobin (g/dl)	8	0	(0.0)	13	0	(0.0)
White blood cell count/cmm	3	0	(0.0)	3	0	(0.0)

¹ See laboratory normal references in attached appendix.

² Total is the number of participants having the lab test at least once at the 18-month follow-up.

July 24, 1995

NET Pellet Phase II-A
 Study 890

168

Table 20.5

Number and Percent of Participants with ¹
 Laboratory Values Outside Laboratory Normal Reference
 at the 24-month Follow-up
 by Treatment Received

	4-Pellet ²			5-Pellet ²		
	Total	n	(%)	Total	n	(%)
Lipids (mg/dl)						
Total Cholesterol	6	0	(0.0)	11	1	(9.1)
HDL	6	3	(50.0)	11	4	(36.4)
LDL	6	0	(0.0)	11	0	(0.0)
Triglycerides	6	1	(16.7)	11	0	(0.0)
SMAC						
Glucose (mg/dl)	7	0	(0.0)	11	1	(9.1)
LDH-340 (mU/ml)	7	0	(0.0)	10	1	(10.0)
SGOT-340 (AST) (mU/ml)	7	0	(0.0)	10	0	(0.0)
SGPT (mU/ml)	7	0	(0.0)	10	0	(0.0)
Alkaline Phosphates (mU/ml)	7	0	(0.0)	10	0	(0.0)
Bilirubin, Total (mg/dl)	7	0	(0.0)	10	0	(0.0)
Creatinine (mg/dl)	7	1	(14.3)	10	0	(0.0)
Sodium (meq/l)	7	0	(0.0)	10	2	(20.0)
Potassium (meq/l)	7	0	(0.0)	10	0	(0.0)
Chloride (meq/l)	7	0	(0.0)	10	3	(30.0)
Calcium (mg/dl)	7	0	(0.0)	11	0	(0.0)
Phosphorus (mg/dl)	7	0	(0.0)	11	0	(0.0)
Protein, Total (gm/dl)	7	0	(0.0)	10	1	(10.0)
Albumin (gm/dl)	7	0	(0.0)	10	0	(0.0)

¹ See laboratory normal references in attached appendix.

² Total is the number of participants having the lab test at least once at the 24-month follow-up.

July 24, 1995

NET Pellet Phase II-A
 Study 890

169

Table 20.5 (Continued)

Number and Percent of Participants with
 Laboratory Values Outside Laboratory Normal Reference¹
 at the 24-month Follow-up
 by Treatment Received

	4-Pellet ²			5-Pellet ²		
	Total	n	(%)	Total	n	(%)
Hematology						
Hemoglobin (g/dl)	7	0	(0.0)	11	0	(0.0)
White blood cell count/cmm	3	0	(0.0)	2	0	(0.0)
Urinalysis						
Specific gravity	7	0	(0.0)	11	0	(0.0)
Protein	7	0	(0.0)	11	1	(9.1)
pH	7	0	(0.0)	11	0	(0.0)
Ketones	7	0	(0.0)	11	0	(0.0)
Glucose	7	0	(0.0)	11	0	(0.0)
Bilirubin	7	0	(0.0)	11	0	(0.0)

¹ See laboratory normal references in attached appendix.

² Total is the number of participants having the lab test at least once at the 24-month follow-up.

July 24, 1995

NET Pellet Phase II-A
 Study 890

170

Table 20.6

1
 List of Participants Who Ever Had a Laboratory Value
 Outside Laboratory Normal Reference Reported at Baseline through the
 24-month Follow-up
 by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
908	2	4-Pellet	Total Cholesterol	225.0	-1
			Triglycerides	164.0	-1
			Triglycerides	158.0	19
			Triglycerides	241.0	25
			Glucose (mg/dl)	117.0	19
			Creatinine (mg/dl)	0.6	-1
			Creatinine (mg/dl)	0.6	7
			Creatinine (mg/dl)	0.6	13
			Creatinine (mg/dl)	0.6	19
			Creatinine (mg/dl)	0.6	25
			Phosphorus (mg/dl)	4.6	19
			Specific gravity	1.0	-1
908	3	4-Pellet	HDL	40.0	-1
			HDL	33.0	7
			HDL	40.0	13
			LDL	136.0	-1
			Hemoglobin (g/dl)	11.5	-1
			Hemoglobin (g/dl)	11.6	7
			Hemoglobin (g/dl)	11.4	13
			Specific gravity	1.0	-1
908	6	4-Pellet	HDL	47.0	-1
			Protein (urine)	Trace	-1
908	8	4-Pellet	HDL	49.0	7

¹ See laboratory normal references in attached appendix.

August 16, 1995

NET Pellet Phase II-A
 Study 890

171

Table 20.6 (Continued)

1
 List of Participants Who Ever Had a Laboratory Value
 Outside Laboratory Normal Reference Reported at Baseline through the
 24-month Follow-up
 by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
908 (Continued)	8	4-Pellet	Phosphorus (mg/dl)	2.1	7
			Protein (urine)	Trace	-1
908	10	4-Pellet	Triglycerides	165.0	12
			Phosphorus (mg/dl)	4.7	-2
			Phosphorus (mg/dl)	4.7	12
908	11	4-Pellet	Total Cholesterol	241.0	-1
			Total Cholesterol	208.0	19
			HDL	41.0	-1
			HDL	50.0	7
			HDL	47.0	13
			HDL	49.0	25
			LDL	171.0	-1
			LDL	130.0	7
			Protein (urine)	Trace	-1
908	15	4-Pellet	HDL	45.0	7
			HDL	44.0	13
			Glucose (mg/dl)	116.0	13
			Ketones	1+	-1
908	17	4-Pellet	Total Cholesterol	243.0	-3
			Total Cholesterol	224.0	-2
			LDL	151.0	-3
			LDL	139.0	-2

¹ See laboratory normal references in attached appendix.

August 16, 1995

NET Pellet Phase II-A
Study 890

172

Table 20.6 (Continued)

1
 List of Participants Who Ever Had a Laboratory Value
 Outside Laboratory Normal Reference Reported at Baseline through the
 24-month Follow-up
 by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
908	17	4-Pellet	White blood cell count/cmm	10.8	-3
(Continued)					
952	1	4-Pellet	HDL	52.0	-2
			HDL	53.0	6
			HDL	54.0	13
			HDL	38.0	19
			Chloride (meq/l)	110.0	13
952	3	4-Pellet	Total Cholesterol	207.0	-1
			HDL	53.0	25
952	6	4-Pellet	HDL	54.0	-1
			HDL	49.0	6
			HDL	49.0	13
			HDL	49.0	18
			HDL	52.0	24
			Chloride (meq/l)	110.0	-1
			Chloride (meq/l)	108.0	13
			Hemoglobin (g/dl)	11.8	-1
			White blood cell count/cmm	3.7	-1
952	11	4-Pellet	HDL	53.0	-1
			HDL	54.0	6
			HDL	44.0	12
			White blood cell count/cmm	12.6	6

¹ See laboratory normal references in attached appendix.

173

Table 20.6 (Continued)

1
 List of Participants Who Ever Had a Laboratory Value
 Outside Laboratory Normal Reference Reported at Baseline through the
 24-month Follow-up
 by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
952	13	4-Pellet	White blood cell count/cmm	3.8	-1
			Protein (urine)	Trace	-1
952	15	4-Pellet	HDL	50.0	-1
			HDL	50.0	7
			HDL	49.0	12
			HDL	52.0	19
			Chloride (meq/l)	108.0	-1
			Chloride (meq/l)	108.0	7
952	18	4-Pellet	Total Cholesterol	231.0	-1
			Total Cholesterol	231.0	7
			Total Cholesterol	209.0	12
			Total Cholesterol	205.0	17
			HDL	44.0	-1
			HDL	52.0	17
			LDL	165.0	-1
			LDL	155.0	7
			LDL	134.0	12
			LDL	135.0	17
			White blood cell count/cmm	3.7	-1
908	1	5-Pellet	HDL	49.0	-1
908	4	5-Pellet	Total Cholesterol	200.0	-2

¹ See laboratory normal references in attached appendix.

August 16, 1995

NET Pellet Phase II-A
Study 890

174

Table 20.6 (Continued)

1
 List of Participants Who Ever Had a Laboratory Value
 Outside Laboratory Normal Reference Reported at Baseline through the
 24-month Follow-up
 by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
908	4	5-Pellet	Potassium (meq/l)	5.9	-1
(Continued)					
908	5	5-Pellet	Glucose (mg/dl)	134.0	12
			Phosphorus (mg/dl)	4.7	-1
908	7	5-Pellet	HDL	52.0	7
			HDL	47.0	19
			Glucose (mg/dl)	119.0	7
908	9	5-Pellet	HDL	38.0	-1
			HDL	46.0	7
			HDL	54.0	13
			Hemoglobin (g/dl)	11.9	7
908	12	5-Pellet	HDL	47.0	-2
			HDL	54.0	7
			HDL	49.0	12
			Hemoglobin (g/dl)	11.9	-2
			Hemoglobin (g/dl)	11.0	7
			Hemoglobin (g/dl)	11.0	12
908	16	5-Pellet	HDL	48.0	24
			Protein, Total (gm/dl)	5.9	18
			Protein, Total (gm/dl)	5.9	24
			White blood cell count/cmm	12.6	13

¹ See laboratory normal references in attached appendix.

August 16, 1995

NET Pellet Phase II-A
Study 890

176

Table 20.6 (Continued)

1
 List of Participants Who Ever Had a Laboratory Value
 Outside Laboratory Normal Reference Reported at Baseline through the
 24-month Follow-up
 by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
908	18	5-Pellet	HDL	44.0	-1
			HDL	42.0	7
			HDL	42.0	13
			Hemoglobin (g/dl)	15.8	13
908	20	5-Pellet	Total Cholesterol	231.0	-1
			Total Cholesterol	201.0	6
			HDL	51.0	12
			LDL	151.0	-1
			Triglycerides	162.0	6
			Triglycerides	172.0	12
			White blood cell count/cmm	10.7	-1
952	2	5-Pellet	Total Cholesterol	212.0	13
			White blood cell count/cmm	3.8	7
952	4	5-Pellet	HDL	42.0	-1
			HDL	51.0	7
			HDL	52.0	13
			HDL	53.0	24
			SGPT (mU/ml)	61.0	-1
			Chloride (meq/l)	109.0	-1
			Chloride (meq/l)	109.0	7
			Chloride (meq/l)	109.0	13
			Chloride (meq/l)	108.0	24
Phosphorus (mg/dl)	5.1	-1			

¹ See laboratory normal references in attached appendix.

176

Table 20.6 (Continued)

1
 List of Participants Who Ever Had a Laboratory Value
 Outside Laboratory Normal Reference Reported at Baseline through the
 24-month Follow-up
 by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
952 (Continued)	4	5-Pellet	White blood cell count/cmm	3.8	-1
			Protein (urine)	Trace	24
952	5	5-Pellet	HDL	51.0	-1
			HDL	53.0	13
			LDH-340 (mU/ml)	109.0	13
			LDH-340 (mU/ml)	108.0	24
			Chloride (meq/l)	110.0	-1
			Chloride (meq/l)	110.0	7
			Chloride (meq/l)	110.0	13
952	8	5-Pellet	Total Cholesterol	205.0	-3
			Sodium (meq/l)	149.0	24
			Chloride (meq/l)	111.0	24
952	9	5-Pellet	HDL	48.0	-2
			HDL	44.0	6
			HDL	43.0	13
			HDL	45.0	18
			HDL	41.0	25
			LDL	131.0	-2
			Alkaline Phosphates (mU/ml)	143.0	-2
			Alkaline Phosphates (mU/ml)	134.0	1
			Phosphorus (mg/dl)	2.2	18
			Hemoglobin (g/dl)	11.6	1
			White blood cell count/cmm	3.7	-2

¹ See laboratory normal references in attached appendix.

177

Table 20.6 (Continued)

1
 List of Participants Who Ever Had a Laboratory Value
 Outside Laboratory Normal Reference Reported at Baseline through the
 24-month Follow-up
 by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
952	9	5-Pellet	White blood cell count/cmm	3.7	1
(Continued)					
952	10	5-Pellet	HDL	50.0	-2
			HDL	53.0	6
			HDL	48.0	13
			HDL	53.0	19
			Sodium (meq/l)	146.0	25
			Chloride (meq/l)	108.0	-2
			Chloride (meq/l)	108.0	6
			Chloride (meq/l)	108.0	19
			Chloride (meq/l)	108.0	25
			Protein (urine)	Trace	-2
952	14	5-Pellet	HDL	52.0	-1
			HDL	46.0	7
			HDL	50.0	12
			HDL	48.0	19
			HDL	52.0	25
			Glucose (mg/dl)	121.0	25
			Chloride (meq/l)	108.0	19
952	16	5-Pellet	Total Cholesterol	219.0	-1
			Total Cholesterol	207.0	7
			Total Cholesterol	218.0	12
			Total Cholesterol	206.0	18
			Total Cholesterol	207.0	24

¹ See laboratory normal references in attached appendix.

August 16, 1995

NET Pellet Phase II-A
Study 890

178

Table 20.6 (Continued)

1
 List of Participants Who Ever Had a Laboratory Value
 Outside Laboratory Normal Reference Reported at Baseline through the
 24-month Follow-up
 by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
952 (Continued)	16	5-Pellet	LDL	136.0	12
			Chloride (meq/l)	108.0	7
952	17	5-Pellet	Total Cholesterol	215.0	-2
			Total Cholesterol	210.0	18
			Total Cholesterol	235.0	22
			HDL	48.0	-2
			HDL	41.0	7
			HDL	49.0	13
			HDL	53.0	18
			HDL	47.0	22
			LDL	143.0	-2
			LDL	135.0	7
			LDL	134.0	18
			LDL	170.0	22
			Potassium (meq/l)	3.1	-2
			Potassium (meq/l)	2.8	-1
			Potassium (meq/l)	3.4	18
			Chloride (meq/l)	95.0	-2
			Chloride (meq/l)	94.0	-1
			Phosphorus (mg/dl)	4.7	18
			Hemoglobin (g/dl)	11.5	-2
			Protein (urine)	2+	-2
Protein (urine)	3+	-1			
Protein (urine)	3+	22			
pH	9.0	-1			

¹ See laboratory normal references in attached appendix.

179

Table 20.6 (Continued)

1
List of Participants Who Ever Had a Laboratory Value
Outside Laboratory Normal Reference Reported at Baseline through the
24-month Follow-up
by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
952	19	5-Pellet	Triglycerides	170.0	-2

1
See laboratory normal references in attached appendix.

August 16, 1995

NET Pellet Phase II-A
Study 890

121

Table 20.7

1

List of Participants Who Ever Had a Laboratory Value
Outside Laboratory Normal Reference Reported After
the First 24 Months (760 Days) of Follow-up
by Treatment Received

Center	PON	Treatment received	Name of test	Value	Study Month
952	15	4-Pellet	HDL Protein (urine)	50.0 Trace	25 25

¹ See laboratory normal references in attached appendix.

August 16, 1995

NET Pellet Phase II-A
Study 890

Table 21
 Comparison of Blood Pressure (mm Hg) Between
 Baseline and Follow-up
 by Treatment Received

Blood Pressure	4-Pellet			5-Pellet				
	Total ¹	Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>Systolic</u>								
Baseline	19	111.7	(08.95)		20	112.3	(10.18)	
3-month	16	114.2	(12.44)		19	111.6	(09.37)	
6-month	15	114.0	(10.51)		19	114.8	(10.42)	
9-month	13	110.9	(10.28)		18	112.8	(07.46)	
12-month	13	113.5	(11.35)		19	113.3	(07.80)	
15-month	13	116.6	(19.12)		13	117.9	(04.77)	
18-month	8	110.8	(14.00)		13	116.1	(08.85)	
21-month	7	116.9	(11.94)		10	119.4	(03.41)	
24-month	7	112.0	(16.57)		11	119.5	(06.27)	

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the systolic comparisons for the baseline to 3, 12, and 21-month changes in the 4-Pellet group and for all baseline to follow-up changes in the 5-Pellet group. No comparisons are made between treatment groups.

181

Table 21 (continued)
 Comparison of Blood Pressure (mm Hg) Between
 Baseline and Follow-up
 by Treatment Received

Blood Pressure	4-Pellet				5-Pellet			
	Total ¹	Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>Diastolic</u>								
Baseline	19	75.4	(6.08)		20	74.9	(06.41)	
3-month	16	76.0	(6.70)		19	73.3	(08.15)	
6-month	15	74.5	(8.05)		19	74.4	(07.38)	
9-month	13	72.9	(8.82)		18	73.9	(07.50)	
12-month	13	73.7	(8.36)		19	75.5	(06.73)	
15-month	13	75.5	(11.59)		13	78.0	(03.92)	
18-month	8	75.4	(8.82)		13	77.5	(04.67)	
21-month	7	78.9	(10.45)		10	78.8	(03.16)	
24-month	7	73.1	(14.23)		11	76.2	(06.72)	

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the diastolic comparisons for the baseline to 9, 12, 15, and 21-month changes in the 4-Pellet group and for all baseline to follow-up changes in the 5-Pellet group. No comparisons are made between treatment groups.

183

Table 21 (continued)
 Comparison of Blood Pressure (mm Hg) Between
 Baseline and Follow-up
 by Treatment Received

Blood Pressure	4-Pellet				5-Pellet			
	Total ¹	Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>Percent change in systolic</u>								
Baseline to 3-month change	16	2.9	(11.38)	.43	19	-1.5	(06.09)	.46
Baseline to 6-month change	15	1.8	(11.78)	.57	19	2.2	(11.23)	.38
Baseline to 9-month change	13	-2.2	(07.24)	.29	18	0.6	(07.57)	1.00
Baseline to 12-month change	13	1.7	(10.67)	.58	19	0.7	(06.23)	1.00
Baseline to 15-month change	13	4.7	(16.55)	.69	13	3.6	(10.68)	.31
Baseline to 18-month change	8	-2.2	(08.34)	.48	13	1.7	(09.12)	.81
Baseline to 21-month change	7	2.2	(10.71)	1.00	10	3.5	(07.16)	.12
Baseline to 24-month change	7	-0.4	(10.81)	.93	11	3.9	(07.38)	.25

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the systolic comparisons for the baseline to 3, 15, and 21-month changes in the 4-Pellet group and for all baseline to follow-up changes in the 5-Pellet group. No comparisons are made between treatment groups.

102

Table 21 (continued)
 Comparison of Blood Pressure (mm Hg) Between
 Baseline and Follow-up
 by Treatment Received

Blood Pressure	Total ¹	4-Pellet			5-Pellet			
		Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>Percent change in diastolic</u>								
Baseline to 3-month change	16	2.0	(10.92)	.48	19	-3.1	(05.92)	.09
Baseline to 6-month change	15	-1.2	(107.00)	.52	19	-0.5	(09.95)	.95
Baseline to 9-month change	13	-3.2	(06.21)	.12	18	-0.9	(08.35)	.95
Baseline to 12-month change	13	-2.9	(07.06)	.25	19	0.8	(07.16)	.82
Baseline to 15-month change	13	0.1	(10.54)	.41	13	2.0	(06.15)	.50
Baseline to 18-month change	8	-1.5	(05.65)	.47	13	1.3	(08.67)	.75
Baseline to 21-month change	7	2.2	(11.22)	.75	10	1.3	(04.25)	.50
Baseline to 24-month change	7	-4.4	(11.70)	.35	11	-1.3	(05.59)	1.00

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a *t*-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the diastolic comparisons for the baseline to 9, 12, 15, and 21-month changes in the 4-Pellet group and for all baseline to follow-up changes in the 5-Pellet group. No comparisons are made between treatment groups.

187

Table 22

Comparison of Weight (kg) Between
Baseline and Follow-up
by Treatment Received

Weight (kg)	4-Pellet				5-Pellet			
	Total ¹	Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>Weight (kg)</u>								
Baseline	19	61.3	(7.76)		20	61.4	(8.18)	
3-month change	15	60.5	(7.32)		18	60.9	(7.42)	
6-month change	15	61.5	(6.02)		19	61.7	(8.14)	
9-month change	13	61.6	(7.34)		18	61.3	(8.21)	
12-month change	13	63.5	(5.84)		19	62.4	(8.93)	
15-month change	12	61.9	(6.50)		13	59.9	(8.13)	
18-month change	8	61.9	(7.29)		13	60.1	(8.30)	
21-month change	7	62.4	(6.65)		10	61.8	(8.14)	
24-month change	7	60.0	(6.19)		11	60.4	(8.07)	

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the systolic comparisons for the baseline to 6, 12, 18, and 24-month changes in the 4-Pellet group and for all baseline to follow-up changes in the 5-Pellet group. No comparisons are made between treatment groups.

August 15, 1995

Net Pellet Phase II-A
Study 890

Table 22 (continued)
 Comparison of Weight (kg) Between
 Baseline and Follow-up
 by Treatment Received

Weight (kg)	4-Pellet				5-Pellet			
	Total ¹	Mean	(SD)	p-value ²	Total ¹	Mean	(SD)	p-value ²
<u>Percent change in weight:</u>								
Baseline to 3-month change	15	-0.2	(3.29)	.85	18	-0.2	(3.92)	1.00
Baseline to 6-month change	15	-0.3	(4.23)	.76	19	1.2	(6.23)	.50
Baseline to 9-month change	13	0.5	(9.49)	.86	18	1.2	(6.59)	.47
Baseline to 12-month change	13	0.8	(4.65)	.55	19	2.3	(8.31)	.25
Baseline to 15-month change	12	0.0	(4.21)	.99	13	-0.5	(7.22)	.58
Baseline to 18-month change	8	0.5	(2.27)	.58	13	-0.2	(8.69)	.58
Baseline to 21-month change	7	-0.2	(1.60)	.79	10	0.0	(8.67)	.99
Baseline to 24-month change	7	-0.6	(3.23)	.62	11	-1.5	(6.58)	.12

¹ For each time period, total is the number of participants with data.

² Comparisons are made between baseline and each follow-up period within each treatment group using a t-test except where the assumption of normality was violated. The Wilcoxon Signed Rank test was used for the weight comparisons for the baseline to 3, 6, 15, 18, and 24-month changes in the 5-Pellet group. No comparisons are made between treatment groups.

187

Table 23.1

Number and Percent of Participants Whose Pellets Were Removed
by Treatment Received

	4-Pellet		5-Pellet		Total	
	n	(%)	n	(%)	n	(%)
<u>Participants' pellets removed</u>						
No	10	(52.6)	8	(40.0)	18	(46.2)
Yes	9	(47.4)	12	(60.0)	21	(53.8)
Total	19		20		39	
<u>Study month of pellet removal¹</u>						
≤12	3		1		4	
13-24	1		1		2	
25-36	4		8		12	
≥37	1		2		3	
Total	9		12		21	

Note: Percentages may not sum to 100 due to rounding.

¹ Includes only participants whose pellets were removed.

August 15, 1995

NET Pellet Phase II-A
Study 890

188

Table 23.2

Number and Percent of Incisions Required for Pellet Removal
by Treatment Received

	4-Pellet		5-Pellet		Total	
	n	(%)	n	(%)	n	(%)
<u>Number of incisions required for removal</u>						
1	7	(77.8)	6	(50.0)	13	(61.9)
2	1	(11.1)	6	(50.0)	7	(33.3)
3	1	(11.1)	0	(0.0)	1	(4.8)
Total ¹	9		12		21	

Note: Percentages may not sum to 100 due to rounding.

¹Total is the total number of participants whose pellets were removed.

August 15, 1995

NET Pellet Phase II-A
Study 890

189

Table 23.3

Length of Incisions (mm) Required for Pellet Removal
by Treatment Received

	4-Pellet			5-Pellet			Total		
	n ¹	median length	range	n ¹	median length	range	n ¹	median length	range
<u>Incisions</u>									
First	9	8	5-20	12	10	5-12	21	8	5-20
Second	2	5	5-5	6	6.5	5-8	8	5.5	5-8
Third	1	5	na	0	na	na	1	5	na
Total ²	12	6	5-20	18	8	5-12	30	8	5-20

¹ 'n' is the number of incisions.

² Total is the total number of incisions required for pellet removal.

August 15, 1995

NET Pellet Phase II-A
Study 890

Table 23.4

Time Required (minutes) for Pellet Removal
by Treatment Received

	4-Pellet	5-Pellet	Total
Total ¹	9	12	21
Median	30	25	25
Range	5-90	6-60	5-90

¹ Total is the total number of participants whose pellets were removed.

August 15, 1995

NET Pellet Phase II-A
Study 890

197

Table 24.1

1

Adverse Experiences Probably Related to the Study Product
by Body System and Preferred Term
by Treatment Received

	4-Pellet (N=19)		5-Pellet (N=20)	
	n	(%)	n	(%)
Any adverse experience probably related to the study product	4	(21.1)	7	(35.0)
<u>Nervous/psychiatric</u>	1	(5.3)	0	(0.0)
Sexual dysfunction	1	(5.3)	0	(0.0)
<u>Skin</u>	0	(0.0)	1	(5.0)
Acne vulgaris, all sites	0	(0.0)	1	(5.0)
<u>Urogenital</u>	4	(21.1)	7	(35.0)
Intermenstrual bleeding/spotting	1	(5.3)	1	(5.0)
Menorrhagia	3	(15.8)	4	(20.0)
Menstruation, irregular	1	(5.3)	1	(5.0)
Metrorrhagia	1	(5.3)	1	(5.0)
Ovarian cyst, NOS	0	(0.0)	1	(5.0)

¹ Participants are counted a maximum of once in each body system and a maximum of once in each preferred term within a body system. The percent calculations include all women enrolled in the treatment group.

November 20, 1995

NET Pellet Phase II-A
Study 890

Table 24.2

List of Participants with
Adverse Experiences Probably Related
to the Study Product
by Body System and Preferred Term
4-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Serious	Unexpected
Nervous/psychiatric								
Sexual dysfunction	908	6	21OCT91	2	...	Severe	No	No
Urogenital								
Intermenstrual bleeding/spotting	952	6	05DEC91	1	09DEC91	Mild	No	No
Menorrhagia	908	6	21OCT91	2	...	Moderate	No	No
Menorrhagia	952	6	18DEC91	2	23DEC91	Moderate	No	No
Menorrhagia	952	6	31DEC91	2	07JAN92	Mild	No	No
Menorrhagia	952	6	11JAN92	3	16JAN92	Moderate	No	No
Menorrhagia	952	6	24JAN92	3	28JAN92	Moderate	No	No
Menorrhagia	952	18	24JAN93	10	29JAN93	Mild	No	Yes
Menstruation, irregular	908	17	29NOV92	10	04SEP93	Mild	No	No
Metrorrhagia	952	6	20NOV91	1	25NOV91	Mild	No	No

¹ Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

193

Table 24.3

List of Participants with
Adverse Experiences Probably Related
to the Study Product
by Body System and Preferred Term
5-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	Highest severity during event	Serious	Unexpected
Skin								
Acne vulgaris, all sites	908	1	10OCT91	1	29JAN92	Moderate	No	No
Urogenital								
Intermenstrual bleeding/spotting	952	2	09DEC91	2	31DEC91	Mild	No	No
Menorrhagia	908	1	03NOV91	2	29JAN92	Moderate	No	No
Menorrhagia	908	18	30APR92	3	09MAY92	Mild	No	No
Menorrhagia	952	8	13MAY92	6	23MAY92	Moderate	No	No
Menorrhagia	952	8	26MAY92	7	02JUN92	Moderate	No	No
Menorrhagia	952	8	08JUN92	7	13JUN92	Moderate	No	No
Menorrhagia	952	8	23JUN92	8	26JUN92	Moderate	No	No
Menorrhagia	952	8	07JUL92	8	17JUL92	Moderate	No	No
Menorrhagia	952	8	20JUL92	8	27SEP92	Moderate	No	No
Menorrhagia	952	17	25MAR94	24	02JUN94	Moderate	No	Yes
Menstruation, irregular	952	5	04DEC91	1	05JAN92	Mild	No	No
Metrorrhagia	908	16	02MAR93	13	03AUG93	Mild	No	No
Ovarian cyst, NOS	952	8	31OCT94	36	30NOV94	Mild	No	No

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

Table 25.1

1

Adverse Experiences Possibly Related to the Study Product
by Body System and Preferred Term
by Treatment Received

	4-Pellet (N=19)		5-Pellet (N=20)	
	n	(%)	n	(%)
Any adverse experience possibly related to the study product	10	(52.6)	10	(50.0)
Body as a whole/site unspecified	0	(0.0)	2	(10.0)
Edema (edematous), NOS, NEC	0	(0.0)	1	(5.0)
Night sweats	0	(0.0)	1	(5.0)
Cardiovascular	1	(5.3)	0	(0.0)
Hypertension	1	(5.3)	0	(0.0)
Digestive	1	(5.3)	0	(0.0)
Abdominal pain, NOS	1	(5.3)	0	(0.0)

1. Participants are counted a maximum of once in each body system and a maximum of once in each preferred term within a body system. The percent calculations include all women enrolled in the treatment group.

November 20, 1995

NET Pellet Phase II-A
Study 890

195

Table 25.1 (Continued)

1
Adverse Experiences Possibly Related to the Study Product
by Body System and Preferred Term
by Treatment Received

	4-Pellet (N=19)		5-Pellet (N=20)	
	n	(%)	n	(%)
<u>Nervous/psychiatric</u>				
	3	(15.8)	2	(10.0)
Brief depressive reaction	0	(0.0)	1	(5.0)
Headache, NOS	1	(5.3)	2	(10.0)
Other neurotic disorders	2	(10.5)	0	(0.0)
<u>Skin</u>				
	3	(15.8)	0	(0.0)
Acne vulgaris, all sites	3	(15.8)	0	(0.0)
Alopecia, NOS	1	(5.3)	0	(0.0)
<u>Urogenital</u>				
	8	(42.1)	8	(40.0)
Adnexal pain/tenderness	1	(5.3)	0	(0.0)
Breast pain (mastalgia)	1	(5.3)	1	(5.0)
Dysmenorrhea (primary or secondary)	3	(15.8)	2	(10.0)
Menorrhagia	4	(21.1)	3	(15.0)
Menstruation, irregular	1	(5.3)	4	(20.0)
Metrorrhagia	2	(10.5)	1	(5.0)
Other specif. problems with uterus	0	(0.0)	1	(5.0)
Ovarian cyst, NOS	1	(5.3)	1	(5.0)

1
Participants are counted a maximum of once in each body system and a maximum of once in each preferred term within a body system. The percent calculations include all women enrolled in the treatment group.

November 20, 1995

NET Pellet Phase II-A
Study 890

196

Table 25.2

List of Participants with
Adverse Experiences Possibly Related
to the Study Product
by Body System and Preferred Term
4-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Serious	Unexpected
Cardiovascular								
Hypertension	908	2	09DEC91	3	08JUN92	Mild	No	No
Hypertension	908	2	07DEC92	15	08MAR93	Moderate	No	No
Digestive								
Abdominal pain, NOS	952	18	06APR93	12	06APR93	Mild	No	Yes
Abdominal pain, NOS	952	18	15APR93	12	15APR93	Mild	No	Yes
Nervous/psychiatric								
Headache, NOS	908	17	12AUG92	7	01SEP92	Mild	No	No
Other neurotic disorders	908	6	21NOV91	3	...	Moderate	No	No
Other neurotic disorders	908	15	01APR92	3	28MAY92	Mild	No	No

¹ Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

661

Table 25.2 (Continued)

List of Participants with
Adverse Experiences Possibly Related
to the Study Product
by Body System and Preferred Term
4-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Serious	Unexpected
Skin								
Acne vulgaris, all sites	908	6	21OCT91	2	...	Moderate	No	No
Acne vulgaris, all sites	908	11	23SEP92	11	25SEP92	Mild	No	No
Acne vulgaris, all sites	908	17	12AUG92	7	25FEB94	Mild	No	No
Alopecia, NOS	908	17	01MAY93	15	01NOV93	Mild	No	No
Urogenital								
Adnexal pain/tenderness	908	10	29SEP92	11	15OCT92	Severe	No	Yes
Breast pain (mastalgia)	952	7	03MAR92	4	02APR92	Moderate	No	No
Dysmenorrhea (primary or secondary)	908	2	30DEC92	16	07JAN93	Mild	No	No
Dysmenorrhea (primary or secondary)	908	11	22SEP92	11	25SEP92	Mild	No	No
Dysmenorrhea (primary or secondary)	908	15	01FEB93	13	18FEB93	Mild	No	No
Menorrhagia	908	2	30DEC92	16	07JAN93	Mild	No	No
Menorrhagia	908	11	22SEP92	11	25SEP92	Mild	No	No
Menorrhagia	908	15	01FEB93	13	18FEB93	Mild	No	No
Menorrhagia	952	6	07SEP92	11	27OCT92	Mild	No	No
Menstruation, irregular	952	6	10JUL92	9	26JUL92	Moderate	No	No
Metrorrhagia	952	6	06FEB92	4	28APR92	Mild	No	No
Metrorrhagia	952	18	26AUG93	17	31AUG93	Mild	No	No
Ovarian cyst, NOS	908	13	18MAY93	17	29JUN93	Mild	No	Yes

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

Table 25.3

List of Participants with
Adverse Experiences Possibly Related
to the Study Product
by Body System and Preferred Term
5-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	Highest severity during event	Serious	Unexpected
Body as a whole/site unspecified								
Edema (edematous), NOS, NEC	908	7	02APR92	7	03AUG92	Mild	No	Yes
Night sweats	908	16	01FEB93	12	17MAR93	Mild	No	Yes
Nervous/psychiatric								
Brief depressive reaction	908	4	03SEP92	12	08SEP92	Mild	No	No
Headache, NOS	908	1	16SEP91	1	29JAN92	Severe	No	No
Headache, NOS	908	4	03SEP92	12	08SEP92	Mild	No	No
Headache, NOS	908	4	12SEP92	12	12SEP92	Mild	No	No
Urogenital								
Breast pain (mastalgia)	908	7	02APR92	7	20MAY92	Mild	No	Yes
Dysmenorrhea (primary or secondary)	908	12	20JUL92	8	20JUL92	Mild	No	No
Dysmenorrhea (primary or secondary)	908	18	17JUL92	5	20AUG92	Mild	No	Yes
Menorrhagia	908	18	17JUL92	5	20AUG92	Mild	No	Yes
Menorrhagia	952	8	12FEB93	15	19FEB93	Moderate	No	No
Menorrhagia	952	17	23JAN94	22	31JAN94	Mild	No	Yes
Menstruation, irregular	952	8	09DEC91	1	17FEB92	Mild	No	No

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

Table 25.3 (Continued)

List of Participants with
Adverse Experiences Possibly Related
to the Study Product
by Body System and Preferred Term
5-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Serious	Unexpected
Menstruation, irregular	952	10	03FEB92	2	29FEB92	Mild	No	No
Menstruation, irregular	952	14	20APR92	2	23JUN92	Mild	No	No
Menstruation, irregular	952	17	23JAN94	22	31JAN94	Mild	No	No
Metrorrhagia	952	10	10SEP93	21	...	Mild	No	No
Other specif. problems with uterus	908	4	03SEP92	12	08SEP92	Mild	No	No
Other specif. problems with uterus	908	4	12SEP92	12	12SEP92	Mild	No	No
Ovarian cyst, NOS	908	18	20JUL92	5	20AUG92	Mild	No	No

¹ Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

100

Table 26.1

1

Serious and/or Unexpected Adverse Experiences¹
by Body System and Preferred Term
by Treatment Received

	4-Pellet (N=19)		5-Pellet (N=20)	
	n	(%)	n	(%)
Any serious and/or unexpected adverse experience reported	4	(21.1)	4	(20.0)
Body as a whole/site unspecified	0	(0.0)	2	(10.0)
Edema (edematous), NOS, NEC	0	(0.0)	1	(5.0)
Night sweats	0	(0.0)	1	(5.0)
Digestive	1	(5.3)	1	(5.0)
Abdominal pain, NOS	1	(5.3)	0	(0.0)
Abscess of tooth	0	(0.0)	1	(5.0)
Nervous/psychiatric	1	(5.3)	0	(0.0)
Encephalitis (cerebritis) due to lupus	1	(5.3)	0	(0.0)
Vestibular neuronitis	1	(5.3)	0	(0.0)

¹ Participants having any serious and/or unexpected AE are counted a maximum of once in each body system and a maximum of once in each preferred term within a body system. The percent calculations for the Total column include all women enrolled in the treatment group.

July 24, 1995

NET Pellet Phase II-A
Study 890

102

Table 26.1 (Continued)
 Serious and/or Unexpected Adverse Experiences¹
 by Body System and Preferred Term
 by Treatment Received

	4-Pellet (N=19)		5-Pellet (N=20)	
	n	(%)	n	(%)
Respiratory				
Mycoplasma pneumonia	1	(5.3)	0	(0.0)
Urogenital				
Adnexal pain/tenderness	1	(5.3)	0	(0.0)
Breast pain (mastalgia)	0	(0.0)	1	(5.0)
Dysmenorrhea (primary or secondary)	0	(0.0)	1	(5.0)
In-situ malignant neoplasm of cervix	0	(0.0)	1	(5.0)
Menorrhagia	1	(5.3)	2	(10.0)
Ovarian cyst, NOS	1	(5.3)	0	(0.0)
Pap test, abnormal, NOS	0	(0.0)	1	(5.0)

¹ Participants having any serious and/or unexpected AE are counted a maximum of once in each body system and a maximum of once in each preferred term within a body system. The percent calculations for the Total column include all women enrolled in the treatment group.

202

Table 26.2

List of Participants with Serious and/or Unexpected
Adverse Experiences
by Body System and Preferred Term
4-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Related	Serious	Unexpected
Digestive									
Abdominal pain, NOS	952	18	06APR93	12	06APR93	Mild	Poss yes	No	Yes
Abdominal pain, NOS	952	18	15APR93	12	15APR93	Mild	Poss yes	No	Yes
Nervous/psychiatric									
Encephalitis (cerebritis) due to lupus	908	3	14APR93	19	29APR93	Severe	No	Yes	No
Vestibular neuronitis	908	3	29MAY93	21	31MAY93	Severe	No	Yes	No
Respiratory									
Mycoplasma pneumonia	908	3	14APR93	19	29APR93	Mild	No	Yes	No
Urogenital									
Adnexal pain/tenderness	908	10	29SEP92	11	15OCT92	Severe	Poss yes	No	Yes
Menorrhagia	952	18	24JAN93	10	29JAN93	Mild	Prob yes	No	Yes
Ovarian cyst, NOS	908	13	18MAY93	17	29JUN93	Mild	Poss yes	No	Yes

¹ Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

123

Table 26.3

List of Participants with Serious and/or Unexpected
Adverse Experiences
by Body System and Preferred Term
5-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	Highest severity during event	Related	Serious	Unexpected
Body as a whole/site unspecified									
Edema (edematous), NOS, NEC Night sweats	908	7	02APR92	7	03AUG92	Mild	Poss yes	No	Yes
	908	16	01FEB93	12	17MAR93	Mild	Poss yes	No	Yes
Digestive									
Abscess of tooth	908	18	10AUG93	18	14AUG93	Moderate	No	No	Yes
Urogenital									
Breast pain (mastalgia)	908	7	02APR92	7	20MAY92	Mild	Poss yes	No	Yes
Dysmenorrhea (primary or secondary)	908	18	17JUL92	5	20AUG92	Mild	Poss yes	No	Yes
In-situ malignant neoplasm of cervix	908	18	08JUL93	17	22FEB94	Severe	No	Yes	Yes
Menorrhagia	908	18	17JUL92	5	20AUG92	Mild	Poss yes	No	Yes
Menorrhagia	952	17	23JAN94	22	31JAN94	Mild	Poss yes	No	Yes
Menorrhagia	952	17	25MAR94	24	02JUN94	Moderate	Prob yes	No	Yes
Pap test, abnormal, NOS	908	18	01JUN93	16	22FEB94	Mild	No	No	Yes

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

hcl

Table 27.1
 1
 All Adverse Experiences
 by Body System and Preferred Term
 by Treatment Received

	4-Pellet (N=19)		5-Pellet (N=20)	
	n	(%)	n	(%)
Any adverse experience reported	15	(78.9)	17	(85.0)
Body as a whole/site unspecified	7	(36.8)	5	(25.0)
Assault or injury damage (ecchymosis)	0	(0.0)	1	(5.0)
Dizziness specified	0	(0.0)	1	(5.0)
Dizziness/vertigo, NOS	1	(5.3)	0	(0.0)
Drug reaction, NOS	0	(0.0)	1	(5.0)
Edema (edematous), NOS, NEC	0	(0.0)	2	(10.0)
Influenza (flu), NOS	6	(31.6)	1	(5.0)
Night sweats	0	(0.0)	1	(5.0)
Thrush	1	(5.3)	0	(0.0)
Cardiovascular	1	(5.3)	0	(0.0)
Hypertension	1	(5.3)	0	(0.0)
Digestive	4	(21.1)	3	(15.0)
Abdominal cramping	0	(0.0)	1	(5.0)
Abdominal pain, NOS	3	(15.8)	0	(0.0)

1
 Participants having any serious and/or unexpected AE are counted a maximum of once in each body system and a maximum of once in each preferred term within a body system. The percent calculations for the Total column include all women enrolled in the treatment group.

July 24, 1995

NET Pellet Phase II-A
 Study 890

get

Table 27.1 (Continued)
¹
 All Adverse Experiences
 by Body System and Preferred Term
 by Treatment Received

	4-Pellet (N=19)		5-Pellet (N=20)	
	n	(%)	n	(%)
Abscess of tooth	0	(0.0)	1	(5.0)
Dyspepsia/indigestion	0	(0.0)	1	(5.0)
Flu (influenza), gastrointestinal, NOS	0	(0.0)	1	(5.0)
Gastroenteritis, NOS	1	(5.3)	0	(0.0)
Hematic				
Anemia, NOS	1	(5.3)	1	(5.0)
Musculoskeletal				
Backache	0	(0.0)	3	(15.0)
Injury, knee, NOS	0	(0.0)	1	(5.0)
Muscular pain	0	(0.0)	1	(5.0)
Sprain, elbow	0	(0.0)	1	(5.0)
Tenosynovitis	0	(0.0)	1	(5.0)
Nervous/psychiatric				
Anxiety disorder	5	(26.3)	8	(40.0)
Brief depressive reaction	0	(0.0)	1	(5.0)
Conjunctivitis, NOS	0	(0.0)	1	(5.0)
	1	(5.3)	0	(0.0)

¹ Participants having any serious and/or unexpected AE are counted a maximum of once in each body system and a maximum of once in each preferred term within a body system. The percent calculations for the Total column include all women enrolled in the treatment group.

July 24, 1995

NET Pellet Phase II-A
 Study 890

906

Table 27.1 (Continued)
 1
 All Adverse Experiences
 by Body System and Preferred Term
 by Treatment Received

	4-Pellet (N=19)		5-Pellet (N=20)	
	n	(%)	n	(%)
Deafness (hypacusia, hypoacusia)	0	(0.0)	1	(5.0)
Depressive disorder, NEC	0	(0.0)	1	(5.0)
Earache	0	(0.0)	1	(5.0)
Encephalitis (cerebritis) due to lupus	1	(5.3)	0	(0.0)
Headache, NOS	1	(5.3)	3	(15.0)
Other neurotic disorders	2	(10.5)	1	(5.0)
Otitis, site to be specified	0	(0.0)	3	(15.0)
Peripheral neuropathy	1	(5.3)	0	(0.0)
Sexual dysfunction	1	(5.3)	0	(0.0)
Vestibular neuronitis	1	(5.3)	0	(0.0)
Respiratory	4	(21.1)	6	(30.0)
Bronchitis, NOS	0	(0.0)	3	(15.0)
Chest pain, NOS	0	(0.0)	2	(10.0)
Common cold (coryza)	1	(5.3)	0	(0.0)
Mycoplasma pneumonia	1	(5.3)	0	(0.0)
Respiratory allergies, NOS	0	(0.0)	1	(5.0)
Sinusitis, NOS	2	(10.5)	1	(5.0)
Streptococcal pharyngitis	0	(0.0)	1	(5.0)
Upper respiratory tract infection, NOS	2	(10.5)	2	(10.0)

1
 Participants having any serious and/or unexpected AE are counted a maximum of once in each body system and a maximum of once in each preferred term within a body system. The percent calculations for the Total column include all women enrolled in the treatment group.

July 24, 1995

NET Pellet Phase II-A
 Study 890

107

Table 27.1 (Continued)
 1
 All Adverse Experiences
 by Body System and Preferred Term
 by Treatment Received

	4-Pellet (N=19) n (%)	5-Pellet (N=20) n (%)
Skin	5 (26.3)	7 (35.0)
Acne vulgaris, all sites	3 (15.8)	4 (20.0)
Alopecia, NOS	1 (5.3)	0 (0.0)
Itching, device or implant related	1 (5.3)	1 (5.0)
Lump, shoulder, NOS, NEC	0 (0.0)	1 (5.0)
Mass, inguinal area, superficial	0 (0.0)	1 (5.0)
Pain related to device/implant site	1 (5.3)	0 (0.0)
Pain, inguinal and/or thigh	0 (0.0)	1 (5.0)
Paresthesia, NEC	1 (5.3)	0 (0.0)
Pilonidal cyst, not infected	0 (0.0)	1 (5.0)
Scabies, site NS	1 (5.3)	0 (0.0)
Skin infections, NOS	0 (0.0)	1 (5.0)
Surgical injury, implant site	1 (5.3)	0 (0.0)
Swelling related to device/implant site	1 (5.3)	1 (5.0)
Urogenital	10 (52.6)	15 (75.0)
Abscess of perineum	0 (0.0)	1 (5.0)
Adnexal pain/tenderness	1 (5.3)	0 (0.0)
Breast hyperplasia, benign	0 (0.0)	1 (5.0)
Breast pain (mastalgia)	1 (5.3)	1 (5.0)
Cystitis, NOS	1 (5.3)	0 (0.0)

1
 Participants having any serious and/or unexpected AE are counted a maximum of once in each body system and a maximum of once in each preferred term within a body system. The percent calculations for the Total column include all women enrolled in the treatment group.

July 24, 1995

NET Pellet Phase II-A
 Study 890

206

Table 27.1 (Continued)
¹
 All Adverse Experiences
 by Body System and Preferred Term
 by Treatment Received

	4-Pellet (N=19)		5-Pellet (N=20)	
	n	(%)	n	(%)
Dysmenorrhea (primary or secondary)	4	(21.1)	2	(10.0)
Dyspareunia, female	1	(5.3)	0	(0.0)
Dysuria	0	(0.0)	1	(5.0)
Fibrocystic breast disease	0	(0.0)	1	(5.0)
Genital herpes, NOS	0	(0.0)	2	(10.0)
In-situ malignant neoplasm of cervix	0	(0.0)	1	(5.0)
Intermenstrual bleeding/spotting	1	(5.3)	1	(5.0)
Menorrhagia	6	(31.6)	4	(20.0)
Menstrual disorders, NOS (not pain)	0	(0.0)	1	(5.0)
Menstruation, irregular	2	(10.5)	5	(25.0)
Metrorrhagia	2	(10.5)	2	(10.0)
Other specif. problems with uterus	0	(0.0)	1	(5.0)
Ovarian cyst, NOS	2	(10.5)	2	(10.0)
Pain, pelvic, NOS	1	(5.3)	1	(5.0)
Pap test, abnormal, NOS	1	(5.3)	2	(10.0)
Urinary tract infect, NOS(UTI,bacteruria	2	(10.5)	2	(10.0)
Vaginitis, candida or monilia	0	(0.0)	1	(5.0)
Operative treatment procedures				
	1	(5.3)	0	(0.0)
Surgical extraction of tooth	1	(5.3)	0	(0.0)

¹ Participants having any serious and/or unexpected AE are counted a maximum of once in each body system and a maximum of once in each preferred term within a body system. The percent calculations for the Total column include all women enrolled in the treatment group.

209

Table 27.2

List of Participants with any Adverse Experience
by Body System and Preferred Term
4-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	Highest severity during event ¹	Related	Serious	Unexpected
Body as a whole/site unspecified									
Dizziness/vertigo, NOS	908	15	04MAY92	4	04MAY92	Mild	Prob no	No	No
Influenza (flu), NOS	908	3	21DEC92	16	23DEC92	Mild	No	No	No
Influenza (flu), NOS	908	13	11DEC92	12	15DEC92	Mild	No	No	No
Influenza (flu), NOS	952	1	09MAR93	18	15MAR93	Moderate	No	No	No
Influenza (flu), NOS	952	3	17DEC91	2	28DEC91	Moderate	No	No	No
Influenza (flu), NOS	952	6	15APR93	18	08MAY93	Moderate	No	No	No
Influenza (flu), NOS	952	13	30MAR93	14	10APR93	Mild	No	No	No
Thrush	908	3	14APR93	19	29APR93	Mild	No	No	No
Cardiovascular									
Hypertension	908	2	09DEC91	3	08JUN92	Mild	Poss yes	No	No
Hypertension	908	2	07DEC92	15	08MAR93	Moderate	Poss yes	No	No
Hypertension	908	2	07MAY93	20	...	Mild	Prob no	No	No
Digestive									
Abdominal pain, NOS	908	11	26AUG92	10	10SEP92	Mild	Prob no	No	No
Abdominal pain, NOS	952	11	17JUL92	5	18JUL92	Moderate	No	No	No
Abdominal pain, NOS	952	18	06APR93	12	06APR93	Mild	Poss yes	No	Yes
Abdominal pain, NOS	952	18	15APR93	12	15APR93	Mild	Poss yes	No	Yes

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

010

Table 27.2 (Continued)

List of Participants with any Adverse Experience
by Body System and Preferred Term
4-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Related	Serious	Unexpected
Gastroenteritis, NOS	952	7	16JAN92	3	17JAN92	Mild	No	No	No
Hematic									
Anemia, NOS	908	3	14APR93	19	...	Mild	No	No	No
Nervous/psychiatric									
Conjunctivitis, NOS	908	2	13APR92	8	19APR92	Mild	No	No	No
Encephalitis (cerebritis) due to lupus	908	3	14APR93	19	29APR93	Severe	No	Yes	No
Headache, NOS	908	17	12AUG92	7	01SEP92	Mild	Poss yes	No	No
Other neurotic disorders	908	6	21NOV91	3	...	Moderate	Poss yes	No	No
Other neurotic disorders	908	15	01APR92	3	28MAY92	Mild	Poss yes	No	No
Peripheral neuropathy	908	3	14APR93	19	...	Mild	No	No	No
Sexual dysfunction	908	6	21OCT91	2	...	Severe	Prob yes	No	No
Vestibular neuronitis	908	3	29MAY93	21	31MAY93	Severe	No	Yes	No
Respiratory									
Common cold (coryza)	908	2	04NOV92	14	07DEC92	Mild	No	No	No
Mycoplasma pneumonia	908	3	14APR93	19	29APR93	Mild	No	Yes	No
Sinusitis, NOS	908	11	17JAN92	2	18JAN92	Moderate	No	No	No

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

Table 27.2 (Continued)

List of Participants with any Adverse Experience
by Body System and Preferred Term
4-Pellet

Body system/ preferred term	Center	PCN	Onset date	Study Month	Resolution date	¹ Highest severity during event	Related	Serious	Unexpected
Sinusitis, NOS	908	13	15NOV93	23	29NOV93	Mild	No	No	No
Upper respiratory tract infection, NOS	908	11	15FEB94	27	11MAR94	Mild	No	No	No
Upper respiratory tract infection, NOS	908	13	15NOV93	23	29NOV93	Mild	No	No	No
Skin									
Acne vulgaris, all sites	908	6	21OCT91	2	...	Moderate	Poss yes	No	No
Acne vulgaris, all sites	908	11	23SEP92	11	25SEP92	Mild	Poss yes	No	No
Acne vulgaris, all sites	908	17	12AUG92	7	25FEB94	Mild	Poss yes	No	No
Alopecia, NOS	908	17	01MAY93	15	01NOV93	Mild	Poss yes	No	No
Itching, device or implant related	952	18	08MAY92	1	13MAY92	Mild	Prob no	No	No
Pain related to device/implant site	952	18	08MAY92	1	11MAY92	Mild	No	No	No
Paresthesia, NEC	908	17	30NOV92	10	30NOV92	Mild	No	No	No
Scabies, site NS	908	2	01SEP93	24	18OCT93	Mild	No	No	No
Surgical injury, implant site	908	6	20DEC91	4	23DEC91	Mild	No	No	No
Swelling related to device/implant site	952	18	08MAY92	1	13MAY92	Mild	Prob no	No	No
Urogenital									
Adnexal pain/tenderness	908	10	29SEP92	11	15OCT92	Severe	Poss yes	No	Yes
Breast pain (mastalgia)	952	7	03MAR92	4	02APR92	Moderate	Poss yes	No	No
Cystitis, NOS	908	13	24JUN92	7	04JUL92	Mild	No	No	No
Dysmenorrhea (primary or secondary)	908	2	30DEC92	16	07JAN93	Mild	Poss yes	No	No
Dysmenorrhea (primary or secondary)	908	10	28FEB92	4	28FEB92	Mild	No	No	No

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

012

Table 27.2 (Continued)

List of Participants with any Adverse Experience
by Body System and Preferred Term
4-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Related	Serious	Unexpected
Dysmenorrhea (primary or secondary)	908	11	22SEP92	11	25SEP92	Mild	Poss yes	No	No
Dysmenorrhea (primary or secondary)	908	15	01FEB93	13	18FEB93	Mild	Poss yes	No	No
Dyspareunia, female	908	10	28SEP92	11	28SEP92	Moderate	No	No	No
Intermenstrual bleeding/spotting	952	6	05DEC91	1	09DEC91	Mild	Prob yes	No	No
Menorrhagia	908	2	30DEC92	16	07JAN93	Mild	Poss yes	No	No
Menorrhagia	908	6	21OCT91	2	...	Moderate	Prob yes	No	No
Menorrhagia	908	11	22SEP92	11	25SEP92	Mild	Poss yes	No	No
Menorrhagia	908	15	01FEB93	13	18FEB93	Mild	Poss yes	No	No
Menorrhagia	952	6	18DEC91	2	23DEC91	Moderate	Prob yes	No	No
Menorrhagia	952	6	31DEC91	2	07JAN92	Mild	Prob yes	No	No
Menorrhagia	952	6	11JAN92	3	16JAN92	Moderate	Prob yes	No	No
Menorrhagia	952	6	24JAN92	3	28JAN92	Moderate	Prob yes	No	No
Menorrhagia	952	6	07SEP92	11	27OCT92	Mild	Poss yes	No	No
Menorrhagia	952	18	24JAN93	10	29JAN93	Mild	Prob yes	No	Yes
Menstruation, irregular	908	17	29NOV92	10	04SEP93	Mild	Prob yes	No	No
Menstruation, irregular	952	6	10JUL92	9	26JUL92	Moderate	Poss yes	No	No
Metrorrhagia	952	6	20NOV91	1	25NOV91	Mild	Prob yes	No	No
Metrorrhagia	952	6	06FEB92	4	28APR92	Mild	Poss yes	No	No
Metrorrhagia	952	18	26AUG93	17	31AUG93	Mild	Poss yes	No	No
Ovarian cyst, NOS	908	10	02NOV92	12	31MAY93	Moderate	Prob no	No	No
Ovarian cyst, NOS	908	13	18MAY93	17	29JUN93	Mild	Poss yes	No	Yes
Pain, pelvic, NOS	908	10	02NOV92	12	14DEC92	Mild	Prob no	No	No
Pap test, abnormal, NOS	908	10	09NOV92	12	31MAY93	Mild	No	No	No
Urinary tract infect,NOS(UTI,bacteruria	908	2	27MAR92	7	03APR92	Mild	No	No	No
Urinary tract infect,NOS(UTI,bacteruria	908	11	25JUL93	21	06AUG93	Moderate	No	No	No

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

213

Table 27.2 (Continued)

List of Participants with any Adverse Experience
by Body System and Preferred Term
4-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹	Highest severity during event	Related	Serious	Unexpected
Operative treatment procedures										
Surgical extraction of tooth	952	1	27NOV91	3	27NOV91		Mild	No	No	No

¹ Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

224

Table 27.3

List of Participants with any Adverse Experience
by Body System and Preferred Term
5-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Related	Serious	Unexpected
Body as a whole/site unspecified									
Assault or injury damage (ecchymosis)	908	16	27MAR92	2	04MAY92	Moderate	No	No	No
Dizziness specified	908	4	04JAN93	16	07JAN93	Mild	Prob no	No	No
Drug reaction, NOS	908	18	13JAN93	11	15JAN93	Mild	No	No	No
Edema (edematous), NOS, NEC	908	5	14APR93	19	18APR93	Mild	Prob no	No	No
Edema (edematous), NOS, NEC	908	7	02APR92	7	03AUG92	Mild	Poss yes	No	Yes
Edema (edematous), NOS, NEC	908	7	01SEP92	12	22OCT92	Mild	Prob no	No	No
Edema (edematous), NOS, NEC	908	7	02MAR93	18	02APR93	Mild	No	No	No
Influenza (flu), NOS	908	18	19OCT92	8	24OCT92	Mild	No	No	No
Night sweats	908	16	01FEB93	12	17MAR93	Mild	Poss yes	No	Yes
Digestive									
Abdominal cramping	908	16	02MAR93	13	02NOV93	Mild	No	No	No
Abscess of tooth	908	18	26NOV92	10	01DEC92	Moderate	No	No	No
Abscess of tooth	908	18	10AUG93	18	14AUG93	Moderate	No	No	Yes
Dyspepsia/indigestion	908	5	28JAN92	5	18MAR92	Mild	No	No	No
Flu (influenza), gastrointestinal, NOS	908	16	13FEB93	13	14FEB93	Mild	No	No	No

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

Table 27.3 (Continued)

List of Participants with any Adverse Experience
by Body System and Preferred Term
5-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Related	Serious	Unexpected
Hematic									
Anemia, NOS	908	16	01FEB94	24	16NOV94	Mild	No	No	No
Musculoskeletal									
Backache	908	7	02MAR93	18	02APR93	Mild	No	No	No
Injury, knee, NOS	952	8	28FEB93	16	17MAR93	Severe	No	No	No
Muscular pain	908	7	26JUN93	22	15OCT93	Mild	Prob no	No	No
Sprain, elbow	908	9	19MAR92	6	10APR92	Moderate	No	No	No
Tenosynovitis	952	8	10FEB92	3	...	Mild	No	No	No
Nervous/psychiatric									
Anxiety disorder	908	14	11SEP92	9	11SEP92	Mild	No	No	No
Brief depressive reaction	908	4	03SEP92	12	08SEP92	Mild	Poss yes	No	No
Deafness (hypacusia, hypoacusia)	908	16	27MAR92	2	27APR92	Mild	No	No	No
Depressive disorder, NEC	908	5	28JAN92	5	18MAR92	Mild	No	No	No
Depressive disorder, NEC	908	5	20OCT92	14	20APR93	Mild	Prob no	No	No
Earache	908	20	15NOV92	9	25NOV92	Mild	No	No	No
Headache, NOS	908	1	16SEP91	1	29JAN92	Severe	Poss yes	No	No
Headache, NOS	908	4	03SEP92	12	08SEP92	Mild	Poss yes	No	No
Headache, NOS	908	4	12SEP92	12	12SEP92	Mild	Poss yes	No	No

¹ Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

Table 27.3 (Continued)

List of Participants with any Adverse Experience
by Body System and Preferred Term
5-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Related	Serious	Unexpected
Headache, NOS	908	18	11MAR93	13	13MAY93	Mild	Prob no	No	No
Other neurotic disorders	908	5	20OCT92	14	21JUN93	Mild	Prob no	No	No
Otitis, site to be specified	908	5	22SEP92	13	30SEP92	Mild	No	No	No
Otitis, site to be specified	908	12	02MAR93	15	08MAR93	Mild	No	No	No
Otitis, site to be specified	908	16	01AUG93	18	01SEP93	Moderate	No	No	No
Respiratory									
Bronchitis, NOS	908	9	08FEB93	17	12MAR93	Mild	No	No	No
Bronchitis, NOS	908	16	27NOV92	10	04JAN93	Moderate	No	No	No
Bronchitis, NOS	908	18	31DEC92	11	18JAN93	Mild	No	No	No
Chest pain, NOS	908	1	22OCT91	2	12NOV91	Severe	No	No	No
Chest pain, NOS	908	18	20JUL92	5	20AUG92	Mild	Prob no	No	No
Respiratory allergies, NOS	908	9	16MAR92	6	...	Mild	No	No	No
Sinusitis, NOS	908	7	27DEC93	28	06JAN94	Mild	No	No	No
Streptococcal pharyngitis	908	4	07MAY92	8	16MAY92	Mild	No	No	No
Upper respiratory tract infection, NOS	908	9	24DEC92	15	28DEC92	Moderate	No	No	No
Upper respiratory tract infection, NOS	908	16	16DEC93	23	05JAN94	Moderate	No	No	No
Skin									
Acne vulgaris, all sites	908	1	10OCT91	1	29JAN92	Moderate	Prob yes	No	No
Acne vulgaris, all sites	908	5	14JUN93	21	...	Mild	Prob no	No	No
Acne vulgaris, all sites	908	7	03NOV92	14	27SEP93	Mild	Prob no	No	No

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

217

Table 27.3 (Continued)

List of Participants with any Adverse Experience
by Body System and Preferred Term
5-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	Highest severity during event	Related	Serious	Unexpected
Acne vulgaris, all sites	908	20	20AUG93	18	07MAR94	Moderate	No	No	No
Itching, device or implant related	908	14	24SEP93	21	27SEP93	Mild	Prob no	No	No
Lump, shoulder, NOS, NEC	908	12	10JUN93	18	...	Mild	No	No	No
Mass, inguinal area, superficial	908	16	12JUL93	18	02NOV93	Mild	No	No	No
Pain, inguinal and/or thigh	908	16	02MAR93	13	02NOV93	Mild	No	No	No
Pilonidal cyst, not infected	908	1	11SEP91	1	10OCT91	Moderate	No	No	No
Skin infections, NOS	908	16	15SEP92	8	17SEP92	Mild	No	No	No
Swelling related to device/implant site	908	7	15NOV91	2	20NOV91	Mild	Prob no	No	No
Urogenital									
Abcess of perineum	908	16	03JUL92	5	07JUL92	Mild	Prob no	No	No
Breast hyperplasia, benign	952	16	04AUG93	16	...	Mild	No	No	No
Breast pain (mastalgia)	908	7	02APR92	7	20MAY92	Mild	Poss yes	No	Yes
Dysmenorrhea (primary or secondary)	908	12	20JUL92	8	20JUL92	Mild	Poss yes	No	No
Dysmenorrhea (primary or secondary)	908	18	17JUL92	5	20AUG92	Mild	Poss yes	No	Yes
Dysuria	908	16	02NOV93	21	03DEC93	Mild	Prob no	No	No
Fibrocystic breast disease	952	16	04AUG93	16	...	Mild	No	No	No
Genital herpes, NOS	908	4	11MAR92	6	15MAR92	Mild	No	No	No
Genital herpes, NOS	908	4	25APR92	8	06MAY92	Moderate	No	No	No
Genital herpes, NOS	908	4	27MAY92	9	28MAY92	Mild	No	No	No
Genital herpes, NOS	908	4	03SEP92	12	07SEP92	Moderate	No	No	No
Genital herpes, NOS	908	4	12NOV92	14	19NOV92	Moderate	No	No	No
Genital herpes, NOS	908	4	13DEC92	15	15DEC92	Mild	No	No	No
Genital herpes, NOS	908	4	09JAN93	16	12JAN93	Mild	No	No	No
Genital herpes, NOS	908	4	10FEB93	17	20FEB93	Mild	No	No	No

1

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

Table 27.3 (Continued)

List of Participants with any Adverse Experience
by Body System and Preferred Term
5-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Related	Serious	Unexpected
Genital herpes, NOS	908	4	14MAR93	18	16MAR93	Mild	No	No	No
Genital herpes, NOS	908	4	24MAR93	19	26MAR93	Mild	No	No	No
Genital herpes, NOS	908	4	13JUN93	21	18JUN93	Mild	No	No	No
Genital herpes, NOS	908	14	04JAN93	13	01FEB93	Mild	No	No	No
Genital herpes, NOS	908	14	04JAN94	25	...	Mild	No	No	No
In-situ malignant neoplasm of cervix	908	18	08JUL93	17	22FEB94	Severe	No	Yes	Yes
Intermenstrual bleeding/spotting	952	2	09DEC91	2	31DEC91	Mild	Prob yes	No	No
Menorrhagia	908	1	03NOV91	2	29JAN92	Moderate	Prob yes	No	No
Menorrhagia	908	18	30APR92	3	09MAY92	Mild	Prob yes	No	No
Menorrhagia	908	18	17JUL92	5	20AUG92	Mild	Poss yes	No	Yes
Menorrhagia	952	8	13MAY92	6	23MAY92	Moderate	Prob yes	No	No
Menorrhagia	952	8	26MAY92	7	02JUN92	Moderate	Prob yes	No	No
Menorrhagia	952	8	08JUN92	7	13JUN92	Moderate	Prob yes	No	No
Menorrhagia	952	8	23JUN92	8	26JUN92	Moderate	Prob yes	No	No
Menorrhagia	952	8	07JUL92	8	17JUL92	Moderate	Prob yes	No	No
Menorrhagia	952	8	20JUL92	8	27SEP92	Moderate	Prob yes	No	No
Menorrhagia	952	8	12FEB93	15	19FEB93	Moderate	Poss yes	No	No
Menorrhagia	952	17	23JAN94	22	31JAN94	Mild	Poss yes	No	Yes
Menorrhagia	952	17	25MAR94	24	02JUN94	Moderate	Prob yes	No	Yes
Menstrual disorders, NOS (not pain)	908	16	27JUN93	17	27JUN93	Mild	No	No	No
Menstruation, irregular	952	5	04DEC91	1	05JAN92	Mild	Prob yes	No	No
Menstruation, irregular	952	8	09DEC91	1	17FEB92	Mild	Poss yes	No	No
Menstruation, irregular	952	10	03FEB92	2	29FEB92	Mild	Poss yes	No	No
Menstruation, irregular	952	14	20APR92	2	23JUN92	Mild	Poss yes	No	No
Menstruation, irregular	952	17	23JAN94	22	31JAN94	Mild	Poss yes	No	No
Metrorrhagia	908	16	02MAR93	13	03AUG93	Mild	Prob yes	No	No
Metrorrhagia	952	10	10SEP93	21	...	Mild	Poss yes	No	No
Other specif. problems with uterus	908	4	03SEP92	12	08SEP92	Mild	Poss yes	No	No

¹ Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

Table 27.3 (Continued)

List of Participants with any Adverse Experience
by Body System and Preferred Term
5-Pellet

Body system/ preferred term	Center	PON	Onset date	Study Month	Resolution date	¹ Highest severity during event	Related	Serious	Unexpected
Other specif. problems with uterus	908	4	12SEP92	12	12SEP92	Mild	Poss yes	No	No
Ovarian cyst, NOS	908	18	20JUL92	5	20AUG92	Mild	Poss yes	No	No
Ovarian cyst, NOS	952	8	07OCT92	11	20NOV92	Moderate	Prob no	No	No
Ovarian cyst, NOS	952	8	31OCT94	36	30NOV94	Mild	Prob yes	No	No
Pain, pelvic, NOS	952	8	07OCT92	11	10OCT92	Moderate	No	No	No
Pap test, abnormal, NOS	908	16	01FEB93	12	16NOV94	Mild	Prob no	No	No
Pap test, abnormal, NOS	908	16	01FEB94	24	...	Mild	No	No	No
Pap test, abnormal, NOS	908	18	01JUN93	16	22FEB94	Mild	No	No	Yes
Urinary tract infect,NOS(UTI,bacteruria	908	14	04JAN94	25	20JAN94	Mild	No	No	No
Urinary tract infect,NOS(UTI,bacteruria	908	16	26OCT92	9	03NOV92	Moderate	No	No	No
Urinary tract infect,NOS(UTI,bacteruria	908	16	03FEB93	13	01MAR93	Moderate	No	No	No
Vaginitis, candida or monilia	908	5	26SEP92	13	01OCT92	Mild	No	No	No

¹

Ellipses (...) indicate AE is ongoing. Information on relatedness and severity is determined by the highest relatedness or severity ever reported for that event. An AE is reported as serious or unexpected if it was ever reported as serious or unexpected.

July 24, 1995

NET Pellet Phase II-A
Study 890

020

Table 28

Follow-up of Adverse Events Reported as Unresolved
at Participant Discontinuation
by Treatment Received

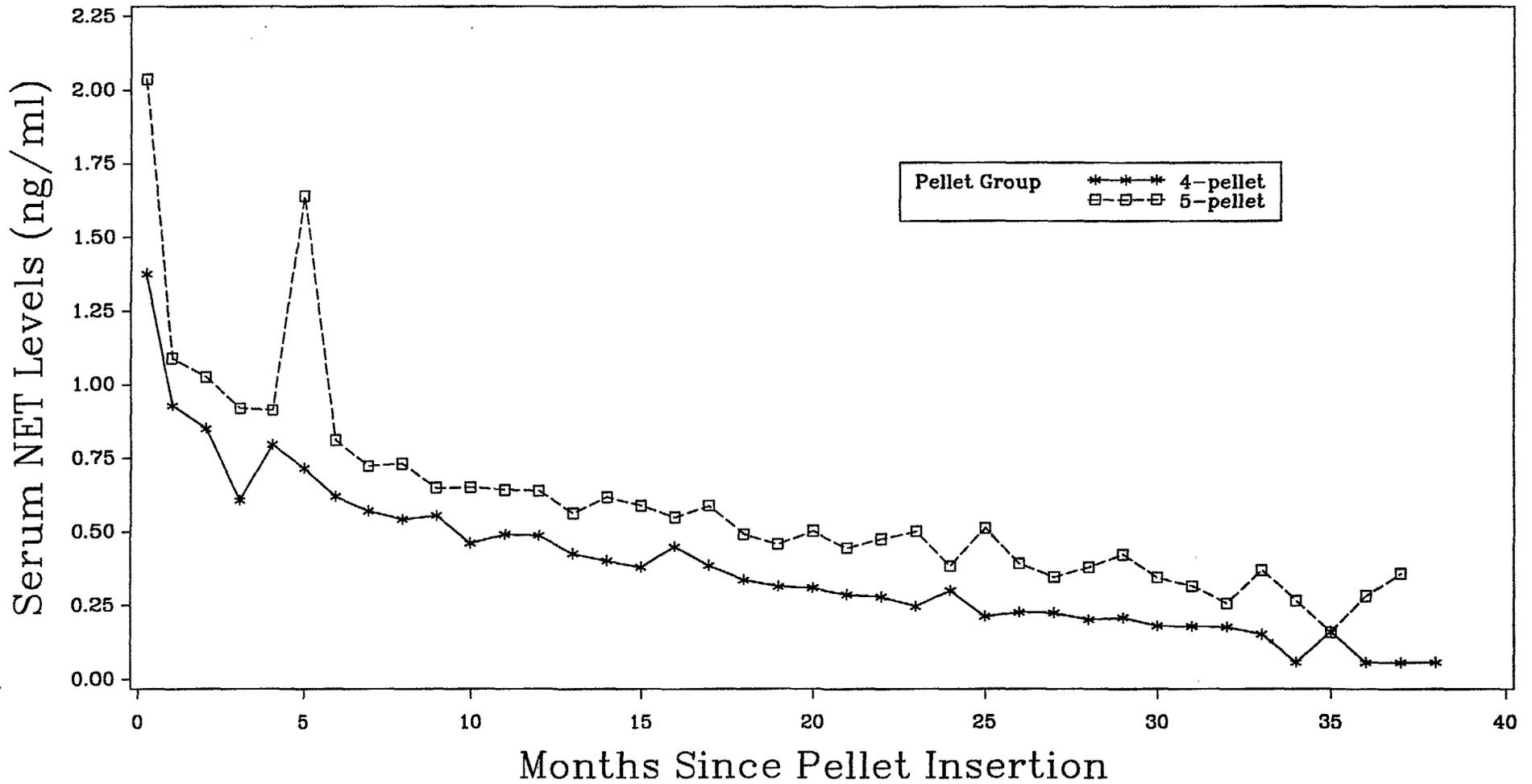
Center	PON	Adverse Event	Onset Date	Last Contact ¹ Date	Status at Last Contact ²
<u>4-Pellet</u>					
908	2	Hypertension	07MAY93	18OCT93	Not resolved (now LTFU)
908	3	Anemia, NOS	14APR93	30MAR95	Resolved 01JUL93
908	3	Peripheral neuropathy	14APR93	30MAR95	Continuing, but better
908	6	Acne vulgaris, all sites	21OCT91	23DEC91	Not resolved (now LTFU)
908	6	Menorrhagia	21OCT91	23DEC91	Not resolved (now LTFU)
908	6	Sexual dysfunction	21OCT91	23DEC91	Not resolved (now LTFU)
908	6	Other neurotic disorders	21NOV91	23DEC91	Not resolved (now LTFU)
<u>5-Pellet</u>					
908	5	Acne vulgaris, all sites	14JUN93	03AUG93	Not resolved (now LTFU)
908	7	Dysplasia/metaplasia, cervix	30NOV94	20JAN95	Colposcopic biopsies normal; no rx needed
908	9	Respiratory allergies, NOS	16MAR92	16JAN95	Still present
908	12	Lump, shoulder, NOS, NEC	10JUN93	30MAR95	Resolved, unknown date
908	14	Genital herpes, NOS	04JAN94	05MAY94	Not resolved (now LTFU)
908	16	Pap test, abnormal, NOS	01FEB94	16NOV94	Colposcopic biopsies showed HPV; no rx; PAP 16NOV94 normal
952	8	Tenosynovitis	10FEB92	20FEB92	Not resolved (no recent FU)
952	10	Metrorrhagia	10SEP92	15SEP93	Not resolved (no recent FU)
952	16	Breast hyperplasia, benign	04AUG93	26JUN94	Chronic condition (no recent FU)
952	16	Fibrocystic breast disease	04AUG93	26JUN94	Chronic condition (no recent FU)

¹ The last date on which the status of the Adverse Event was known.

² LTFU = Lost to Follow-up. FU = Follow-up.

Figure 1

Mean NET Levels over time
by Treatment Received



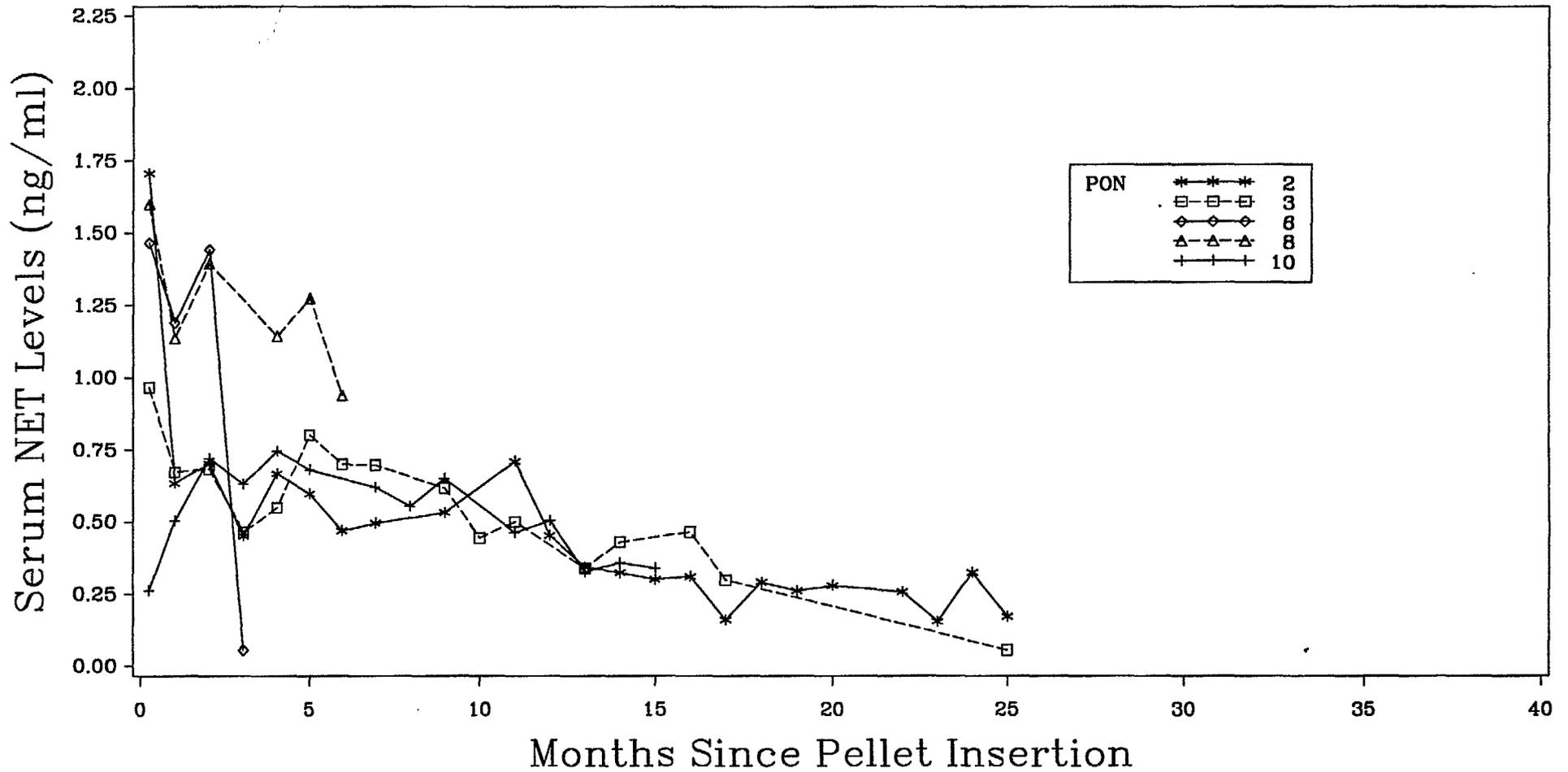
NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. Total varies at each timepoint. Refer to Tables 12.1 and 12.2.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 2a.1

Individual NET Levels over time
4-Pellet, Center 908

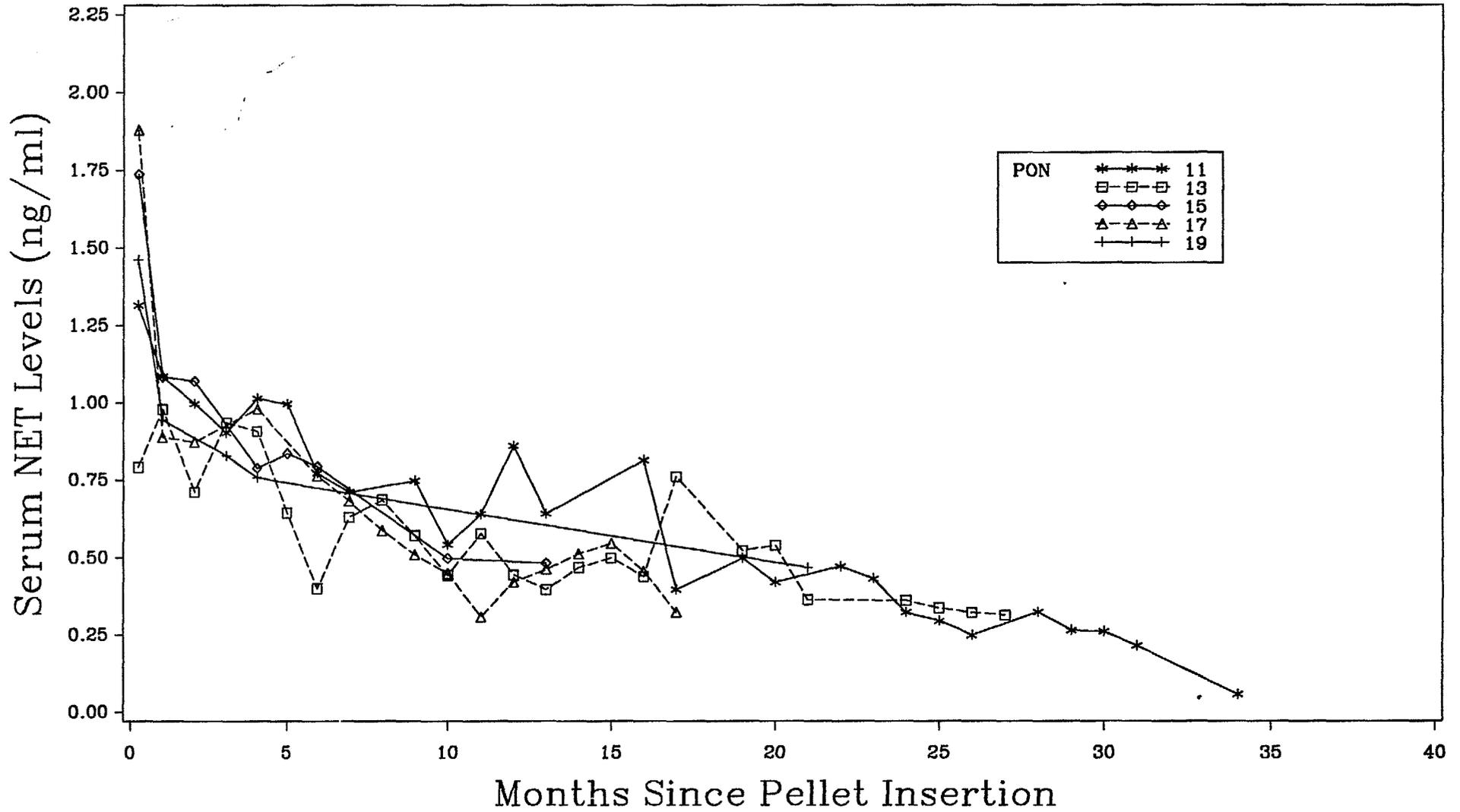


NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels.
All values > 2.25 have been changed to 2.25.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 2a.2



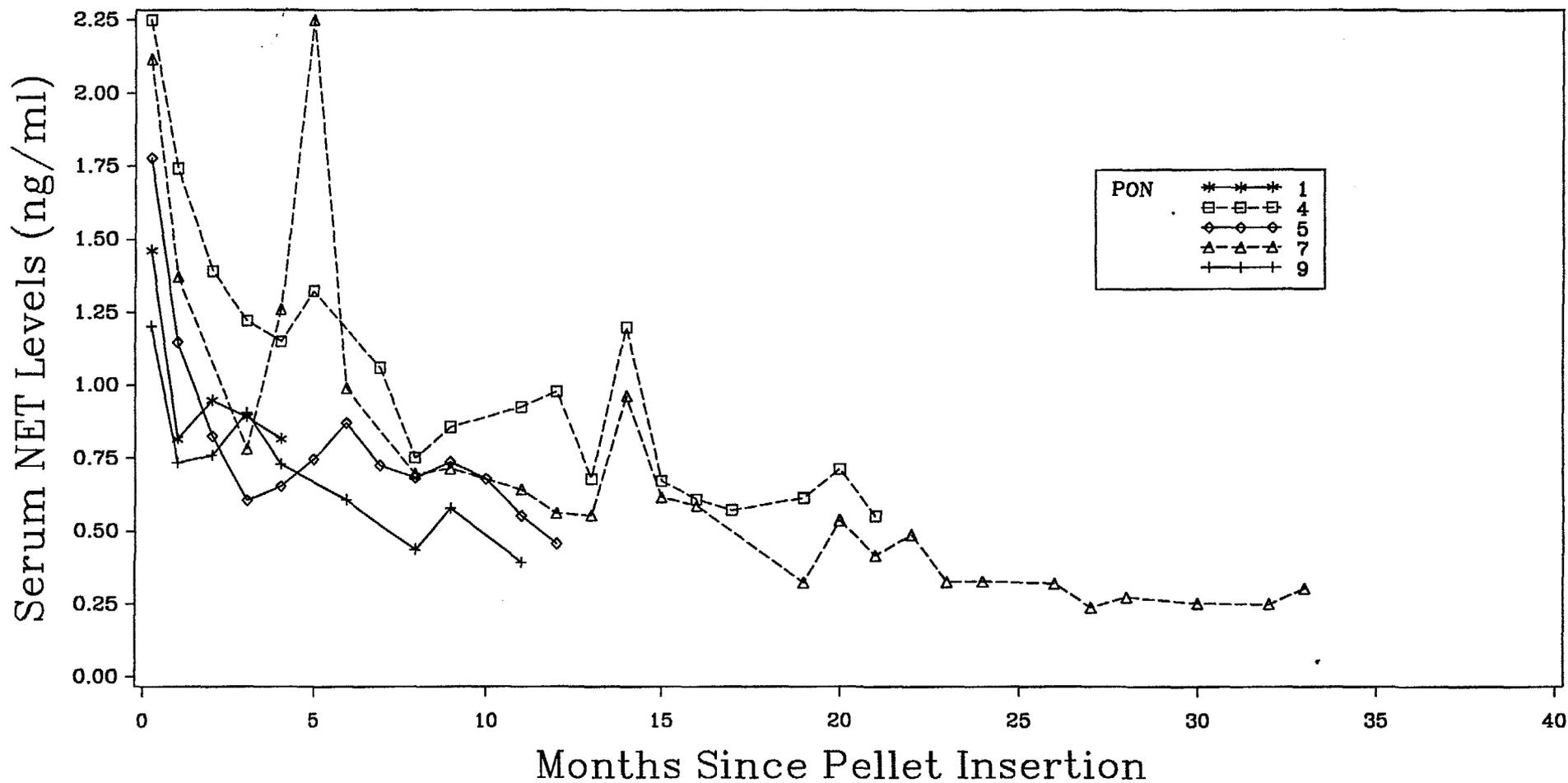
NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. All values > 2.25 have been changed to 2.25.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 2b.1

Individual NET Levels over time
5-Pellet, Center 908

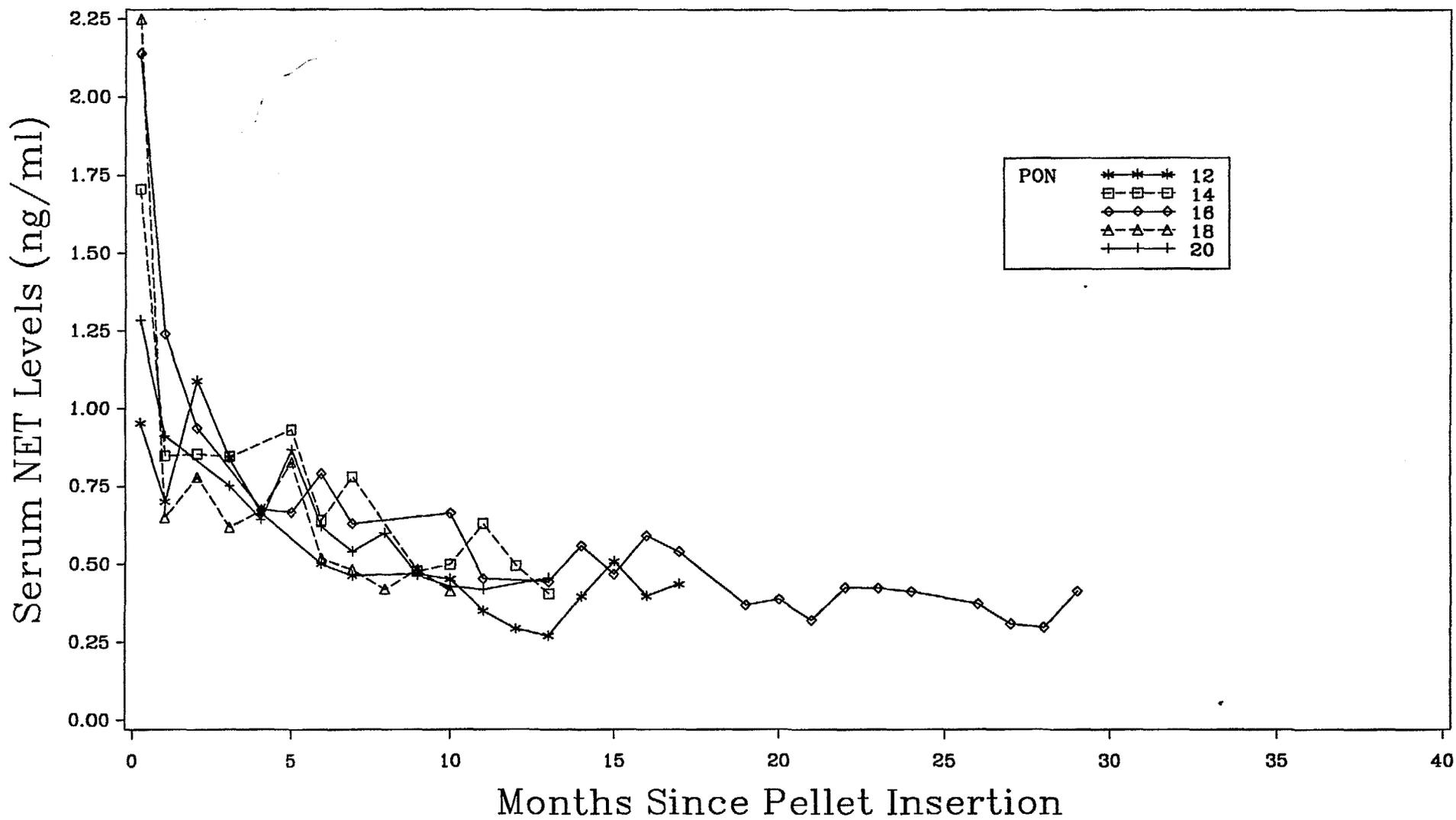


NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. All values > 2.25 have been changed to 2.25.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 2b.2



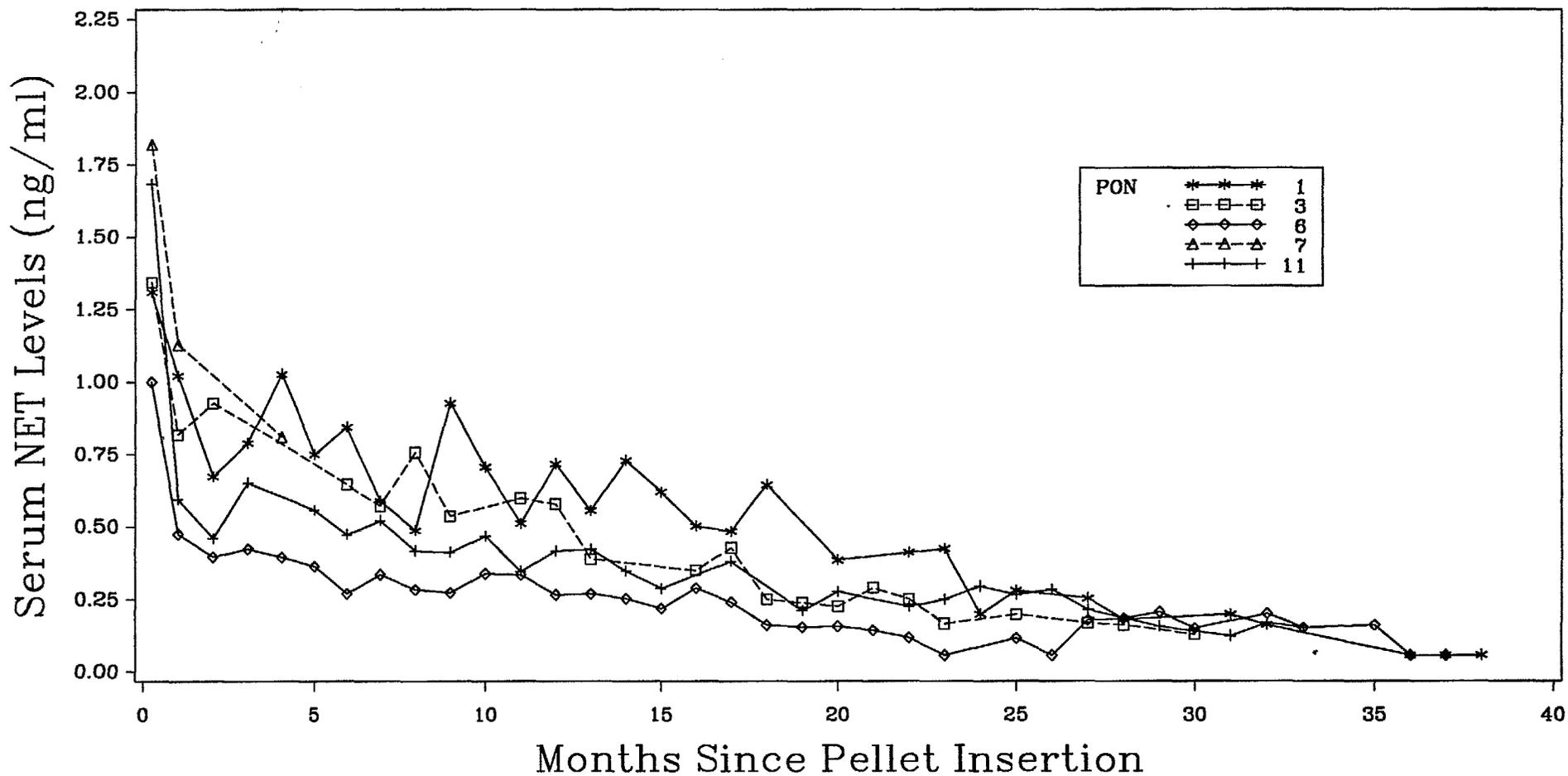
NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. All values > 2.25 have been changed to 2.25.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 2c.1

Individual NET Levels over time
4-Pellet, Center 952

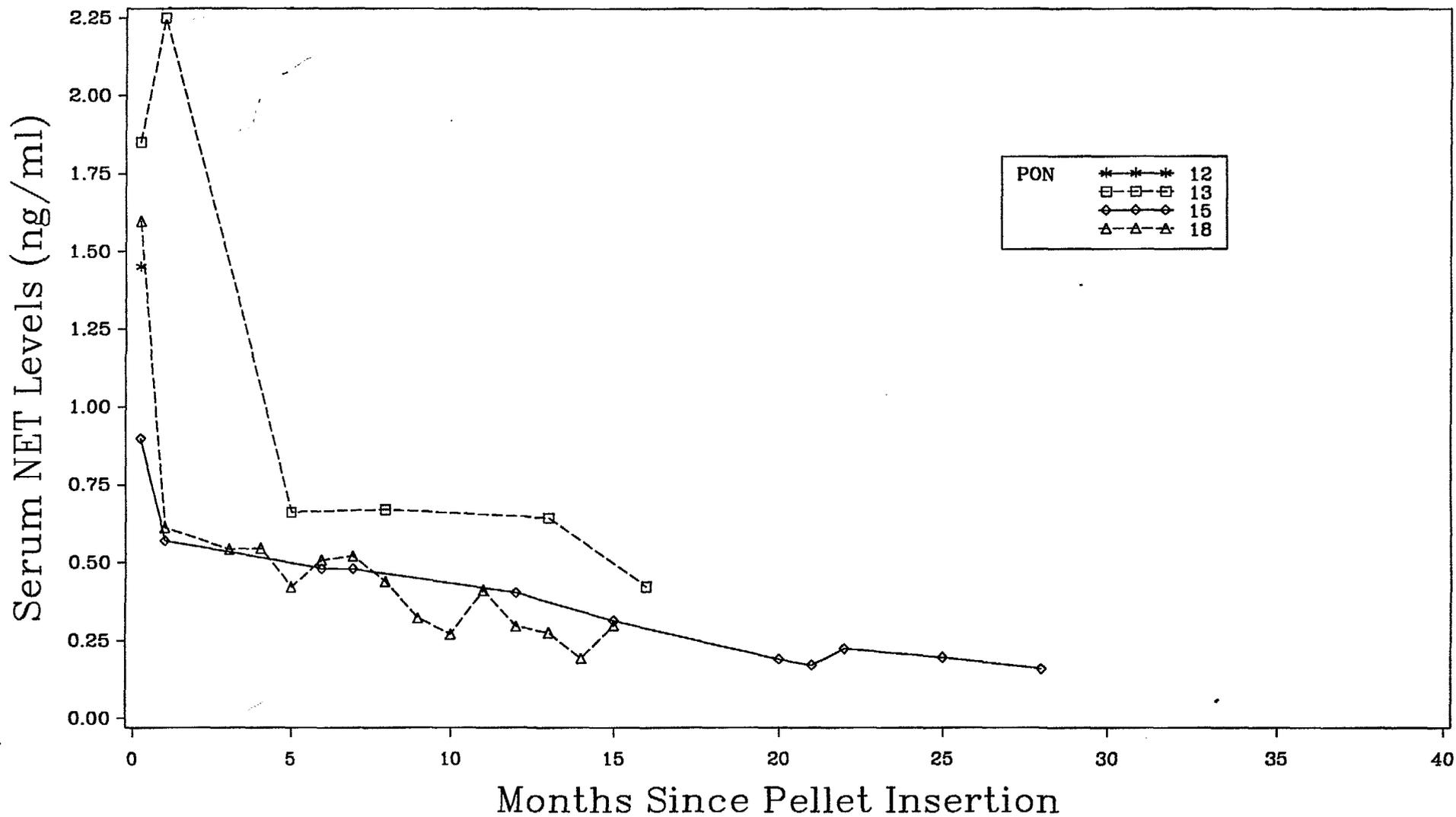


NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. All values > 2.25 have been changed to 2.25.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 2c.2



NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. All values > 2.25 have been changed to 2.25.

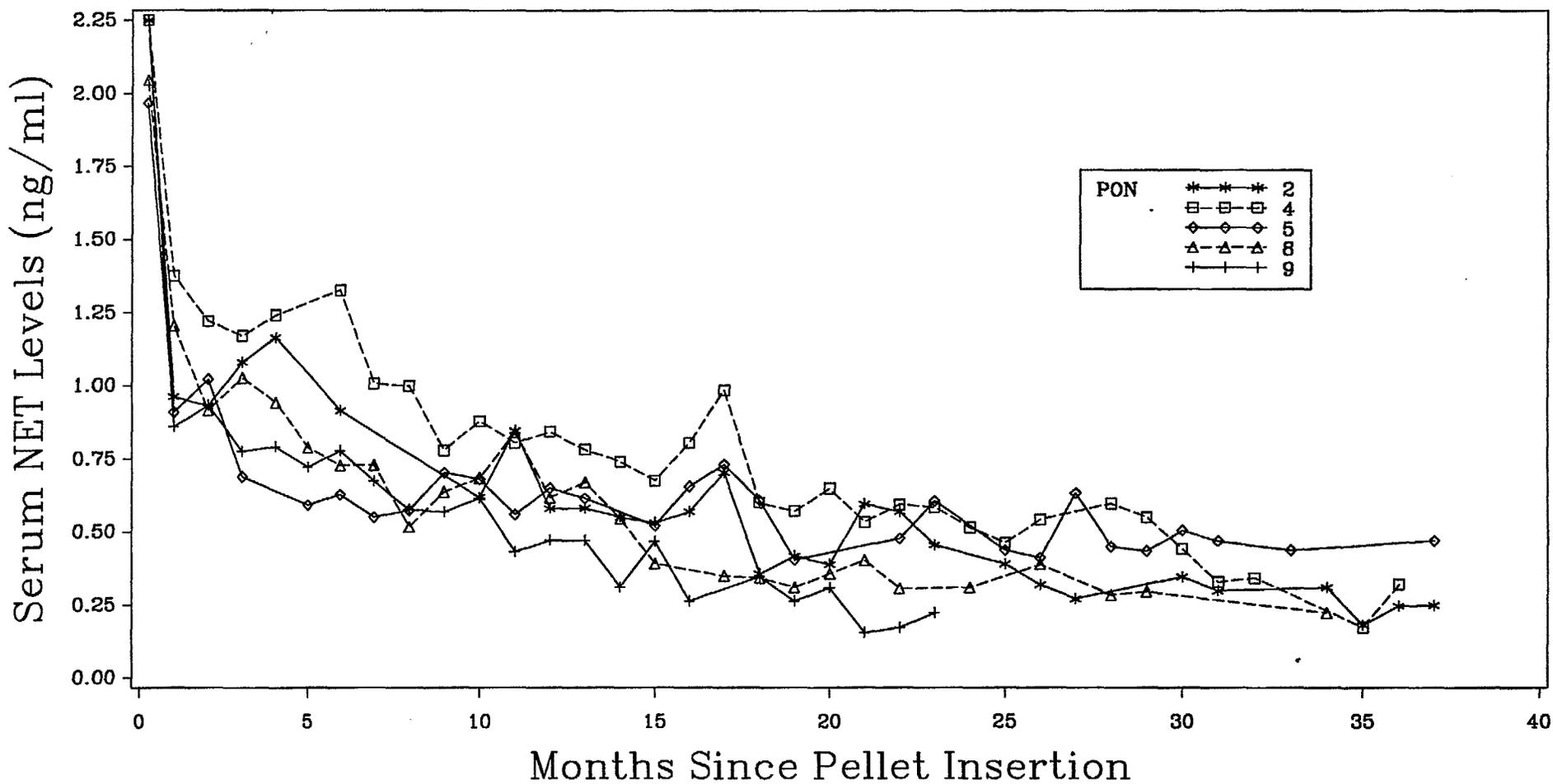
August 18, 1995

NET Pellet Phase II-A
Study 890

222

Figure 2d.1

Individual NET Levels over time
5-Pellet, Center 952

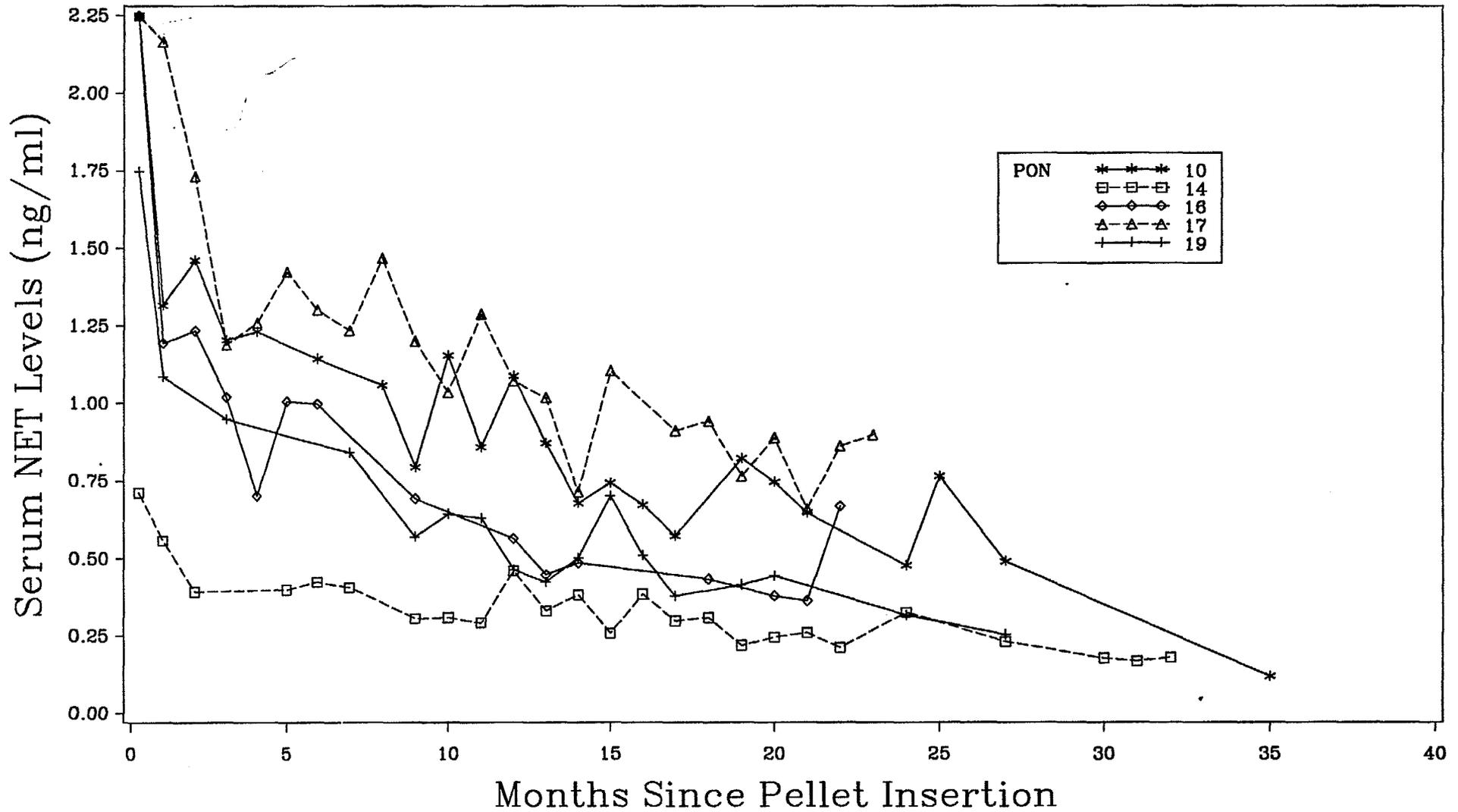


NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. All values > 2.25 have been changed to 2.25.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 2d.2



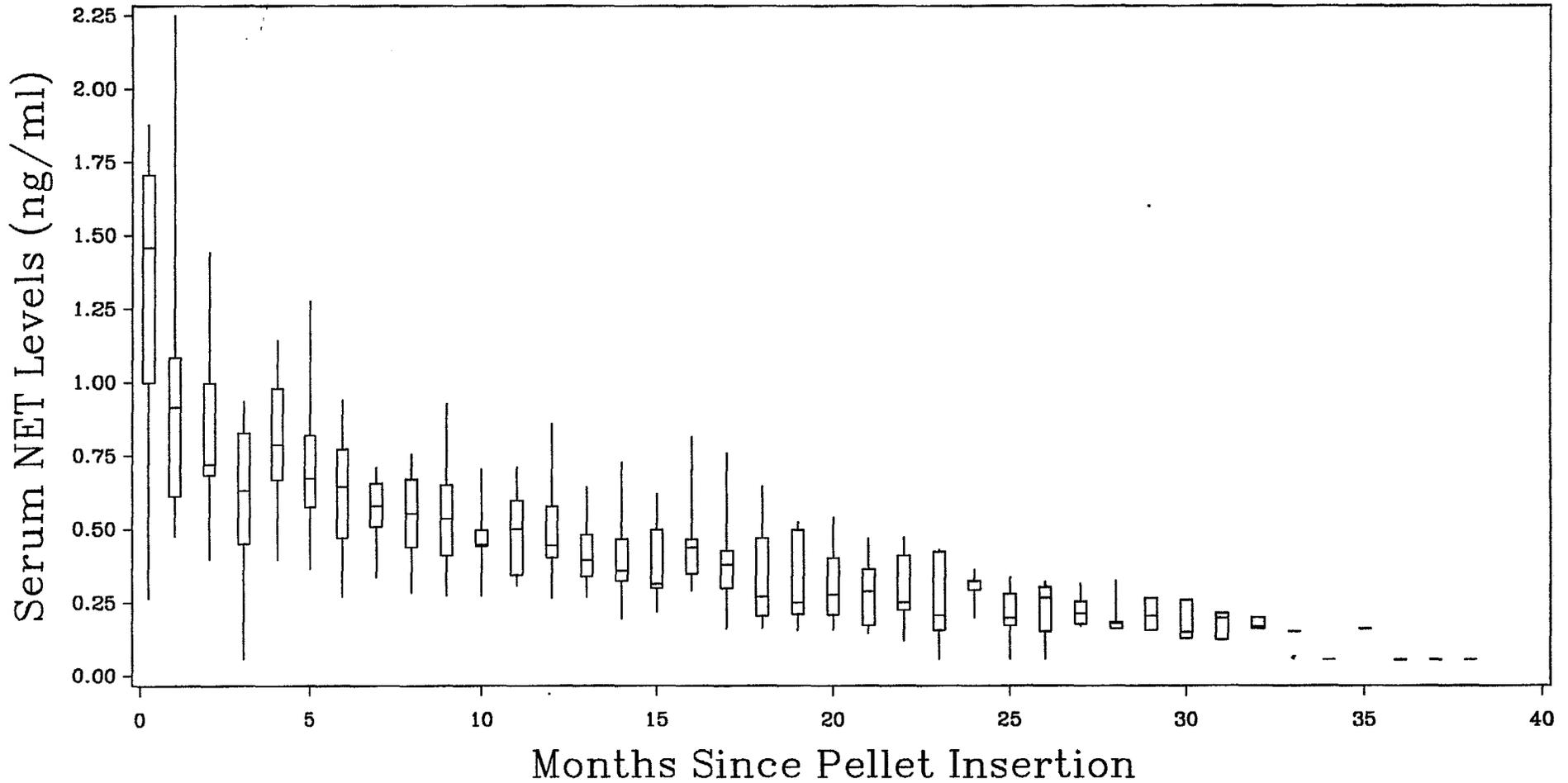
NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. All values > 2.25 have been changed to 2.25.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 3a

Box Plots of NET Levels over time
4-Pellet



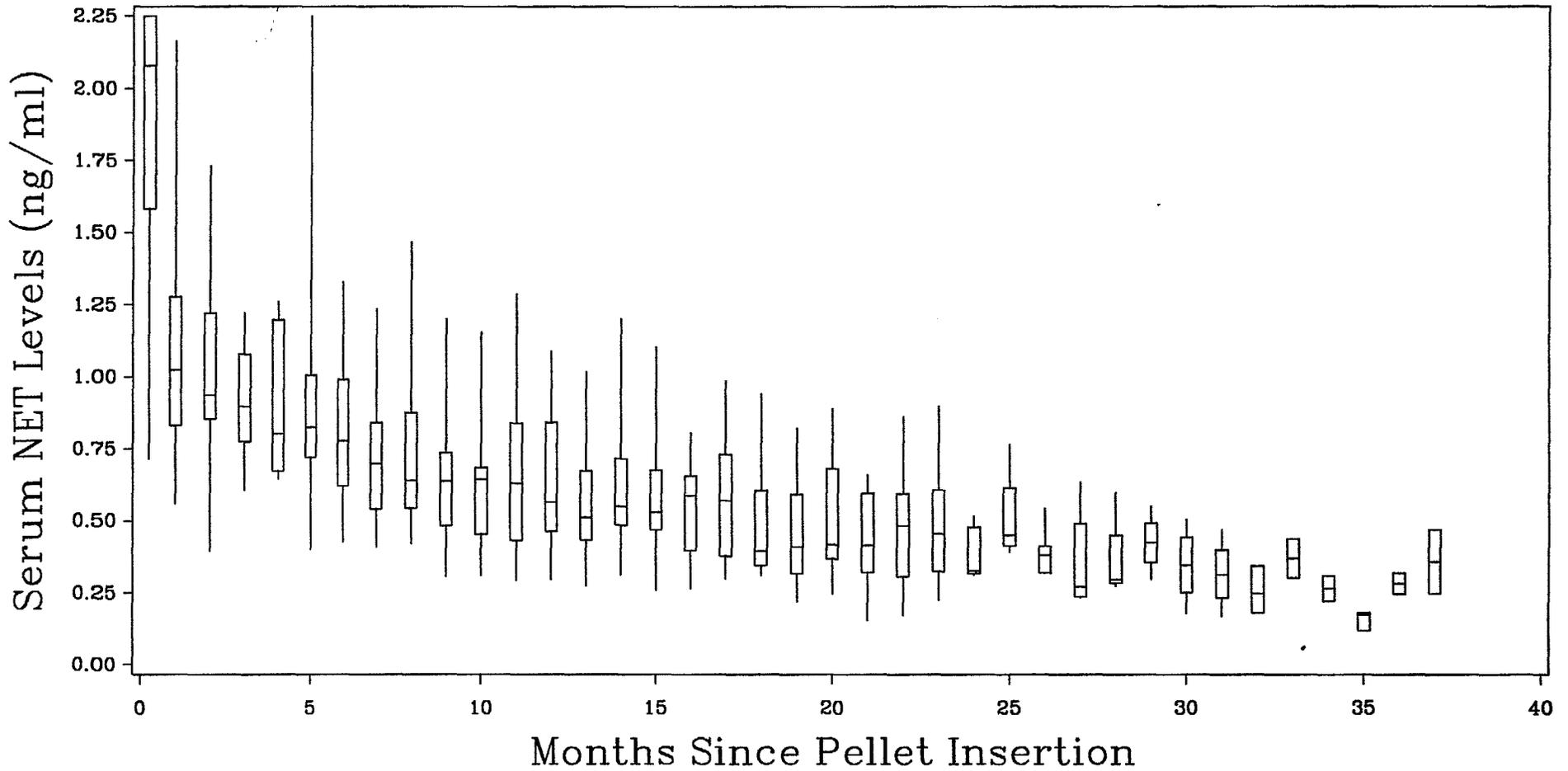
NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. While the actual values were used in calculations creating the box plots, for plotting purposes, all extreme values > 2.25 have been truncated to 2.25. Total varies at each timepoint. Refer to Tables 12.1 and 12.2.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 3b

Box Plots of NET Levels over time
5-Pellet



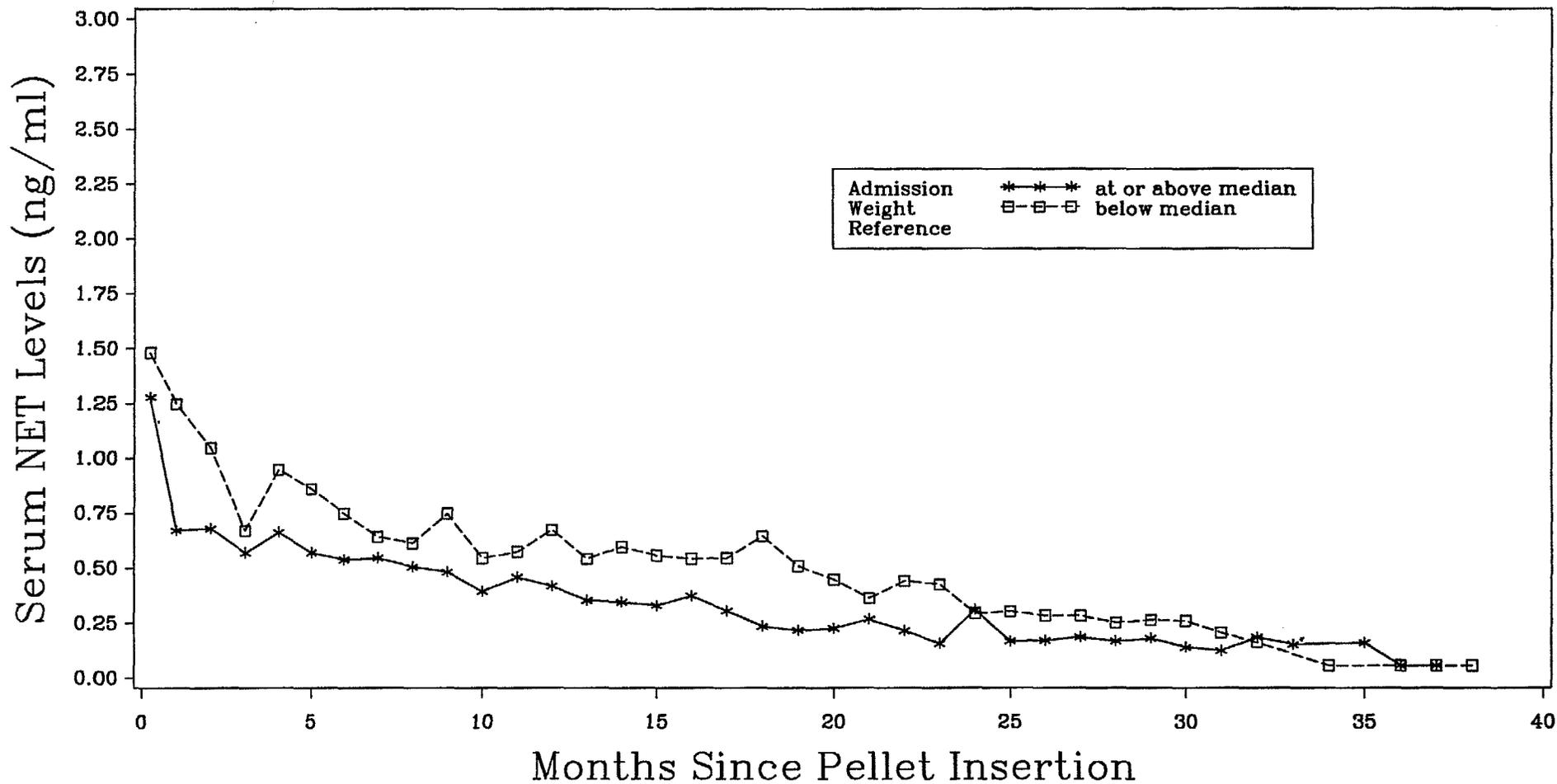
NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. While the actual values were used in calculations creating the box plots, for plotting purposes, all extreme values > 2.25 have been truncated to 2.25. Total varies at each timepoint. Refer to Tables 12.1 and 12.2.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 4a

Mean NET Levels over time
by Admission Weight Reference and Treatment Received
4-Pellet



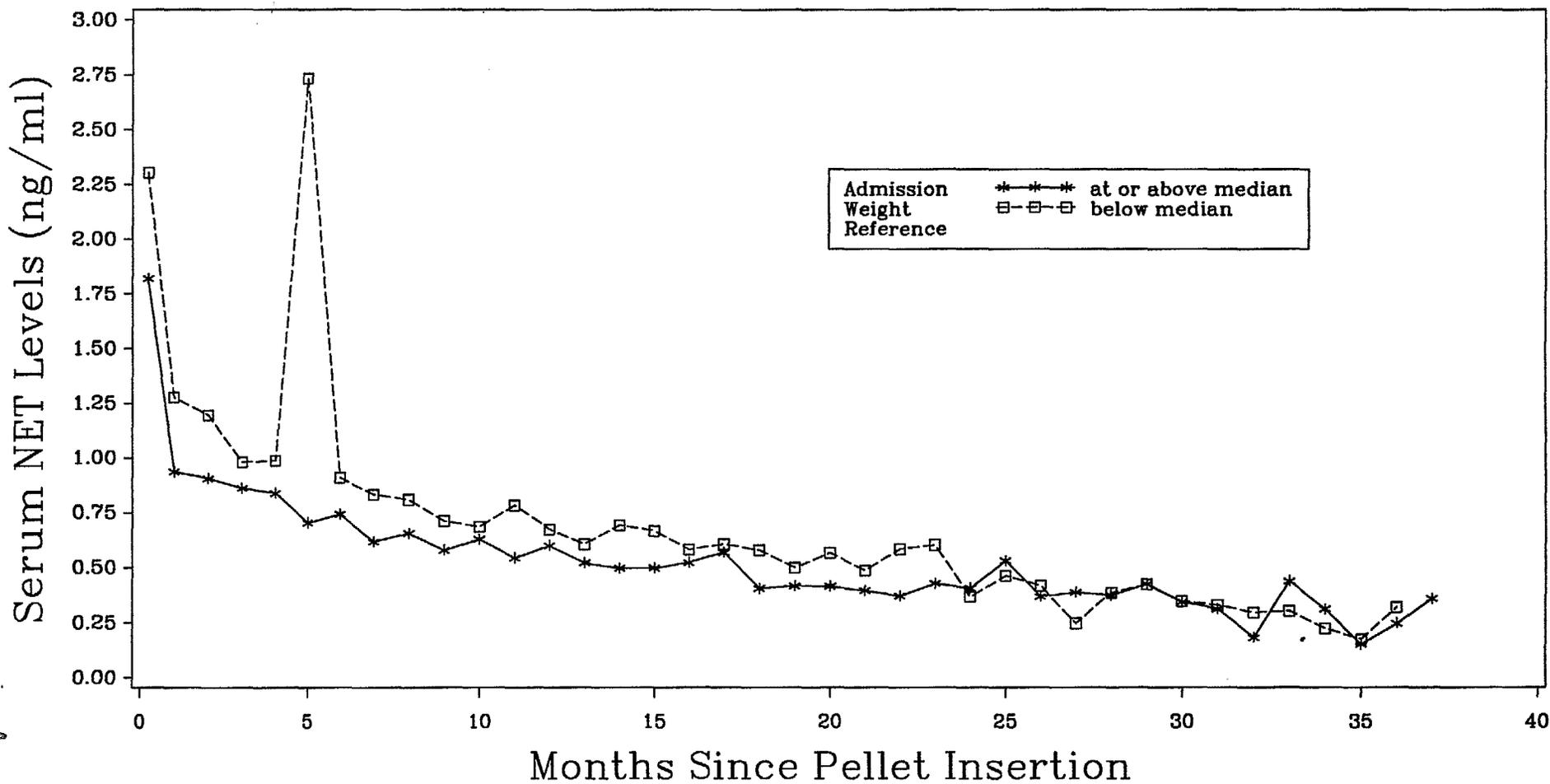
NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. Total varies at each timepoint. Refer to Table 12.1.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 4b

Mean NET Levels over time
by Admission Weight Reference and Treatment Received
5-Pellet



NOTE: Values at all timepoints except 24-hours are plotted. The 1-week level is the first value plotted, followed by the monthly levels. Total varies at each timepoint. Refer to Table 12.1.

August 18, 1995

NET Pellet Phase II-A
Study 890

Figure 5a
 Frequency of Clinically Important
 Bleeding Patterns by 90-Day
 Reference Period (4-pellet group)

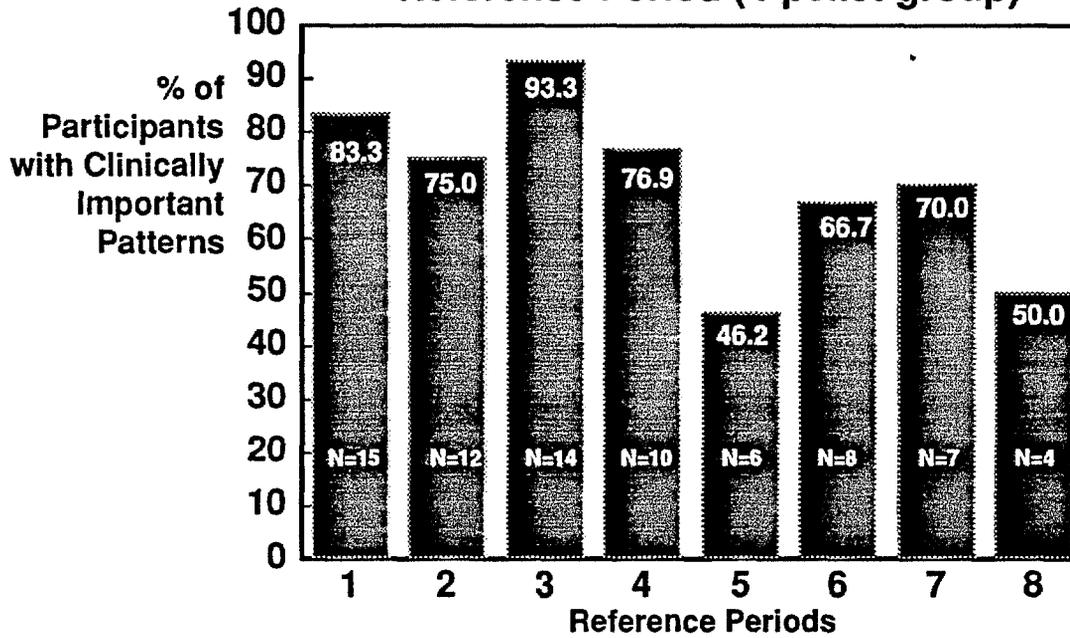
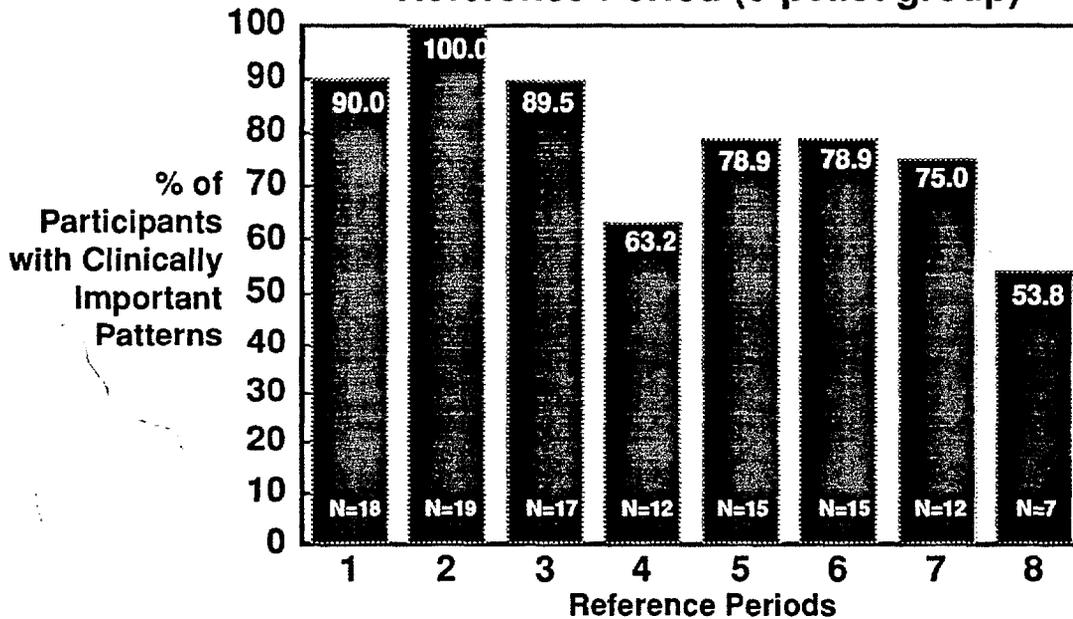
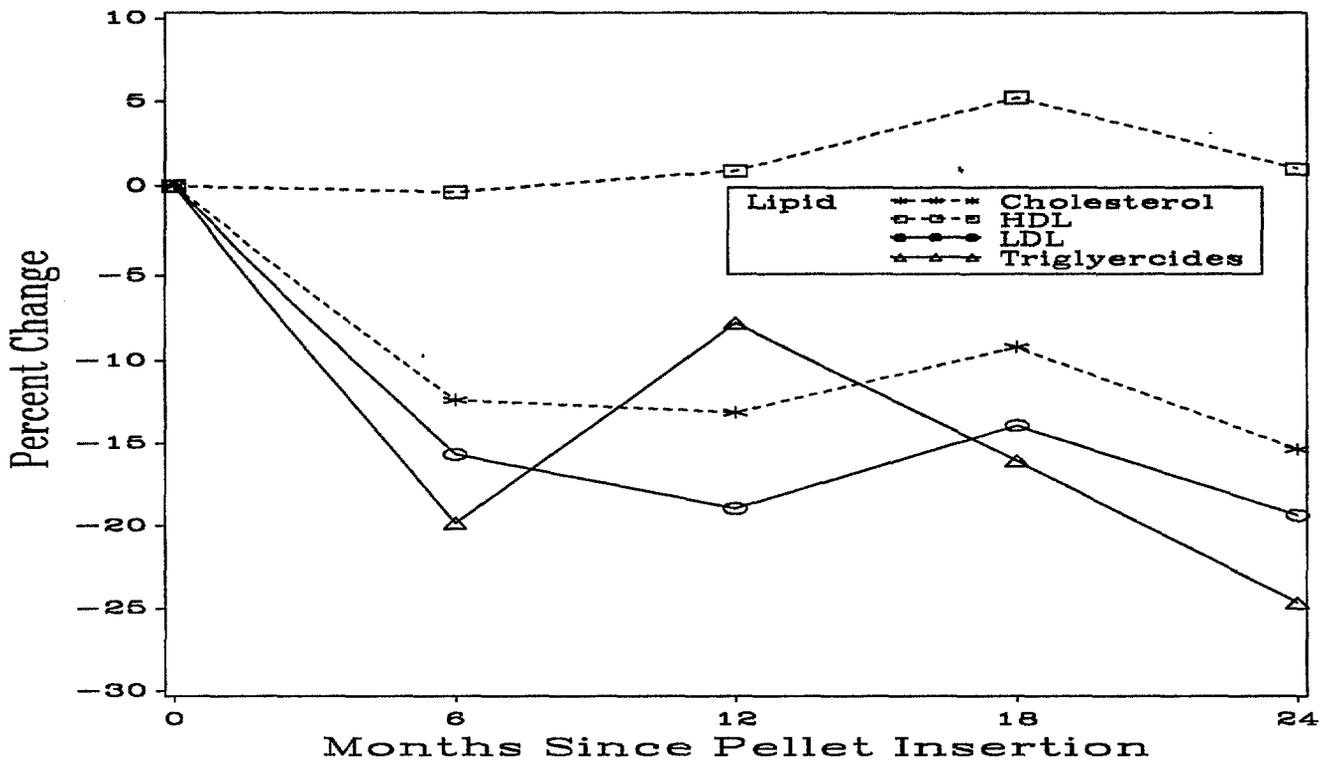


Figure 5b
 Frequency of Clinically Important
 Bleeding Patterns by 90-Day
 Reference Period (5-pellet group)

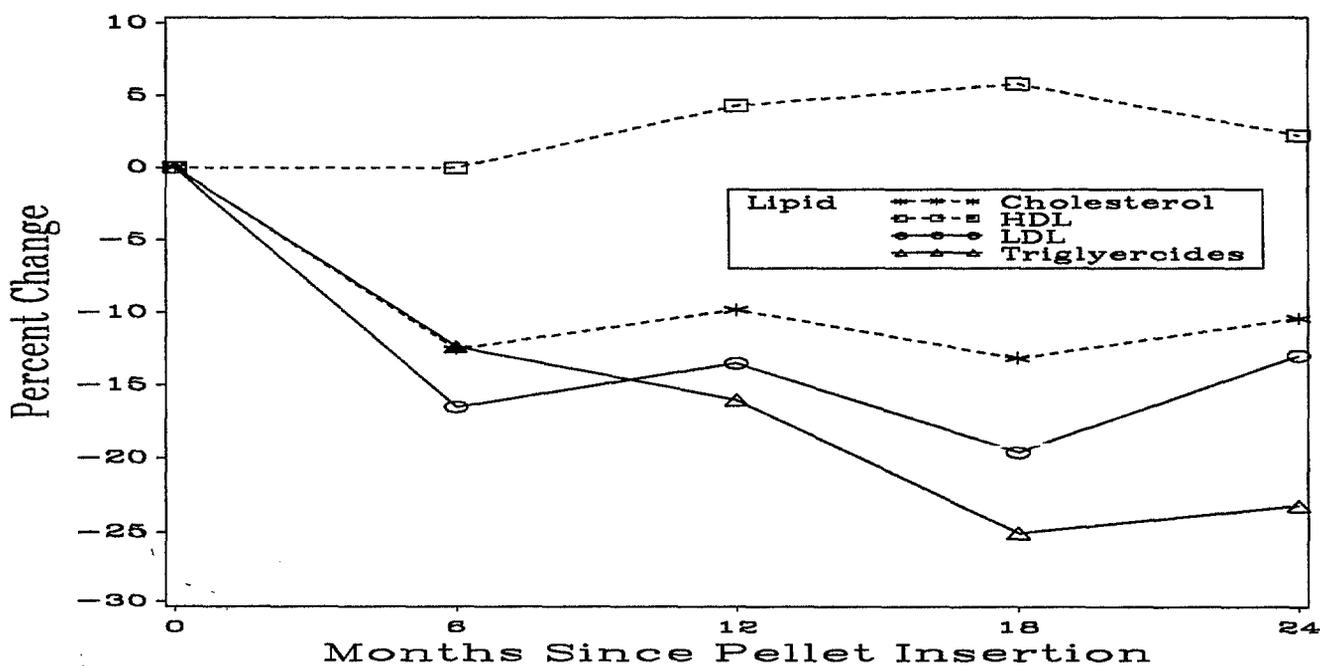


235

Figure 6
Percent Change in Lipids over time
a: 4-Pellet



b: 5-Pellet

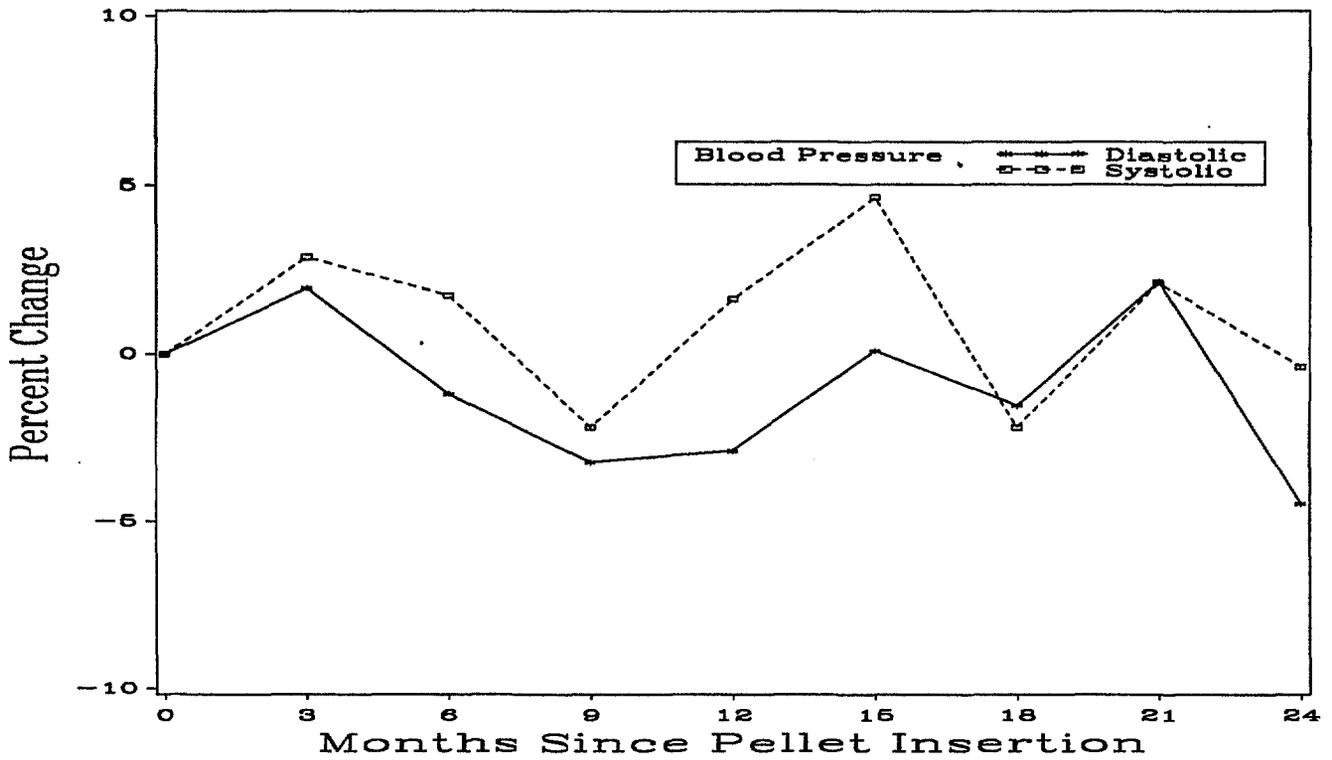


Percent change is from baseline to the follow-up month indicated.
Total varies at each timepoint. Refer to Table 15.

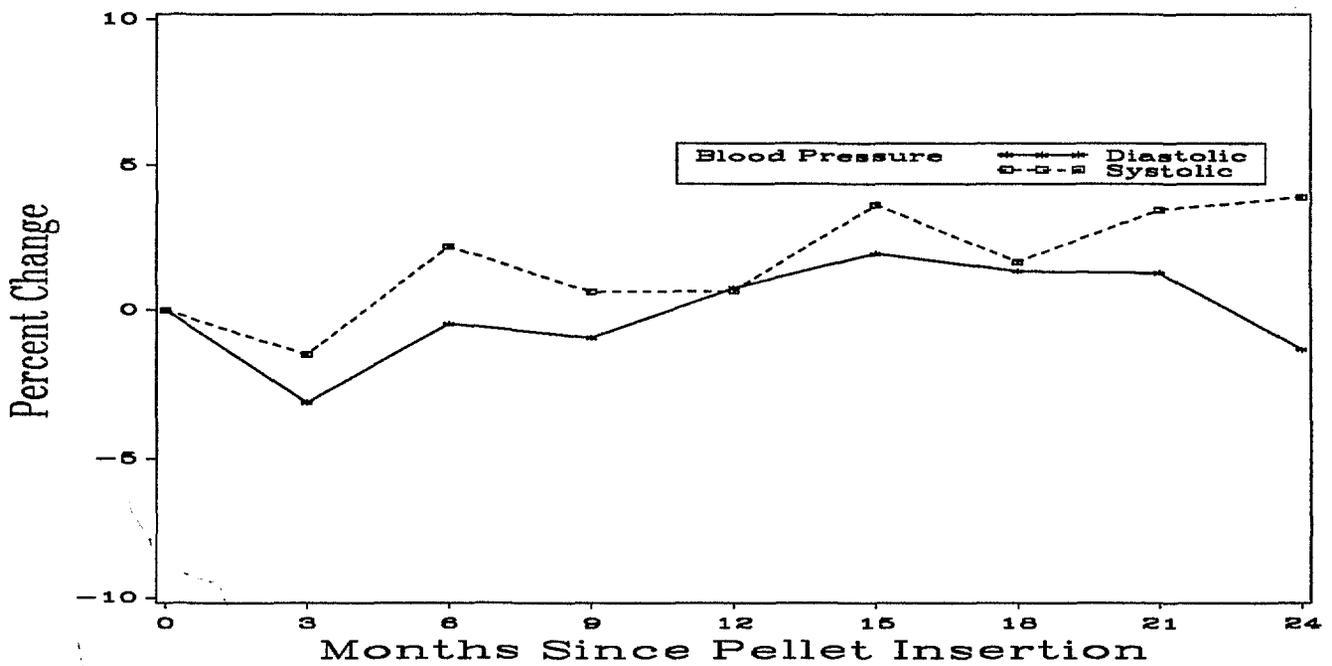
August 18, 1996

NET Pellet Phase II-A
Study 890

Figure 7
 Percent Change in Blood Pressure over time
 a: 4-Pellet



b: 5-Pellet

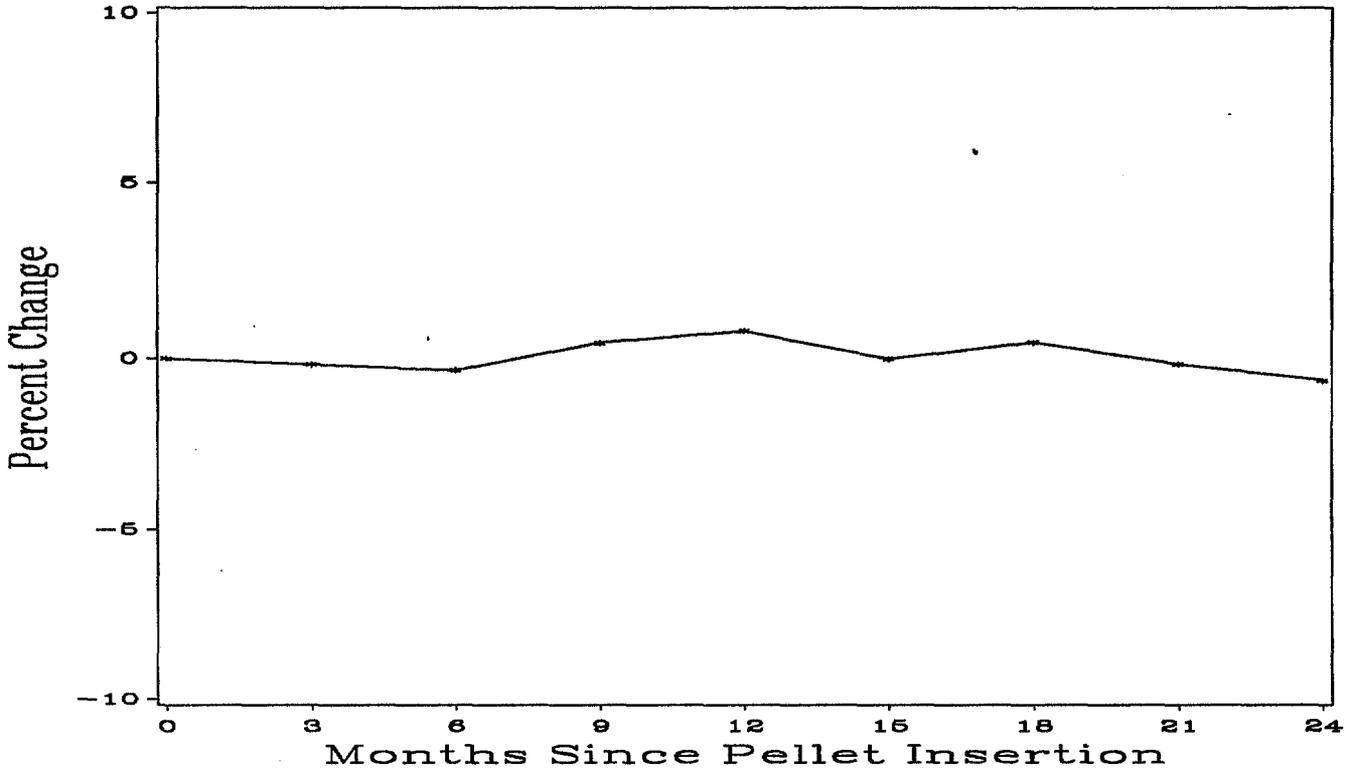


Percent change is from baseline to the follow-up month indicated. Total varies at each timepoint. Refer to Table 21.

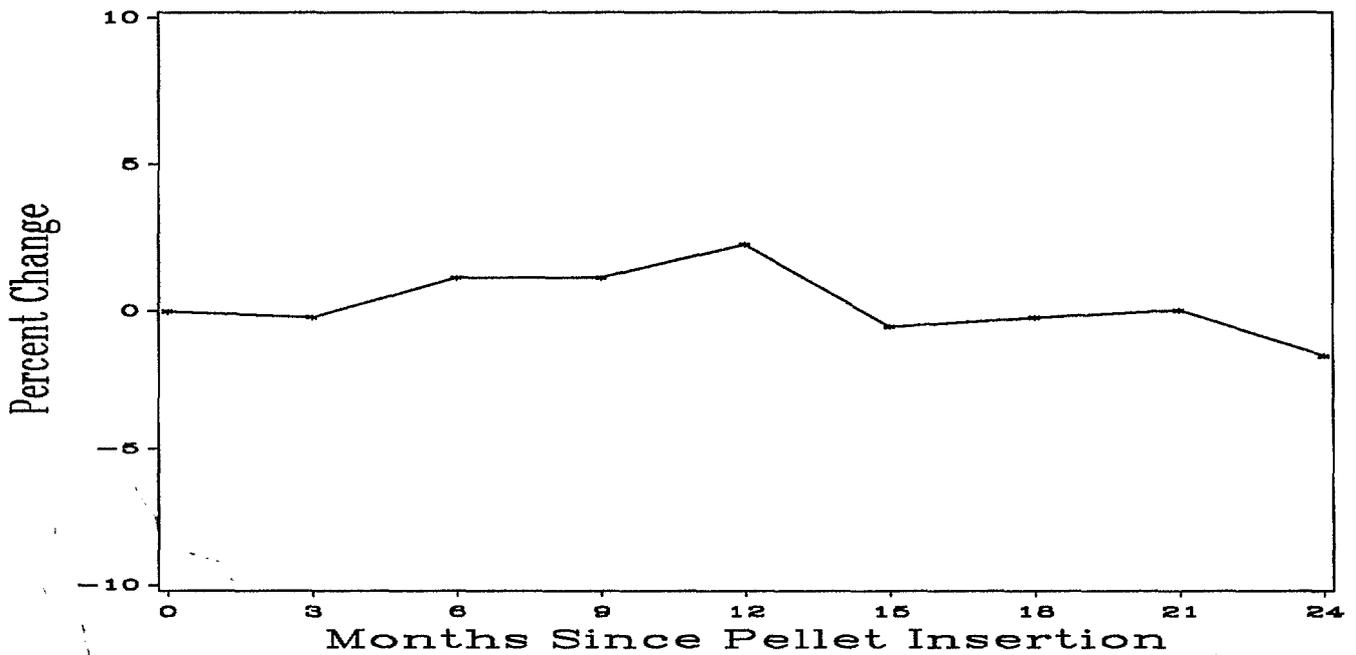
August 18, 1995

NET Pellet Phase II-A
 Study 890

Figure 8
 Percent Change in Weight over time
 a: 4-Pellet



b: 5-Pellet



Percent change is from baseline to the follow-up month indicated. Total varies at each timepoint. Refer to Table 22.

August 18, 1996

NET Pellet Phase II-A
 Study 890