CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-874

MEDICAL REVIEW

SEP 26 2000

Medical Officer's Review of Supplemental Information to NDA 20-874 (Draft of Phase IV Clinical Protocol: Change in Bone Mineral Density)

NDA:	20-874
Sponsor:	Pharmacia & Upjohn
Type of submission:	Summary of Clinical Protocol for Phase IV Commitment (Protocol No 839-FEH-0034-009 – A comparison of Lunelle™ and Depo-Provera effect on BMD to document benefit of added estrogen)
Drug (generic name):	Medroxyprogesterone acetate and estradiol cypionate
Proposed trade name:	Lunelle™ Monthly Contraceptive Injection
Proposed indication:	Prevention of pregnancy
Dose and route of administration:	25 mg of medroxyprogesterone acetate and 5 mg of estradiol cypionate by once monthly IM injection
Date(s) of this submission:	July 11, 2000
Date(s) submission received:	July 12, 2000
Date review completed:	August 9, 2000
Reviewer:	Scott E. Monroe, MD Medical Officer, DRUDP

BACKGROUND

Depo-Provera has been widely used for many years outside of the United States for contraception, and more recently, it also has been approved for prevention of pregnancy by the FDA. Depo-Provera for contraception consists of 150 mg of medroxyprogesterone acetate and is administered IM once every 13 weeks. It does not contain an estrogenic component. In contrast, Lunelle (subject of NDA 20-874) is administered by monthly IM injection and contains 25 mg of medroxyprogesterone acetate and 5 mg of estradiol cypionate.

Several, but not all, cross-sectional studies have shown that long-term users of Depo-Provera (generally at least 2 years of use) have decreased bone mineral density (BMD) of the lumbar spine and, in some instances, decreased BMD of the femoral neck. This effect of Depo-Provera on BMD appears be greatest in women who begin to use it prior to attaining peak bone mass and who continue its use for many years. Other cross-sectional studies, however, have shown little, if any decrease in BMD in long-term users of Depo-Provera. Only limited prospective data on the possible effects of Depo-Provera on BMD are available. A small prospective study, however, compared changes in lumbar BMD in adolescent girls using Depo-Provera, Norplant, oral contraceptives, or nonhormonal methods for prevention of pregnancy. After one year, BMD decreased 1.5% in Depo-Provera users (n=15) compared with increases of 2.5 % in Norplant users (n=7), 1.5 % in oral contraceptives users (n=9), and 2.9% in nonhormonal users (n=17).

In October 1999, Pharmacia & Upjohn received an Approvable Letter for Lunelle (IND 20-874). The Approvable Letter included a request that the Sponsor conduct one or more Phase IV clinical trials to assess further the likely benefit(s) of the estrogenic component of Lunelle. It was requested that one of these studies investigate if women using Lunelle for prevention of pregnancy would experience less of a decrease in BMD than that reported for women using Depo-Provera for contraception. In April 2000, Pharmacia & Upjohn submitted a protocol

summary for a Phase IV study to investigate changes in BMD in women receiving Lunelle for contraception. The proposed study did not include a comparator group, and the protocol summary did not include any sample size or power estimates and lacked important details of study design. The proposed study was not considered to have met the request in the Approvable Letter of October 1999. This was conveyed to the sponsor in a teleconference on June 2, 2000. In response to the issues raised during the teleconference, the Sponsor submitted a revised protocol summary on July 11, 2000 (Protocol No 839-FEH-0034-009 – A comparison of Lunelle™ and Depo-Provera effect on BMD to document benefit of added estrogen).

Overview of Study Design

Subjects, 18-35 years of age, will be randomized into 1 of 2 treatment groups in this open-label, multicenter study. Subjects with a history of bone disease, conditions likely to be associated with changes in BMD, or need to use concomitant medications known to affect BMD will be excluded. Subjects will receive either IM Lunelle at 28 ±5-day intervals or Depo-Provera at 13-week intervals for 2 years. Lumbar spine, hip, and total body BMD will be evaluated by DXA at screening and at 6-month intervals.

Medical Reviewer's Comments

1. **The overall study design is appropriate.**
2. **Entry criteria are acceptable although subjects, who have been treated with a drug likely to have affected BMD (e.g., a GnRH analog) within the prior 6-12 months, also should be excluded.**
3. **The value of measuring total body BMD is questionable but does not expose subjects to significant added risk.**

Study Endpoints and Statistical Methods

Endpoints. The primary endpoint will be whether a patient experienced BMD loss at 1 and 2 years after initiating treatment with Study Drug as measured by DXA. A subject will be defined as having experienced BMD loss at the analysis time point (1 year or 2 years) if the DXA value at that time point is less than the baseline value. Other endpoints will include the percent change from baseline in BMD at 1 and 2 years after initiating treatment.

Statistical Methods. The primary efficacy analysis will include all subjects receiving at least one dose of Study Drug and with at least one DXA value after baseline. In the intent to treat analysis, an imputation for any missing DXA value at the analysis time point will be done by projecting linearly from baseline. An analysis will also be done on only the available data at the analysis time point. A chi-square test will be used to compare the percent of subjects in each treatment group experiencing BMD loss. An interim analysis will be performed on the primary endpoint of percent of subjects experiencing BMD loss after 1 year as measured by DXA. The significance level for the interim analysis will be set to 0.01. The study will be terminated if the difference between the 2 treatment groups is significant.

Medical Reviewer's Comments

1. **Basing the primary analysis on a comparison of the percentage of subjects in each treatment group experiencing BMD loss has not previously been used or accepted by the FDA as the primary endpoint in osteoporosis studies in support of drug approval or drug labeling. Loss of BMD as the primary endpoint, applied to individual subjects in a meaningful manner, will be difficult to define, as it will depend on the precision of the BMD measurements over a 2-year period. The problem with this approach is further compounded by the likelihood that the actual decrease in BMD in a subject treated with Depo-Provera will be small (only a few percent), thus leading to the misclassification of a high percentage of subjects.**
2. **Even if subjects could be reliably classified as BMD losers or non-losers, such an analysis would provide no estimate of the magnitude of the difference in change in BMD across the 2 treatment groups.**

3. **Because of No. 1 and 2 above, it is recommended that the primary analysis be based on percent change from baseline as is usually done in studies involving measurement of BMD.**
4. **The primary analysis should be based on actual data and not on actual and imputed data. The sponsor's proposal for handling missing data (i.e., imputation of any missing DXA value at the analysis time point by projecting linearly from baseline) is not appropriate as it assumes a linear change in BMD over time, which may not be true.**
5. **Since the primary purpose of this study is to determine if long-term use of Lunelle for prevention of pregnancy is associated with less of a decrease in BMD than long-term use of Depo-Provera, a primary analysis based on "completers" (i.e., BMD after 2 years of treatment) would probably be most appropriate. Alternatively, an analysis based on the rate of change (i.e., slope) of BMD measurements for all subjects treated for at least 6 months, with no imputation for missing BMD data after a subject discontinued treatment, would be an acceptable alternative for the primary analysis.**

Sample size and power

The sponsor has calculated that a sample size of — subjects in the Lunelle group and — in the Depo-Provera group will give — power with an overall type 1 error — to (a) detect a difference of — in the response rate in BMD loss between the 2 treatment groups or (b) detect a difference of — in BMD after 2 years with respect to percent change from baseline assuming a standard deviation of — The sponsor also states the following: " ——— ——— patients should be enrolled in the Lunelle group and — in the Depo-Provera group."

Medical Reviewer's Comments

1. **The anticipated high drop rate requires the enrollment of a large number of subjects to achieve adequate study power based on an analysis of 2-year completers.**
2. **The likely sample size of the proposed study is not clear from the protocol summary. Although the statistical section of the protocol summary cites the numbers of ——— as targets for enrollment in the Lunelle and Depo-Provera treatment groups, respectively, it does not actually commit the sponsor to enrolling these numbers of subjects. Elsewhere in the protocol summary (Table labeled "Medications") reference is made to —Lunelle subjects and — Depo-Provera subjects. The sponsor has been contacted for clarification of the number of subjects likely to be enrolled into the Study.**

Medical Reviewer's overall assessment of proposed study

- **The overall design of the proposed study – 2-year, open-label, randomized, comparative design – is appropriate for the study objectives. Although the anticipated drop out rate of — before completion of 2 years of treatment will require enrollment of a large number of subjects to achieve power and may complicate to some extent analysis and interpretation, the study is otherwise straight forward.**
- **If conducted as proposed by the Sponsor and with appropriate modification of the statistical analysis plan as suggested, the study is likely to provide meaningful information about the effects of treatment with Lunelle or Depo-Provera on BMD, assuming that (a) an adequate number of subjects are enrolled and (b) appropriate quality control for the BMD measurements is implemented and maintained.**
- **An important unknown is to what extent, if any, BMD will be reduced after 2 years of use of Depo-Provera since reported studies, to date, are not in agreement. If the decrease in BMD in the lumbar spine (the site most likely to exhibit the greatest decrease) is not at least 1.5-2.0% per annum in the Depo-Provera group, there is little likelihood of this study showing a statistically significant benefit of treatment with Lunelle.**

/S/ 9 Aug. 2000

Scott E. Monroe, MD Date
Medical Reviewer, DRUDP

/S/

Copies: NDA 20-874/ HFD 580/ S. Allen/ D. Shames/ G. Willett/ S. Monroe/ E. De-Guia

Medical Officer's Review of Response to Deficiencies Noted in Non-Approvable Letter

SEP 23 1999

NDA 20-874	
Date of Submission	April 15, 1999
Date Received	May 5, 1999
Date Review Completed	September 22, 1999
Applicant	Pharmacia & Upjohn
Drug (generic name) Proposed trade name	Medroxyprogesterone Acetate and Estradiol Cypionate Injection **Lunelle™ Monthly Contraceptive Injection**
Pharmacologic Category	Estrogen and progestin combination
Proposed Clinical Indication	Prevention of pregnancy
Dosage and route of administration	25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate given as a 0.5 ml intramuscular injection q 28-30 days (not to exceed 33 days)
Manufacturing Control Data	See Chemistry Review
Pharmacologic Data	See Pharmacology Review
Biopharmaceutics Data	See Biopharmaceutics Review

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1.0 RESUME

This submission is the sponsor's complete response to a Non-Approvable Letter from the US Food and Drug Administration (FDA) September 25, 1998 following review of NDA 20-874 submitted September 25, 1997.

The current submission contains data from protocol M/5415/0004, a U.S. multicenter trial conducted to compare the efficacy, patient acceptability, pharmacokinetics, and safety of Lunelle™ Monthly Contraceptive Injection (Lunelle™) and Ortho-Novum 7/7/7, 28 tablets. The trial used a nonrandomized, open-label design in which women selected the contraceptive they preferred. Duration of treatment was up to 60 weeks. 782 women used Lunelle™, 321 used Ortho-Novum 7/7/7. Efficacy was measured by pregnancy and discontinuation rates and menstrual bleeding patterns. Patient acceptability was determined from quality of life and user satisfaction questionnaires. Pharmacokinetic parameters by site of injection were assessed in a subset of women. Safety data included adverse events, categorical changes in laboratory assays, change in physical examinations, gynecological examinations, or cytological evaluations, change in body weight or blood pressure. Lipid profile and coagulation profile data were assessed in a subset of subjects.

Reference is also made to Protocol 0006, a multiple-dose, open-label trial to characterize steady-state pharmacokinetics and pharmacodynamics (return of ovulation) after repeated monthly administration of Lunelle™. Effects on serum androgen and sex hormone binding globulin were also evaluated in Protocol 0006. 14 women were studied for 1 control cycle, 3 consecutive months of treatment, and 3 to 5 months of follow-up.

2.0 BACKGROUND

Lunelle™ Monthly Contraceptive Injection, also known by the previously submitted name CYCLO-PROVERA®, was developed by The Upjohn Company over 30 years ago and was first tested in a large scale safety and efficacy trial conducted by the World Health Organization (WHO) in 1984. In 1990, Upjohn turned over the development rights for this product to WHO which subsequently licensed the product to the [redacted], and its associated nonprofit organization, the [redacted] has licensed CYCLO-PROVERA® to several companies in Asia and Latin America. As of mid-1997, [redacted] units of CYCLO-PROVERA® had been sold worldwide, with no withdrawals from marketing in any country for safety reasons.

2.1 Regulatory History

On September 26, 1997, the current sponsor (Pharmacia & Upjohn) submitted an original New Drug Application (NDA) for CYCLO-PROVERA®, seeking FDA-approval for marketing the product in the United States. Up to the date of NDA submission, the following meetings were held with the sponsor or with investigators participating in clinical trials:

February 8, 1993—Pre-IND meeting with [redacted] to discuss expected approval of Cyclofem for use in Mexico and requirements for approval of this product in the US.

November 15, 1993—Pre-IND meeting with [redacted] and [redacted] It was noted that pharmacological studies had been conducted outside the U.S. in the 1970s with no teratology or pharmacokinetic studies completed. It was further noted that toxicological requirements might be abbreviated, but that bridging studies between the older formulation and the formulation proposed for marketing would be needed. The sponsor noted that due to the time that had passed, information regarding the manufacture of supplies for the early clinical trials was no longer available. Required biopharmaceutical data and studies were discussed.

June 6, 1995—Pre-NDA meeting with Pharmacia & Upjohn. Limitations of the database were noted and discussed. The sponsor was informed that the data to be submitted in the application was weak and that the lack of case report forms (CRFs) was a serious concern. The possibility of performing several phase IV studies to address these concerns was discussed.

Clinical review of the September 26, 1997 submission revealed deficiencies that resulted in a Non-Approvable decision by the FDA. Of a total of 44 study sites worldwide, only 2 were deemed auditable, making it impossible to verify data collection and adherence to the study protocol or to explain variability in results between study sites.

The quality of the data from the pivotal trials was compromised by many components of the study protocol. Information was lacking on specific patient populations who might not have been at risk for pregnancy at enrollment. Adequate pregnancy testing for method failure was not done, compromising interpretation of efficacy data. Safety data was inadequate. Treatment of bleeding during the pivotal trials confounded the observations of menstrual bleeding patterns associated with the drug and could have confounded efficacy results.

The lack of withdrawal from marketing in any country would imply that serious safety or efficacy concerns with Lunelle™ are not common. However, the pivotal trials presented for the original NDA were not sufficient for a confident assessment of safety or efficacy.

In light of the fact that a large scale U.S. trial, #M/5415/0004, was ongoing at the time of the original review with efficacy as a secondary endpoint, the agency agreed to review the data from this study to assess efficacy and safety and determine approvability based upon this data. The sponsor was advised that a minimum of 200 patients must complete 13 treatment cycles of Lunelle™ with pregnancy testing at discontinuation in order to assess efficacy. Appropriate inclusion of patients at risk of pregnancy, appropriate pregnancy testing, and avoidance of treatment of bleeding disturbances were specified for the trial in telephone conferences on July 10, 1998 and August 4, 1998.

Of the 782 women in the Lunelle™ arm, the sponsor identified 391 women that were believed to comply with all the inclusion/exclusion criteria specified by the Division of Reproductive and Urologic Drug Products (DRUPD). The current submission is presented as a complete response to the deficiencies outlined in the FDA action letter. Components of and requirements from that letter are included as "FDA Specifications" in this review.

2.2 Clinical background and proposed mechanism of action

Injectable contraceptives have been available in some countries for many years. The most widely used injectable contraceptives are the progestin-only methods, depot-medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN). Currently, DMPA is the only injectable contraceptive approved for use in the U.S.

The most common reason for discontinuation of both oral and injectable progestin-only contraceptives is disruption of menstrual bleeding patterns which result in unsatisfactory acceptability profiles for these products. Lunelle™ was designed to provide low, stable serum concentrations of medroxyprogesterone acetate (MPA) for ovulation suppression in addition to providing serum levels of estradiol [administered as estradiol cypionate (E_2C)] that mimic a normal preovulatory estradiol surge, thereby creating more regular monthly bleeding patterns.

If approved, Lunelle™ would be the first monthly injectable contraceptive available in the U.S. and the first such contraceptive containing estrogen in addition to a progestin. Previous dose-ranging studies have demonstrated that ovulation was completely suppressed with the proposed combination of 25 mg MPA and 5 mg of E_2C. With the combination of 12.5 mg MPA and 2.5 mg E_2C, 5% of subjects ovulated in the third treatment month, and with 12.5 mg MPA and 5 mg of E_2C, 42% ovulated in the third treatment month. Although ovulation was not consistently suppressed with those combinations, 25 mg or 12.5 mg of MPA alone inhibited ovulation for at least one month after intramuscular (IM) injection. Furthermore, ovulation

returned earlier with Lunelle™ or 12.5 mg MPA with 2.5 mg E_2C than with either dose of MPA alone. By 90 days after the final injection, 71% of 21 Lunelle™ subjects ovulated, and 90% of subjects taking the low dose (12.5 mg MPA plus 2.5 mg E_2C) ovulated.

Medroxyprogesterone acetate and estradiol have been used in products for the treatment of gynecologic conditions as well as in contraceptive products for decades. The contraceptive mechanism of action of the combination product Lunelle™ is based upon the actions of its component products. MPA is a derivative of progesterone which has little androgenic or anabolic activity and no estrogenic activity. Exogenous administration of MPA suppresses luteinizing hormone (LH) secretion, thereby preventing ovulation. Estradiol cypionate is an ester of 17-β-estradiol that is rapidly hydrolyzed to estradiol (E_2) and ——— ——— upon entering the systemic circulation. This component of Lunelle™ suppresses follicle stimulating hormone (FSH) secretion, thereby preventing emergence of a dominant follicle, stabilizes the endometrium, and potentiates the action of progesterone via increasing the concentration of intracellular P-receptors.

2.3 Human Pharmacology, Pharmacokinetics, and Pharmacodynamics

Lunelle™ Monthly Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) inhibits the secretion of gonadotropins, which, in turn, prevents follicular maturation and ovulation. Although the primary mechanism of this action is inhibition of ovulation, other alterations include progestational effects on the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

After 3 months of treatment with Lunelle™, endometrial biopsies have shown regressed non-functioning endometrium in 9 of 10 studies. In another, the investigator was unable to collect enough tissue for assessment. There was no suggestion of endometrial neoplasia in any study of Lunelle™. These findings indicate that endometrial proliferation is suppressed during treatment with Lunelle™. The effect is reversible after cessation of therapy.

Absorption of medroxyprogesterone acetate and estradiol from the injection site is prolonged after an IM injection of Lunelle™. The time to maximum plasma concentration occurs typically within 1 to 10 days postinjection for medroxyprogesterone acetate and 1 to 7 days for estradiol. Peak concentrations generally range from ——— for MPA and from ——— for E_2. The peak concentrations of 17β-E_2 are similar to the normal pre-ovulatory range and return to untreated baseline by approximately 14 days after injection.

The mean MPA maximum concentration (C_{max}) was higher (average 6 to 12%) when Lunelle™ was injected into the deltoid compared with the gluteus maximus or the anterior thigh muscle. However, the average MPA trough (C_{min}) concentrations and the half-lives ($t_{½}$) were comparable for the three injection sites. Steady-state conditions are achieved after the first injection; no further MPA or 17β-E_2 accumulation occurs beyond the first monthly injection.

The mean AUC_{0-28} estimate was higher in thin/normal women with BMI 18-28 kg/m^2 compared to heavier women, but the average C_{min} and the $t_{½}$ were comparable.

It appears that after Lunelle™ injection, androgen levels steadily decline by the second week after injection, then begin to recover thereafter but remain lower at the end of the injection interval. Mean values for total and free testosterone declined by 38% (day 14 after the 3rd dose) and DHEA-S levels were reduced by more than 17% (day 7 after the 3rd dose). In contrast, sex hormone binding globulin (SHBG) showed a tendency to increase within the first 2 weeks after Lunelle™ injection then decline thereafter. There is a high degree of intersubject variability in these observations.

The pharmacokinetics of MPA and E_2 have been evaluated in different populations in separate studies. With the exception of one study in Thai women, which showed higher C_{max} and shorter time to reach maximum concentration (T_{max}) values for both MPA and E_2, the pharmacokinetics of MPA and E_2 after the

administration of Lunelle were similar in women from various ethnic backgrounds. Although pharmacokinetic differences were observed, the contraceptive efficacy was similar among all women. However, ovulation returned earlier after discontinuation in Thai women, reflecting the more rapid absorption of the drug.

2.4 International Marketing Experience

Human experience with Lunelle™ includes both comparative and introductory studies that have been conducted in over twenty countries. Lunelle™ (also known as CYCLO-PROVERA™, CYCLOFEM™, CYCLOFEMINA™, CycloGeston or Novafem) is currently marketed in several Latin American and Asian countries. Approximately ——— units were sold worldwide during 1996, primarily in Indonesia and Mexico. During the first six months of 1997, ——— units had been sold worldwide, with no withdrawal from marketing in any country for safety reasons.

3.0 CLINICAL STUDY M/5415/0004

3.1 Title

CYCLO-PROVERA™Contraceptive Injection: A Comparative Study of Safety, Patient Acceptability and Efficacy to ORTHO-NOVUM®7/7/7, 28 Tablets

3.2 Study objective

To compare the safety, patient acceptability, and efficacy of Lunelle™ Once-A-Month Contraceptive for up to 60 weeks to a cohort group, using Ortho-Novum 7/7/7, 28 Tablets, matched approximately 8:3 at each study site. The primary variable was the uterine bleeding pattern. Secondary variables were continuation rates, patient acceptability of method use, and prevention of pregnancy. Safety was evaluated by medical event reporting and laboratory evaluations.

3.3 Study Design

Open-label, controlled, non-randomized, multiple fixed dose, prospective matched cohort, parallel group

3.4 Study population

Inclusion Criteria

1. Sexually active females desiring contraception
2. Age 18 through 49 years
3. Must have a negative urine (ELISA) pregnancy test at screen and Week 0 visit, except those subjects who were post-abortion (within 5 days of abortion) or post-partum (within four weeks post-partum)
4. Willing to rely upon Lunelle™ Once-A-Month Contraceptive or Ortho-Novum 7/7/7, 28 Tablets for contraception for at least 60 weeks
5. Willing to enter the study and comply with the study's specific procedures
6. Willing and able to return at the prescribed intervals for follow-up clinic visits
7. Not presently lactating
8. For post-partum subjects, initiation of treatment for contraception could be given up to four weeks post-partum in women who elected not to breast-feed.
9. For post-abortion subjects, initiation of treatment for contraception could be given within 5 days of the abortion.
10. For all other subjects, they must have been menstruating regularly during the last three months (cycle length 25-35 days). This includes those patients who were post abortion, had been placed on oral contraceptives within 5 days of procedure, had a negative pregnancy test at Week 0, and had been menstruating regularly during the three months prior to their pregnancy/abortion.
11. Ability to keep a menstrual and medication diary
12. Ability and willingness to complete Quality of Life Questionnaires (QOL)
13. Ability and willingness to complete subject Patient Satisfaction Questionnaire (PSQ)
14. Signed, informed consent

Exclusion Criteria

1. Concomitant medication exclusion-- use of aminoglutethimide. For coagulation/lipid specialty sites, concomitant medication exclusion -- use of the following lipid lowering drugs: cholestyramine, clofibrate, colestipol, gemfibrizol, lovastatin and similar drugs, niacin, omega three fatty acids (fish oils), and probucol
2. Cervical Cytology: Any epithelial cell abnormality as reported in The Bethesda System, would exclude the subject. Reactive and reparative changes such as atypical squamous cells of undetermined significance (ASCUS) would not exclude the subject.
3. Mammogram results which were suspicious of malignant disease or require six month follow-up. Note: Mammograms were only required for women who were over 35 years of age.
4. Suspected, present or past history of cancer, except carcinoma-in-situ of the cervix which had been treated and basal cell cancer of the skin
5. Suspected/undiagnosed pelvic disease
6. Thromboembolic disease, past or present, or immediate family (parents or siblings) history, with the exception of superficial thrombophlebitis
7. Active or history of cerebral vascular or coronary artery disease
8. Undiagnosed abnormal genital bleeding
9. Known or suspected pregnancy
10. History, within the last 5 years of alcoholism or other drug abuse
11. Cholestatic jaundice of pregnancy or past history of jaundice with prior use of hormonal contraception
12. Current confirmed hypertension: defined as systolic >160 or diastolic > 90
13. Depo Medroxyprogesterone Acetate administered within previous six months
14. Any subject who was hypersensitive to study medications or in whom the investigator believed estrogen and/or a progestin were contraindicated
15. Any subject incapable of understanding the necessary instructions or not reasonably expected to complete the 60 week study
16. Concurrent use of other investigational medications
17. Previous participation in this study
18. Active hepatic or renal disease
    18.a. Hepatic disease defined as having an aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), gamma glutamyltransferase (GGT) 2.5 times upper normal; total bilirubin greater than 1.5 mg/dL
    18.b. Renal disease defined as having a creatinine greater than 1.5 mg/dL
19. Fasting blood glucose > 120 mg/dL or random blood glucose > 160 mg/dL
20. Women over 35 years of age who smoke cigarettes

FDA specification: The trial should provide data on a minimum of 200 subjects completing 13 cycles of product use with pregnancy tests at study discontinuation (minimum requirement) and/or at monthly intervals (preferred).

Sponsor's statement:

"The original protocol required a pregnancy test before treatment began and at the final visit, and no woman in this trial was pregnant when she began treatment with Lunelle™. After enrollment was closed and the trial was about 75% complete, the protocol was amended (per FDA recommendation) to require a pregnancy test before each treatment. Women who discontinued without a final pregnancy test were contacted retrospectively to determine whether they had become pregnant since leaving the trial. There were 14 women who met the criteria as described above but did not have a pregnancy test at their final visit. Those 14 women were not included in the 391 noted above who met all of the specified criteria."

Reviewer's comment:

The protocol specified a pregnancy test at the screening visit and then as needed for noncompliant patients who wished to continue the study. It did not require pregnancy testing at discontinuation or at the final study visit. An amendment on 7/17/98 added pregnancy tests at each study visit and at the final visit.

FDA specification: If emergency contraception is allowed, provide a data analysis plan that incorporates this use.

Sponsor's response:
" Emergency contraception was not allowed. Review of concomitant medications reveals no indication of any patient receiving a known chemical abortifacient for pregnancy termination during the trial. One woman in the Lunelle™ group took several doses of methotrexate for rheumatoid arthritis."

FDA specification: Along with the usual inclusion/exclusion criteria, the following criteria should apply for these 200 women.

- *Subjects should be in a heterosexual relationship and at risk for pregnancy*

  Sponsor's response:
  " Women were not asked to provide marital status or information regarding frequency of heterosexual activity or number of partners. However, the following information implies that the women enrolled considered themselves to be at risk for pregnancy:

  All 782 women agreed to rely on Lunelle™ as a method of birth control.
  One or more prior pregnancies were reported by 64% of the women treated with Lunelle™.
  Data at screen indicate that 93% used some form of contraception prior to enrollment.
  86% of participants at visit 1 indicated that their partners knew that they were using Lunelle™."

  Reviewer's Comment:
  However, at each visit 8.9% to 16.4% of participants responded "not applicable" to condom use, and review of selected CRFs showed this response to indicate no sexual activity for the interval. 12 women who completed 15 cycles answered "every time" or "not applicable" to condom use at every visit.

- *Subjects enrolled post-abortion and post-partum should have experienced at least one normal menstrual period prior to initiation of treatment.*

  Sponsor's response:
  "Inclusion criteria specified that women who entered the trial post-abortion or postpartum have been menstruating regularly during the 3 months prior to the pregnancy. This differs from the FDA requirement that women enrolled post-abortion or postpartum should have experienced at least one normal menstrual period prior to initiation of treatment. 48 women who received at least 13 Lunelle™ injections were post-abortion or post-partum and had their last menstrual period more than 35 days before the first injection." Those 48 women were not included in the 391 noted above who met all of the specified criteria.

- *Subjects using injectable contraceptives should have a washout period of at least 10 months prior to enrollment.*

  Sponsor's response:
  "Exclusion criteria specified that women who had received an injectable contraceptive within the past 6 months be excluded, while the FDA requirement specifies a 10-month washout period. Only 3 women who completed 13 cycles had received an injectable contraceptive without a 10-month washout period prior to the first injection of Lunelle™."

Reviewer's Comments:

- **The possibility of decreased fertility in women over age 35 may compromise evaluation of efficacy in these individuals but provides valuable information for women at risk for pregnancy in the pre-menopausal period.**

- **As previously noted, several aspects of study design (such as lack of adequate pregnancy testing) and inclusion and exclusion criteria (e.g., inadequate washout periods after hormonal contraception) were brought to the sponsor's attention after trial initiation.**

Sponsor's additional response:
"Of the 782 women treated with Lunelle™ in study /0004, 391 women meet all the criteria specified by FDA. Over the 60-week treatment period (15 treatment cycles), 782 women received a total of 8920 monthly injections of Lunelle™. Of these, 456 completed 13 or more cycles, and 434 completed 15 cycles."

Reviewer's Comments:
FDA analysis of eligible patients revealed the following:

782 subjects enrolled in the Lunelle™ arm at study initiation.

- **456 completed at least 13 cycles of Lunelle™. (326 discontinued before completing 13 cycles.)**
- **434 completed 15 cycles.**
- **22 completed at least 13 but less than 15 cycles.**

Of those subjects completing 15 cycles of Lunelle use, the following were excluded from efficacy analyses for the reasons listed below.

- **5 Lunelle™ subjects who completed 15 cycles did not have a pregnancy test at their final visit.**
- **3 Lunelle™ subjects who completed 15 cycles had received a prior injectable contraceptive without a 10 month washout period.**
- **57 of those who completed 15 cycles were age 35 or older and therefore may have been at lower risk for pregnancy.**
- **At each visit 4.8% to 8.9% of Lunelle™ users reported using condoms "every time," 3.2% to 10.3% "sometimes", and another 8.9% to 16.4% of Lunelle™ subjects answered "not applicable" to condom use. Review of a subset of CRFs revealed that these individuals were not sexually active during the interval in question. Only 70.6% to 77.6% of subjects at each visit "never" used condoms. Therefore, efficacy of Lunelle™ alone could only be assessed in these individuals. 12 subjects who completed 15 cycles used condoms "every time" or responded "not applicable" at every visit.**
- **One Lunelle™ subject who completed the trial had taken Provera® to treat heavy menstrual bleeding.**
- **46 subjects who were postpartum or post-abortion and completed 15 cycles started the trial with more than 35 days since their last menstrual period and therefore may not have been ovulating and not at risk for pregnancy.**
- **10 subjects who were not postpartum or post-abortion and who completed the trial did not have regular menstrual cycles (e.g., cycle length 25-35 days) during the 6 months prior to the first injection.**

After subtracting subjects who may have been at reduced risk or not at risk for pregnancy as described above, there were 300 women who completed 15 cycles of Lunelle™ use and who met all of the criteria specified by the FDA nonapproval letter. However, it should be noted that 175 of the 348 subjects who discontinued before 15 cycles of use had no pregnancy test at discontinuation. 72 Lunelle subjects who discontinued without a final pregnancy test were not successfully contacted to determine pregnancy status. This has implications for the efficacy determination as described on pages 13-14 and 30.

Demographics of the study population
The Lunelle™ group was 67.9% White, 15.5% Hispanic, 13.6% Black, 2.4% Asian, and 0.6% other. The Ortho-Novum 7/7/7 group was 74.1% White, 8.1% Hispanic, 15.6% Black, 1.2 % Asian, and 0.9% other.

12.8% of the Lunelle™ group and 13.1% of the Ortho-Novum 7/7/7 group were age 35 or older.

44.4% of the Lunelle™ users and 33.6% of the Ortho-Novum 7/7/7 users had previous term pregnancies.

41.3% of the Lunelle™ users and 24.3% of the Ortho-Novum 7/7/7 users had previous abortions.

43.7% of Lunelle™ users and 56.3% of Ortho-Novum 7/7/7 users reported using hormonal contraception in the 30 days prior to the trial. A 2-month washout period was not required.

30.6% of Lunelle™ users and 25.2% of Ortho-Novum 7/7/7 users had a body mass index (BMI) > 27.3 kg/m^2 at baseline.

Reviewer's comment:
Demographic characteristics of the two treatment groups appear comparable; however, because the trial was not randomized comparability between the treatment groups was not required.

3.5 Screening Period

During the screening period, informed consent was obtained from all trial participants. A medical history was taken and a complete physical examination, including breast and pelvic examination was performed to assess the subject's eligibility to participate. Cervical Cytology was obtained on all subjects who did not have documentation of the procedure in the previous six months meeting entrance criteria. Mammography was performed on all subjects over age 35 years who did not have documentation of the procedure in the previous six months meeting entrance criteria. Baseline laboratory studies were performed, including urine pregnancy test, serum chemistry panel, hematology, urinalysis, and at designated study sites serum lipid measurements and coagulation profile.

3.6 Treatment Period

Subjects in this study received their choice of either Lunelle™ Once-A-Month Contraceptive Injection or Ortho-Novum 7/7/7, 28 Tablets every 28 days plus or minus 5 days, according to the protocol. Each participant was given a diary card to record bleeding patterns and instructed regarding its completion. Lunelle™ subjects received their first injection between cycle days 1 and 5. Ortho-Novum 7/7/7 subjects were instructed to take their first tablet on the first day of menses.

Study visits were conducted every 28 days plus or minus 5 days. At each visit weight and blood pressure were taken. Diary Cards were evaluated. Interval History was taken for concurrent medications and adverse events. Study medication compliance was monitored and additional medication given. As of 7/20/98, per FDA recommendation, a urine pregnancy test was required at each visit, including the final visit and at discontinuation.

Quality of Life Questionnaires and Patient Satisfaction Questionnaires were completed at weeks 0, 20, 40, and 60. Blood chemistries, hematology, urinalysis, and at designated sites lipids and coagulation profiles were repeated at weeks 20, 40, and 60. Mammography was repeated at week 60 for all subjects over age 35.

At the final visit (week 60), all subjects had a general history and physical, including breast and pelvic examination and cervical cytology.

During the trial, patients were discontinued for any of the following reasons:

1. diagnosis of cancer, except for carcinoma-in-situ of the cervix or basal cell carcinoma of the skin that has been treated
2. subject request
3. lack of compliance
4. clinical or laboratory evaluation resulting in the investigator's determination that it is in the best interest of the subject to be removed from the study.

5. use of sex hormone therapy or concomitant medications specifically excluded during the study
6. pregnancy

Women who discontinued without a final pregnancy test prior to implementation of the 7/98 protocol amendment were contacted retrospectively to determine whether they had become pregnant since leaving the trial.

Reviewer's Comment:
As described previously, 72 women who discontinued without a final pregnancy test were not successfully contacted.

Any subject who discontinued medication to become pregnant was required to notify the study coordinator if pregnancy was achieved within 12 months after discontinuation. The time from discontinuation to presumed date of conception was calculated if possible.

3.7 Statistical procedures

All subjects who received at least a single injection of Lunelle™ or a single package of Ortho-Novum 7/7/7 were included in an Intent-to-Treat Analysis. Since this study is a non-randomized open-label design, the comparison between the two treatment groups is primarily based on descriptive statistics such as percentage, means, standard deviations, and ranges. P-values are considered as additional descriptive statistics or indices only and are not treated as a formal basis for hypothesis testing.

3.8 Evaluation criteria

The primary endpoint for this study was the overall rate of irregular bleeding pattern during the 60 weeks of treatment with the emphasis being placed on the last two reference periods. Variables include the following:

occurrence of irregular bleeding pattern
questions in the Quality of Life Questionnaire and Patient Satisfaction Questionnaire
reasons for discontinuation from the study
pregnancy due to treatment failure
time to discontinuation

Reviewer's comment:
Because previous trials in the original NDA submission were considered insufficient, FDA agreed to accept the current trial for assessments of both efficacy and safety.

Safety variables

Medical events by body system
Treatment emergent signs and symptoms
Change of laboratory assays
Change in physical and gynecological exams or cytology

3.9 Withdrawals and compliance

Discontinuation for a medical reason was highest for women who had used a hormonal form of contraception within the 30 days prior to enrollment and received Lunelle™ and lowest for women who had used hormonal contraceptives prior to enrollment and received Ortho-Novum 7/7/7, suggesting a positive survivor bias for Ortho-Novum 7/7/7 and a negative selection bias for Lunelle™.

Discontinuation rates varied by investigational site. For sites enrolling 34 or more subjects, the discontinuation rate ranged from 20% to 59%. At these sites, discontinuation for a medical reason ranged from 3% to 31% and for a nonmedical reason from 3% to 40%.

18 Lunelle™ users and 5 Ortho-Novum 7/7/7 users were discontinued due to protocol violations.

Compliance for Lunelle™ users was measured by recording dates of injections and calculating the interval between injections. Injection intervals ranged from 19 to 48 days. 99.3% of injection intervals ranged from 23 to 40 days, and 96.8% ranged from 23 to 33 days, the preferred interval. 70% of patients received all injections at 23 to [illegible] day intervals.

Reviewer's comment:
30% of Lunelle™users in this controlled trial did not consistently comply with the recommended dosage schedule. This would suggest the possibility of even lower compliance with typical use.

Compliance for Ortho-Novum 7/7/7 users was measured by active pill counts from returned packages. 98.6% of the pill packages were returned with no active tablets remaining. 86% of patients never returned more than one active pill during any cycle.

4.0 EFFICACY ANALYSIS

4.1 Pregnancy Rates

FDA specification: Life Table pregnancy rates as well as a Pearl Index should be calculated as measures of failure rates during the trial.

Sponsor's response:
"No pregnancies were reported in women receiving Lunelle™. Therefore, these pregnancy rates are 0.0%."

Reviewer's Comments:
- **This 0.0% pregnancy rate applies only to subjects in this particular trial who had pregnancy tests at their final visit.**
- **Some of the participants in this and previous trials may not have been at risk for pregnancy throughout their entire participation. Therefore, the rates achieved in these studies may or may not be reflective of what would be seen with typical use.**

There were no pregnancies in Lunelle™ users in the current study, giving both a Pearl Index and Life Table Rate of 0%. A total of 11 pregnancies were reported in the WHO Multicountry Trial, Egypt Trial, China Trial, and the supportive controlled and uncontrolled trials submitted in the original NDA. These include data from over 18,000 women, representing over 155,500 woman-months of exposure to Lunelle™. Life Table pregnancy rates for the individual trials range from 0 to 0.2 % and the Pearl Index ranges from 0 to 0.24.

Reviewer's comment:
The accuracy of these rates is questionable due to deficiencies noted in the previous trials.

Of women who discontinued before completing the trial, no exit pregnancy test was conducted for 175 (50.3%) of 348 Lunelle™ users and 68 (65.4%) of 104 Ortho-Novum 7/7/7 users. A retrospective review was conducted to document each patient's pregnancy status at discontinuation. Seven pregnancies were identified in women who had used Lunelle™ in the trial. Based on estimated date of delivery or date of conception, none of these women were pregnant at the time they discontinued the trial.

PREGNANCIES IN PATIENTS WHO DISCONTINUED THE STUDY

First and Last Dose Reason Discontinued	Estimated Date of Delivery	Estimated Date of Conception	Pregnancy Status	Approx. Time Last Dose to Conception
1. 7/8/97-2/18/98 To get pregnant	4/9/99	7/22/98	Continued	5 months
2. 6/13/97-7/11/97 Noncompliance	1/26/99	5/3/98	Therapeutic Abortion	10 months
3. 10/1/97-10/29/97 Non-serious AE	2/18/99	5/25/98	Continued	7 months
4. 5/28/97-11/13/97 Lost to follow-up	4/25/99	6/31/98	Therapeutic Abortion	7.5 months
5. 6/24/97-11/6/97 Lost to follow-up	1/22/99	4/30/98	Continued	6 months
6. 8/28/97-12/17/97 To get pregnant	5/5/99	8/11/98	Continued	8 months
7. 9/14/97-2/8/98 Non-serious AE	3/3/99	5/26/98	Therapeutic Abortion	3.5 months

Reviewer's Comments:

- **As previously described, 72 women who discontinued their participation without an exit pregnancy test were not successfully contacted. Therefore, no conclusion can be drawn regarding their pregnancy status at discontinuation, and efficacy cannot be ascertained for approximately 10% of the study population using Lunelle™.**
- **5 Lunelle™ users who completed 15 cycles did not have a pregnancy test at their final visit.**

Two pregnancies occurred in the Ortho-Novum 7/7/7 group, giving a Life Table pregnancy rate of 1.0% and a Pearl Index of 0.8 per 100 woman-years.

One unintended pregnancy was reported at visit 3 in an Ortho-Novum 7/7/7 user. She entered the trial within 3 months postpartum and had been using a nonhormonal method of contraception. Her pregnancy ended with a spontaneous abortion at about 6 weeks gestation. Another unintended pregnancy was reported at the end of the trial (week 60) in another Ortho-Novum 7/7/7 user. Her pregnancy was ongoing at the time of the report.

4.2 Patient Acceptance

In general, women who selected Lunelle™ were somewhat less likely to be satisfied with the treatment than those who selected Ortho-Novum 7/7/7. However, the Ortho-Novum 7/7/7 group was heavily weighted with women who had used an oral contraceptive in the month prior to the start of the study and who were likely already satisfied with the use of an oral contraceptive. In the Egypt study (from the WHO trial presented in the original NDA), comparing Lunelle™ with another monthly injectable contraceptive, Mesigyna, satisfaction with the method was rated at 96.1% for continuers and 61.5% for discontinuers. In the present study, it was nearly the same, 95.4% and 67.8% respectively, in the Lunelle™ group. In the present study, 75.1% of completers in the Lunelle™ group would definitely recommend the method to a friend. About 60% gave it the most favorable rating.

4.3 Discontinuation Rates

Over the entire 60 week treatment period, 45% of Lunelle™ users and 32% of Ortho-Novum 7/7/7 users discontinued from the trial. Discontinuation rates for Lunelle™ by Life Table analysis were 42% (13 treatment cycles) and 45% (15 cycles). These rates were higher than discontinuation rates for Lunelle™ users in the WHO Multicountry, Egypt, and China Trials, which ranged from 26% to 39% by 1-year Life

Table analysis. Studies in Brazil and in Colombia revealed 1-year life table discontinuation rates of 49% and 58%, respectively. The higher discontinuation rates in the US trial were for nonmedical reasons and medical reasons other than amenorrhea or bleeding-related problems.

One-year discontinuation rates in the US trial /0004 were the following:

amenorrhea	1.0 %
Bleeding-related problems	6.1%
Other medical problems	17.6%
Nonmedical	26.7%
Total discontinuations	41.7%

Reviewer's comment:
As noted by the sponsor, some or all of these differences in discontinuation rates may be related to cultural differences between the participants in the different trials.

4.4 Bleeding Patterns

FDA specification: Complete information on bleeding pattern changes over a one-year period of study drug use should be submitted

Sponsor's response:
" Over a period of 90 days, the "average woman" using Lunelle™ would experience 3 bleeding/spotting episodes (range 2-3), each lasting about 6 days (range 4-8). During that same 90 days, she would experience 3 intervals free of bleeding or spotting (range 2-3), each lasting 22 days (range 19-27 days). She could expect her menstrual cycle to be about 29 days (range 26-32 days). With continued use of Lunelle™, the incidences of "frequent," "irregular," and "prolonged" bleeding decrease over time while amenorrhea and "infrequent" bleeding increase over time."

Participants kept menstrual diaries during the trial. Data from these diaries were analyzed to determine the rate of clinically undesirable bleeding patterns. Unanticipated menstrual cycle changes were to be reported as adverse events and discontinuation due to menstrual cycle changes has been tabulated.

Clinically undesirable bleeding patterns
Bleeding patterns were classified as "clinically undesirable" by Belsey's criteria using the following definitions:

- Amenorrhea: no bleeding or spotting throughout the reference period.
- Prolonged bleeding: at least 1 bleeding/spotting episode lasting more than 9 days.
- Frequent bleeding: more than 4 bleeding/spotting episodes within the same reference period
- Infrequent bleeding: less than 2 bleeding/spotting episodes in the same reference period.
- Irregular bleeding: a range of bleeding/spotting-free intervals exceeding 17 days.
- Combinations of the above categories: prolonged and infrequent, prolonged and frequent, prolonged and irregular.

Women using Lunelle™ experienced a mean of 3 bleeding episodes over a period of 90 days, each lasting a mean of 6 days. They had a mean of 3 intervals free of bleeding or spotting, each lasting a mean of 22 days. The mean cycle length was 29 days, with a range of 26 to 32 days.

Clinically undesirable bleeding patterns by Belsey's criteria were reported by 68.6% of Lunelle™ users vs. 42.6% of Ortho-Novum 7/7/7 users in the first 90-day reference period and 58.6% of Lunelle™ users vs. 23.7% of Ortho-Novum 7/7/7 users in the fourth (final) reference period, corresponding to 9 to 12 months of use.

"Normal" bleeding patterns were experienced in all five reference periods by only 9.0% of Lunelle™ users compared to 36.8% of Ortho-Novum 7/7/7 users. In the third through fifth reference periods, 18.8% of Lunelle™ users and 59.9% of Ortho-Novum 7/7/7 users had "normal" bleeding patterns.

The median average length of bleeding/spotting episodes is longer with Lunelle™ (6.3 days vs. 4.3 days for Ortho-Novum 7/7/7), and the range of length of bleeding/spotting episodes is 4 days for Lunelle™ vs. 2 days for Ortho-Novum 7/7/7.

Reviewer's comment:
Although the mean and median number and duration of bleeding episodes are suggestive of normal menstrual cycles, 58.6% of Lunelle™ users reported clinically undesirable bleeding patterns in the fourth (final) 90-day reference period. 4.1% reported amenorrhea in the fourth reference period. These rates of clinically undesirable bleeding in Lunelle™ users are higher than those reported in previous clinical trials (30-51% at one year).

Bleeding changes over time
As expected, the median number of bleeding/spotting days in the first reference period is higher than in all other reference periods because treatment was to begin during menses.

With continued use of Lunelle™, the incidences of "frequent" and "prolonged" bleeding decreased over time while amenorrhea and "infrequent" bleeding increased over time. The percentage of subjects experiencing "irregular" bleeding remained at about 30% throughout the first four reference periods. "Prolonged" bleeding occurred in 37% in the first reference period and decreased to 25% by the fourth reference period. "Frequent bleeding" occurred in 20% during the first reference period and dropped below 6% during the remaining reference periods.

Reviewer's comment
Contrary to the sponsor's assessment of bleeding pattern data, the incidence of irregular bleeding in Lunelle users did not decrease with time, but remained constant at 30%.

Menorrhagia
Menorrhagia was reported as an adverse event in 6.6% of Lunelle™ users (vs. 0.3% of Ortho-Novum 7/7/7 users) and resulted in discontinuation for 1.5%.

"Vaginal hemorrhage" was listed as an adverse event for 21 Lunelle™ subjects, and "uterine hemorrhage" for another 2. These were all described as heavy, excessive, or prolonged vaginal bleeding. None of these were considered serious adverse events, and none was associated with a clinically meaningful decrease in hematocrit and hemoglobin. Two patients were treated with Provera® tablets, one with Premarin and Lutoral, and another with Methergine. No hospitalizations or blood transfusions were required in these subjects.

Amenorrhea
Amenorrhea was reported in 1.0% of Lunelle™ users in the first 90-day reference period and 4.1% in the fourth period (vs. 0% of Ortho-Novum 7/7/7 users in the 4th reference period). It led to discontinuation in 0.8% of Lunelle™ users. The one-year discontinuation rates for amenorrhea in earlier trials were 3.4% in Brazil and 8.1% in Colombia. The baseline rate of amenorrhea in untreated subjects is 1.3-1.6%.

Reviewer's comment:
The incidence of amenorrhea with Lunelle use (4.1%) is significantly lower than that typically seen after one year of DMPA use (55%).

Factors associated with bleeding pattern
Prior hormonal contraceptive use appears to predict a higher proportion of "normal" cycles in both treatment groups, particularly during the first reference period. In both groups, the occurrence of "prolonged" bleeding during the first 90 days was more frequent in women who had used a nonhormonal contraceptive in the 30 days prior to the trial.

When bleeding data are stratified by BMI, lighter women (BMI ≤ 27.3 kg/m^2) experienced more bleeding/spotting days and more prolonged bleeding, and heavier women experienced "infrequent" bleeding with continued use of Lunelle™. Higher BMI was associated with more "irregular" bleeding in Lunelle™ users, while lower BMI predicts "irregular" bleeding in Ortho-Novum 7/7/7 users.

In the current study, Asian/Pacific Islander subjects tended to experience more prolonged bleeding throughout the study. Of all racial groups studied, Asian/Pacific Islander subjects experienced the highest median and mean number of bleeding/spotting days in the fifth 3-cycle reference period and the highest maximum length of bleeding/spotting episodes. However, the number of Asian/Pacific Islander subjects in the study was relatively small .

Reviewer's comment
Previous studies have shown relatively higher C_{max} and shorter T_{max} values for both MPA and E_2C in Thai women, indicating faster drug absorption. This could influence bleeding patterns in these women.

"Irregular" bleeding in the first two reference periods occurred more frequently among black women using Lunelle and among white women using Ortho-Novum 7/7/7. Hispanic women experienced progressively lower rates of "prolonged" and "irregular" bleeding in the first through fourth reference periods. "Prolonged" bleeding in white women also declined between the second and third reference periods. Menorrhagia was reported as an adverse event in 0.8% of Hispanic subjects, 4.7% of black subjects, and 7.6% of white subjects. Amenorrhea was most frequent in black subjects (5.7% vs. 2.5% in white and 0.8% in Hispanic subjects).

Discontinuation for bleeding-related problems

Bleeding disturbances led to discontinuation for 67 (8.6%) of 775 Lunelle™ users in this trial. The one-year Life Table bleeding-related discontinuation rate was 7.2% for Lunelle™ users and 1.9% for Ortho-Novum 7/7/7 users. In the previous WHO trials, the one-year discontinuation rates for bleeding-related problems by life table analysis were 6.3% (Multicountry), 7.8% (Egypt), and 12.7% (China). A Brazil study reported a 9.2% discontinuation rate for menstrual disturbances, and one in Colombia reported a discontinuation rate of 5.1%.

Bleeding patterns did not predict discontinuation from this trial for either treatment group. Women who experienced clinically undesirable bleeding patterns were not more likely to discontinue from the trial, and women who discontinued the method of use after two, three, or four reference periods had experienced no change in the incidence of worsening patterns over time.

Reviewer's comment:
The lack of correlation between undesirable bleeding patterns and discontinuation may be indicative of the effect of trial participation and may not predict discontinuation patterns post-approval.

FDA specification: Plans for management and analyses of bleeding disturbances during the trial should be described.

Sponsor's response:
"No specific management of bleeding disturbances was specified in the protocol. Women experiencing bleeding disturbances they considered unacceptable could withdraw from the trial at any time. One subject took Provera® Tablets for 2 days to treat heavy menstrual bleeding, which resolved, and the subject completed the trial with no subsequent adverse events reported. No other women were identified who used hormones during the trial or treated menstrual bleeding with hormones."

Reviewer's Comment
An additional Lunelle™ subject was identified who took Provera for heavy bleeding and discontinued after 7 cycles of use. One subject who completed 13 cycles took Premarin and Lutoral for heavy bleeding in one cycle. Another took Methergine for heavy bleeding and discontinued after 10 cycles.

4.5 Efficacy Analysis Stratified by Body Mass Index

FDA specification: Analyses of efficacy data stratified by body mass index should be provided.

Sponsor's response:

"Because no pregnancies occurred in women treated with Lunelle™, the failure rate is 0.0% regardless of BMI."

"Bleeding pattern data have been stratified by BMI at baseline. At each of the 90-day reference periods, Lunelle™ users with BMI of 27.3 kg/m^2 or less had a higher median number of bleeding/spotting days and a wider interquartile range than those with a higher BMI. Data also suggest that a heavier woman might be more likely to experience "infrequent" bleeding the longer she used Lunelle™."

Reviewer's comment:

Further discussion of bleeding pattern changes with Lunelle™ use is included in section 4.4 on pages 15-17.

5.0 SAFETY ANALYSIS

FDA specification: Data on the following parameters following 1 year of study drug exposure should be submitted: lipids, serum glucose/carbohydrate metabolism, blood pressure, hepatic function, weight change (expressed in increments of 5 pounds), body mass index (BMI), coagulation factors, hemoglobin and hematocrit.

5.1 Lipids

Sponsor's response:

"This study shows a decrease at final visit (last observation) in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides, with maintenance of the total cholesterol/HDL ratio for women treated with Lunelle™. There are week-to-week variations in lipids, reflecting the hormonal components of Lunelle™. Therefore, the timing of sampling for lipid evaluation is critical when following a patient's lipid values."

At eight centers, lipid parameters were assessed at screen and at weeks 20, 40, and 60 (or at the final visit). In a subset of these subjects, blood samples were also collected at weeks 21,22, and 23 to investigate lipid changes that may reflect varying hormone levels during these time periods. No dietary restrictions were specified. Blood samples were obtained after a 14-hour fast.

This study shows a decrease at final visit in total cholesterol, LDL-cholesterol, HDL-cholesterol, apolipoprotein AI, apolipoprotein AII, apolipoprotein B, and triglycerides, with no change in the total cholesterol/HDL ratio for women treated with Lunelle™. This suggests no significant impact of these parameters on cardiovascular disease risk.

There are week-to-week variations in lipids, reflecting the hormonal components of the product. Decreases in all lipid parameters were seen in the first week of the index cycle. During the third week of the injection interval, the lipid values generally returned close to those seen at the start of the cycle.

For the 59 Lunelle™ users and 21 Ortho-Novum 7/7/7 users who had not previously used a hormonal method of contraception, Lunelle™ and Ortho-Novum 7/7/7 had substantially different effects on total cholesterol, total triglycerides, and apolipoprotein B, all of which decreased in Lunelle™ users and increased in Ortho-Novum 7/7/7 users. Decreases in apolipoproteins AI and AII were seen with both drugs, with a greater decrease in apolipoprotein AI with Lunelle™. HDL-cholesterol decreased in both groups. No change in the total cholesterol/HDL ratio was seen with either drug.

Lunelle™ users who had previously used a hormonal method of contraception experienced greater reductions in total cholesterol and total triglycerides than those who had not did, suggesting that some of the unfavorable changes induced by the prior method may have been reversed during use of Lunelle™.

Hyperlipidemia was recorded as an adverse event in cycle 14 for 1 (0.1%) of 775 Lunelle users. This 31-year-old black woman had a history of mild elevation of total cholesterol in the remote past. No lipid-lowering drugs were listed. Her weight increased from 152.2 lb at screen to 164.5 at week 60. Review of CRTs reveals no abnormal laboratory values.

Four Lunelle™users and four Ortho-Novum 7/7/7 users had significant and clinically relevant lipid values (total cholesterol > 240 mg/dl, HDL-cholesterol < 35 mg/dL, LDL-cholesterol > 160 mg/dL, or total triglycerides > 400 mg/dL).

- A 34-year-old subject with BMI of 32.7 kg/m^2 had total cholesterol of 83-98 mg/dL throughout the study. Her HDL was low throughout at 21-25 mg/dL (normal 25-75 mg/dL). Her total cholesterol/HDL ratio was 3.5 to 5.7 (normal 0-4.5).
- A 21-year-old subject had normal total cholesterol levels of 164 mg/dL at screen and 171 mg/dL at final visit. Her HDL-cholesterol levels were normal at 34 and 35 mg/dL at screen and final visit, respectively, and total cholesterol/HDL ratio was slightly above normal at 4.82 at screen and 4.88 at her final visit. She developed cholelithiasis and required laparoscopic surgery during the trial.
- A 24-year-old subject who completed the study had normal cholesterol levels of 196 mg/dL at screen and 178 mg/dL at final visit. Her HDL-cholesterol levels were normal at 36 mg/dL at both screen and final visit. Her total cholesterol/HDL ratios were elevated at 5.4 at screen and 4.9 at final visit. She had no adverse events related to her lipid profile.
- A 32-year-old subject who completed the study had normal cholesterol levels of 212 mg/dL at screen and 237 mg/dL at final visit. Her HDL-cholesterol levels were normal at 44 mg/dL at screen and 52 mg/dL at final visit, and total cholesterol/HDL ratios were elevated at 4.82 at screen and 5.55 at final visit. She reported no adverse events related to her lipid profile.

Reviewer's comment:
This study shows a decrease in total cholesterol, LDL-cholesterol, HDL-cholesterol, apolipoproteins A-I, A-II, and B, and triglycerides and no change in the total cholesterol/HDL ratio. These findings suggest no significant effect on cardiovascular risk.

5.2 Serum glucose/carbohydrate metabolism

Sponsor's Response:
"Women with an elevated fasting or random blood glucose level at baseline were excluded from participation. Differences in median values over time were generally small and not clinically relevant at 20, 40, and 60 weeks. No adverse events were reported which could be attributed to abnormal carbohydrate metabolism."

~~Serum glucose levels were obtained on all participants at screen and weeks 20, 40, and 60. Women with a~~ fasting blood glucose level above 120 mg/dl or a random blood glucose level over 160 mg/dl were to be excluded from participation. Differences in median values of serum glucose from baseline to weeks 20, 40, and 60 were generally small and not clinically relevant. 1.0% of Lunelle™ users and 0.8% of Ortho-Novum 7/7/7 users had a normal glucose level at screen and a value exceeding the normal limits at week 60. No adverse events were reported which could be attributed to abnormal carbohydrate metabolism, and there were no women who had serum glucose above 160 mg/dl at the final evaluation.

Reviewer's comment:
As noted by the sponsor, there is no evidence that Lunelle™ affects carbohydrate metabolism.

5.3 Blood pressure

Sponsor's Response:

"Women with confirmed hypertension were excluded from participation. There was no change from baseline to week 60 in mean systolic or diastolic blood pressure. Hypertension was recorded as an adverse event for 1.0% of 318 women using Ortho-Novum 7/7/7 and for 0.6% of 775 women using Lunelle™."

Women with confirmed hypertension, defined as systolic above 160 mmHg or diastolic above 90 mmHg, were to be excluded. There was no change from baseline to week 60 in mean systolic or diastolic blood pressure. Hypertension was recorded as an adverse event for 5 (0.6%) of 775 women using Lunelle™ (none discontinued due to hypertension) and 6 (1.9%) of 318 women using Ortho-Novum 7/7/7 (3 discontinued due to hypertension).

- A 35-year-old subject with blood pressure 128/72 at screen had a single elevation to 140/92 at her 15th injection. She completed the study with a final BP of 140/78
- A 43-year-old with blood pressure 140/80 at screen had numerous elevations with the maximum blood pressure 150/100 at the time of her 7th and 8th injections. She completed the study with a blood pressure of 130/90.
- A 19-year-old subject with blood pressure 110/80 at screen had a single elevation to 130/90 at the time of her 5th injection. She completed the study with a final blood pressure of 110/80.
- A 40-year-old subject with blood pressure of 142/100 at screen also had an elevation to 160/100 at her 2nd injection. She discontinued after her 8th cycle because her husband had a vasectomy. Her final blood pressure was 134/88.
- A 41-year-old subject with blood pressure 120/80 at screen had no documented elevated blood pressures but took vasotec one time after her 13th injection. Her blood pressure was 90/62 at the time of her 11th injection. She completed the study with a final blood pressure of 126/70.

Reviewer's comment:

As noted by the sponsor, there is no indication of any statistically or clinically significant effect of Lunelle™ on systolic or diastolic blood pressure.

5.4 Hepatic function

Sponsor's Response:

"Median ALP value increased from 66.0 U/L at screen to 74 U/L at week 60, and median GGT increased from 16.0 U/L at screen to 19.0 U/L at week 60 in Lunelle™ users. Clinically significant abnormal hepatic function tests, defined as at least three times the upper limit of normal, were recorded in three Lunelle™ users. Two additional Lunelle™ users had elevated ALT noted as an adverse event. Cholecystitis was reported in 3 Lunelle™ users and cholelithiasis in 2."

The median alkaline phosphatase (ALP) value in Lunelle™ users increased from 66.0 U/L at screen to 74.0 U/L (normal 29-150 U/L) at week 60. The median GGT increased from 16.0 U/L to 19.0 U/L (normal 2-65 U/L). Clinically significant abnormal hepatic function tests, defined as values at least 3 times the upper limit of normal, were recorded in 4 (0.5%) Lunelle™ users (and 2 Ortho-Novum 7/7/7 users).

- A 43-year-old —— had an elevated serum ALP at screen (276 U/L). Her first injection was ——. The elevation continued throughout the study and was reported as an adverse event —— (ALP 395 U/L). She left the study early because she was moving out of state. Her final labs on —— showed ALP 416 U/L. Her bilirubin levels and other hepatic enzyme levels were normal. No follow-up information is available.

- A 27-year old — had normal liver function tests at screen. At the week 60 visit, her AST was elevated to 263 U/L (0-41 U/L), ALT 79 U/L (0-45 U/L), GGTP 78 U/L (2-65 U/L), ALP 127 U/L (29-150 U/L), and bilirubin normal. Her first injection was —— She completed the study with her final injection ——. Her only adverse event was flu virus ——. She took no concomitant medications. She had a history of cholecystectomy with an "infected liver" in ——. It is unknown if these laboratory tests were repeated or if additional evaluation was undertaken.

- A 22-year old ♂ had normal liver function tests recorded at screen. Her ALT and GGTP were elevated (160 and 254) at week 40 but normalized by the final visit. She completed the study. There were no adverse events or concomitant medications recorded.

- A 30-year-old ♂ with BMI 28.1 kg/m^2 who was on oral contraceptives at baseline had an elevated ALT of 58 U/L (0-45 U/L), GGT of 67 U/L (0-65 U/L) and creatinine of 4.4 mg/dL (0.6-1.5 mg/dL) at week 20. All laboratory values returned to normal, and she completed 15 cycles. She had no related adverse events.

Two Lunelle™ users had elevated ALT noted as an adverse event.

- A patient with normal liver function at screen had an elevated ALT of 97 U/L (0-45 U/L) at week 20. It returned to normal (22 U/L) at early discontinuation after 10 injections. She discontinued to get pregnant.

- Another patient had an ALT of 105 U/L (0-45 U/L) at screen 8/4/97, 48 U/L at week 40, and 95 U/L at week 60. AST was also elevated to 61 U/L (0-41 U/L) at screen and 63 U/L at week 60. Her bilirubin level was normal throughout the study. Fat deposits in the liver were recorded on 10/8/98, after the 14th injection; however, no further details were provided.

ALT/SGPT was normal at screen and abnormal at final visit for 2.1% of Lunelle™ users and 1.4% of Ortho-Novum 7/7/7 users. Likewise, AST/SGOT changed from normal to abnormal for 1.0% and 0.7%, respectively, GGT for 0.7% of both groups, ALP for 2.7% and 1.4%, and bilirubin for 2.1% and 1.8%, respectively.

Previously submitted data from the Multicountry study (#A87901) revealed a rise in bilirubin levels with only one subject (0.1%) having an abnormally high value at screen vs. 9 (6.6%) at the end of treatment. This was the only significant result at the 5% level in 20 tests. There was no change in enzymes, and final alkaline phosphatase results were lower than at screen.

In the current study, 5 subjects had bilirubin values above the normal limit at screen , and 16 (2.1%) at the final visit. 15 subjects with a normal value at screen had a level above normal at their final visit, and 4 subjects who had a value above normal at screen had a normal value at their final visit. However, the maximum bilirubin level at any time during the current study was 2.2 mg/dL (normal range 0.1 to 1.2 mg/dL).

Cholecystitis was reported in 3 Lunelle™ users and cholelithiasis in two as described previously.

Reviewer's comment

- **Of the four Lunelle™ users with clinically significant elevations (3 times upper limit of normal) of hepatic function tests, none had elevated bilirubin levels. Two returned to normal by the final visit. For the other two, there is no follow-up information available, and there is no indication that any clinical or laboratory evaluation was done to determine the cause of the abnormal hepatic function test results.**
- **Although 15 subjects had an abnormal bilirubin value at the final visit, no bilirubin values were clinically significant at 3 times the upper limit of normal.**
- **One patient had fat deposits in the liver noted after her 14th cycle of Lunelle™ use. Her hepatic function test results were abnormally elevated at screen, and it is unlikely that this finding is related to the study drug.**

5.5 Weight change

Sponsor's Response:

"Median body weight gain was 4 pounds after 13 injections and 5 pounds after 15 injections. Changes in weight ranged from 62 pounds lost to 54 pounds gained."

Weight gain was the most common adverse event leading to discontinuation of study medication (5.7% of Lunelle™ users vs. 0.9% of Ortho-Novum 7/7/7 users). Lunelle™ users showed a median body weight increase of 4 pounds from screen to visit 8. The median change remained at 3 to 4 pounds at visits 8 through 14. However, changes in weight ranged from 62 pounds lost to 54 pounds gained. 31% of subjects gained more than 10 pounds. 7.2% gained more than 20 pounds, and 2.7% gained more than 25 pounds during participation in the trial (up to 15 months).

- One 35-year-old subject — who weighed 146.2 pounds at screen gained 53 pounds. Her weight at week 60 was 199 pounds. Leg edema was noted as an adverse event. Notes at post-study follow-up indicated that she had chronic lower extremity edema for 18 years.

- A 41-year-old — who weighed 252.2 pounds at screen lost 14.5 pounds and weighed 238 pounds at week 60.

- A 26-year-old — who weighed 254 pounds at screen had used fen-fen for 1 year prior to entry. She gained 6 pounds in the 15 days between screen and her first injection. She was under a great deal of stress, and her father died during the study. She discontinued after her 7th injection because of weight gain of 41 pounds since screen. Her weight gain was felt to be due to an eating disorder and unrelated to Lunelle™.

No information is available about the subject that lost 62 pounds, and it was not reported as an adverse event.

The median change in body weight over time did not differ by use of hormonal contraceptives at baseline. Lunelle™ users with a baseline BMI ≤ 27.3 kg/m^2 experienced a mean weight gain of 4.71 pounds and a median weight gain of 4 pounds to week 60. Those with a baseline BMI > 27.3 kg/m^2 experienced a mean weight gain of 5.87 pounds and a median weight gain of 8 pounds to week 60. The maximum weight gain of 54 pounds was the same for both BMI categories. However, the maximum weight loss (62 pounds) occurred with baseline BMI >27.3 kg/m^2.

Reviewer's comment:
It is of interest that the most common adverse event leading to discontinuation was weight gain. Although the mean weight gain in women with BMI <27.3 kg/m^2 was 4.71 pounds during the first 15 cycles of use, the fact that 31% of Lunelle™ users gained 10 pounds during that time could be of concern to potential users.

5.6 Coagulation factors

Sponsor's Response:

"Potential problems were identified in the handling of blood samples collected for measurement of coagulation factors, raising questions about the validity of the coagulation assays from both arms of the study. Therefore, no definitive conclusions are possible."

A retrospective review and audit of this portion of the trial revealed potential problems with sample handling and sufficient question about the validity of the coagulation assays to recommend that the data not be analyzed for the intent of the protocol.

One previous study has been conducted that involved a longitudinal evaluation of potential changes in coagulation and fibrinolysis in Hispanic and Asian women. The study compared two monthly injectable preparations (Lunelle™ and Mesigyna) and a combined oral contraceptive (Ortho-Novum 1/35) to determine what changes occurred in coagulation and fibrinolysis during two injection intervals, and

whether those changes reversed by 3 months after discontinuation of treatment. The oral contraceptive group showed an increase in procoagulant factors compared to the injectables.. Neither injectable induced a rise of procoagulant factors. Both reduced factor X. Small decreases in antithrombin III activity and protein C during treat. ent with the injectables were not considered clinically relevant. All changes observed during treatment had reversed 3 months after discontinuation. In contrast, the oral contraceptive induced increases in fibrinogen, factor VII and X activities, and plasminogen. These changes were reflected in a shortening of the activated partial thromboplastin time. Protein C was increased. Decreased levels of tissue plasminogen activator inhibitor (t-PAI) suggested an increase in fibrinolysis compensating the rise in procoagulant factors.

Reviewer's comment:
This portion of the trial could not be analyzed because of problems with sample handling and validity of coagulation assays. Previous studies showed no rise in procoagulant factors as seen with combined oral contraceptives, indicating that Lunelle™ would be expected to have less effect than combined oral contraceptives on hemostasis.

5.7 Hematology

Sponsor's Response:

"Lunelle™ users revealed a change in hemoglobin (hgb)from normal at screen to low at week 60 for 7.4% of subjects and similar changes in hematocrit (hct) for 2.5% of subjects. Median change in hematocrit from screen to final visit was 0.0% for Lunelle™ and 0.05% for Ortho-Novum 7/7/7. The median change for hemoglobin was also 0.0 % for Lunelle™ and –0.1 g/dl for Ortho-Novum 7/7/7. Anemia or iron deficiency anemia was reported as an adverse event in 1.3% of 775 Lunelle™ users and 0.9% of 318 Ortho-Novum 7/7/7 users. Data concerning iron use were not systematically collected, but concomitant treatment with iron was reported for 3.7% of 782 Lunelle™ users and 1.6% of 321 Ortho-Novum 7/7/7 users."

The median change in hematocrit was 0.1% for Lunelle™ users and 0.2% for Ortho-Novum 7/7/7 users, and the median hemoglobin change was 0.0 g/dl for both Lunelle™ and Ortho-Novum 7/7/7 users. There were 33 Lunelle™ users with a normal hematocrit at screen and low hematocrit at their final visit vs. 52 with low hematocrit at screen and a normal value at their final visit. Hemoglobin values were normal at screen and low at the final visit for 43 Lunelle™ subjects vs. low at screen and normal at final visit for 60.

Anemia or iron deficiency anemia was reported as an adverse event in 10 (1.3%) of 775 Lunelle™ and 3 (0.9%) of 318 Ortho-Novum 7/7/7 users. Two Lunelle™ users and one Ortho-Novum 7/7/7 user had clinically significant abnormal hematocrit (≤25%), hemoglobin (≤8 g/dL), or RBC ($\leq 3.5 \times 10^6/mm^3$).

- One 31-year old [redacted] with BMI 40.3 kg/m^2 and uterine fibroids had a screen hemoglobin level of 9.5 g/dL and at week 20 had a hemoglobin of 5.0 g/dL. She was then treated with daily iron tablets. She was discontinued from the study at week 44 because she wished to have surgical removal of the [redacted] Her hemoglobin at that time was 6.9 g/dL. Her menstrual diary indicated that she bled on 23 days and spotted on 2 days of the first (25-day) injection cycle, and bled for 9 days and spotted for 15 days of the second (28-day) cycle. On the last cycle, she bled for 15 days and spotted for 2 days of a 31-day cycle.

- A 36-year-old patient had a hemoglobin of 7.9 g/dL at the week 60 visit. Her hemoglobin at screen was 10.6 g/dL, at week 20 it was 10.2 g/dL, and at week 40 it was 10.6 g/dL. She continued into the extension study (0011) but discontinued after her week 4 injection (visit 1) because of hypertension. Hemoglobin values at week 4 and the final visit of Study 0011 were 8.1 and 9.9 g/dL. There is no record that she received iron supplements, and no bleeding-related adverse events were reported.

Of the other subjects who were reported as having anemia as an adverse event, two were anemic at screen and improved during the trial. Four had only one abnormal hematology value and were normal at both screen and the final visit. One subject had hematology values at the lower limit of normal at screen and developed mild anemia. Another had no recorded abnormal values.

Concomitant treatment with iron that coded as a blood modifier in the Standardized Upjohn Drug Dictionary System was reported for 29 (3.7%) of 782 Lunelle™ and 5 (1.6%) of 321 Ortho-Novum 7/7/7 users.

Reviewer's comment:
Use of iron preparations confounds the true incidence of anemia, but at most it would be 5% without iron supplementation.

6.4% of Lunelle™users and 2.5% of Ortho-Novum 7/7/7 users who had normal white blood cell counts (WBC) at screen had low WBC at the final visit. High WBC values at the final visit were observed in 1.3% of Lunelle™users and 1.4 % of Ortho-Novum 7/7/7 users.

- A 30-year-old —— was noted to have leukopenia and anemia at screen (WBC 3.43 $x10^3/mm^3$, Hgb 11.1 g/dl, Hct 38.2%). During her time in the trial, the hemoglobin remained stable and the WBC count fell. She has a history of lifelong intermittent iron deficiency anemia and was treated with daily supplemental iron. There is no history of neutropenia. She left the trial early (first dose July 10, 1997, last dose February 6, 1998) because of neutropenia and anemia. The events were judged not related to the study medication, and no post-study follow-up was obtained. Final WBC was 2.16, Hgb 10.5 and Hct 34.2%.

- A 24-year-old— had a low RBC count ($3.37x10^6/mm^3$) at screen with hemoglobin 10.4 g/dL and hematocrit 32.4% and normal WBC. Her RBC and Hbg/Hct increased during the study but she developed mild leukopenia. She had a history of iron deficiency anemia and was treated with —— from . ———————— She completed the study. Final WBC was $3.01x10^3/mm^3$, RBC 4.19 x $10^6/mm^3$, Hgb 12.8 g/dL, Hct 40.3%.

Reviewer's comment:
These data reveal a trend towards lower WBC with Lunelle™use. However, this does not appear to be clinically significant.

One case of thrombocytopenia was reported. This subject had a platelet count of 111 x $10^3/mm^3$ (normal 140-370 x $10^3/mm^3$) at the 20 week visit, and all other values were normal, including the final visit.

5.8 Breast Examinations and Mammograms

Abnormal breast examinations were reported in 6% of Lunelle™ users at screen and by 6% at their final visit. 2.5% of subjects with a normal breast exam at screen had an abnormal exam at the final visit, and another 2.5% with an abnormal breast exam at screen had a normal exam at their final visit. Abnormal findings included fibrocystic changes, nipple rings, implants, scars, supernumary nipples, and inverted nipple. Only 11 subjects were noted to have breast lumps or masses, and none of those were reported as suspicious.

Breast lumps were reported as adverse events (COSTART term breast neoplasm) in 15 patients, 9 Lunelle™ users and 6 Ortho-Novum 7/7/7 users. Final breast examination results were normal for 6 of these. Another 8 indicated benign disease or false-positive results. No follow-up data are available for one. One Lunelle™ user, had suspicious findings at final breast examination and no follow-up data were available.

Only patients over 35 years of age were required to have a baseline mammogram. 7.8% (7/90) of Lunelle™ users had an abnormal mammogram at screen vs.14.3% (10/70) at final visit. None of these was considered suspicious for malignancy. 5 subjects with a normal mammogram at screen had an abnormal result at their final visit. One subject with an abnormal mammogram at screen had a normal result at her final visit. One Ortho-Novum 7/7/7 user had suspicious findings at final mammogram, and a follow-up coned compression showed normal fibroglandular tissue.

5.9 Pelvic Examinations

7 Lunelle™ users who had an enlarged uterus (6 to 15 weeks) at screen were pregnant and underwent an abortion before receiving their first injection. Another patient had an abnormal pelvic exam at screen that was described as "corpus irregular, 12 weeks size with leiomyoma", and her pregnancy test was negative. Another had a slightly enlarged uterus at screen and had a negative pregnancy test at screen and at subsequent visits.

5 Lunelle™ users had an enlarged uterus at their final visit. Four of these had a negative pregnancy test at the final visit. One did not. However, the investigator noted that there was no subsequent evidence that miscarriage, abortion, or delivery occurred. She discontinued treatment due to menorrhagia, dysmenorrhea, and abdominal pain.

50 Lunelle™ users who discontinued the study early did not have a pelvic examination at their final visit.

5.10 Cervical Cytology

Abnormal cervical cytology, by the Bethesda system, was noted at screen for 9.2% of Lunelle™ users. Two of these showed squamous intraepithelial lesions (SIL), a protocol violation. The others showed ASCUS, reactive or reparative changes, benign cellular changes, Candida, inflammation or bacterial vaginosis.

At final visit, 9.1% of Lunelle™ users had abnormal cervical cytology. ASCUS was found in 45 (7.4%) Lunelle™ users at final visit, low-grade intraepithelial lesion (LGSIL) in 8 (1.3%). 5 more potential cases of LGSIL were identified from subjects with "limited" cytology results. All but 2 of the subjects with LGSIL underwent colposcopy. One had normal results on repeat cytology, and the other had no scheduled follow-up.

Two Lunelle™ users (0.3%) were diagnosed with high grade squamous intraepithelial lesions (HGSIL) by cervical cytology examination or follow-up biopsy.

- One Lunelle™ user, a 25-year-old —— had a Pap smear at screen that showed no cytology abnormalities. Her first dose of Lunelle™ was —— and last dose —— She dropped out of the trial and did not return for a final visit until —— A pap at that time showed HGSIL. Colposcopic biopsy showed grade III cervical intraepithelial neoplasia (CINIII). A follow-up visit was to be scheduled.

- A 29-year-old began Lunelle™ —— An abnormal Pap smear was not recorded at screen. Pap smear at the end of participation —— revealed HGSIL. Colposcopic biopsy showed CINIII, and LEEP was performed. Pathology showed CINII in a background of flat condyloma. This subject discontinued due to menstrual cramps.

5.6% of Lunelle™ users had a normal result at screen and abnormal at their final visit. Another 5.6% had an abnormal result at screen and a normal result at their final visit.

6 Lunelle™ users and one Ortho-Novum 7/7/7 user who had normal/benign cytology at screen did not have cervical cytology performed at week 60, and another 50 Lunelle™ users and 12 Ortho-Novum 7/7/7 users who discontinued the study early did not have cervical cytology performed at their final visit.

Reviewer's comment:
Given that SIL is not an uncommon finding among sexually active women and that the false-negative rate for a single Pap test (e.g., the cytology result at screen)is 10-25% , the finding of SIL in approximately 2.4% of cytology results at the final visit probably does not suggest any significant effect of Lunelle™ use on cervical cytology.

5.11 Return to fertility

FDA specification: Data regarding return to fertility, in utero exposure (e.g., pregnancy outcome information) and lactation should be submitted for review.

Sponsor's response:

"Protocol 0006, a study of pharmacokinetics and pharmacodynamics in 14 subjects, showed that ovulation was inhibited throughout the treatment period, as indicated by the absence of any luteal-like progesterone peaks (serum progesterone levels did not exceed 1 ng/ml). The first normal ovulatory cycle (confirmed by serum progesterone concentrations ≥4.7 ng/ml) in 11 women was observed between days 63 and 112 after the third injection. Seven women who received Lunelle™ in protocol 0004 are known to have conceived following discontinuation from the trial. Estimated dates of conception range from 3.5 to 10 months after the last injection. Four of the 7 pregnancies were ongoing at the time of the report, and the others were terminated."

Protocol 0006 was a multiple-dose, open-label trial conducted to characterize steady-state pharmacokinetics and pharmacodynamics (return of ovulation) after repeated monthly injections of Lunelle.14 women with regular menstrual cycles were studied for one control cycle, 3 consecutive months of treatment, and 3 to 5 months of follow-up. Serum progesterone levels were completely suppressed after Lunelle™ injection in all 14 subjects, and consequently ovulation was inhibited throughout the treatment period. The first normal ovulatory cycle, confirmed by serum progesterone levels ≥ 4.7 ng/ml, occurred between days 63 and 112 in 11 women. The other 3 were lost to follow-up before return of ovulation. One of these was followed to 85 days and then discontinued without having returned to ovulation.

In a 1993 report of introductory studies by WHO, 52% of 21 women who received Cyclofem for 3 months ovulated during the first post-treatment month and 71% during the second month. After 2 years of treatment, 60% ovulated by the third follow-up month. Follicular activity was demonstrated in a Swedish study by 41-49 days after the final injection, and luteal activity by 59-87 days.

Seven Lunelle™ users are known to have conceived following discontinuation from the trial. Two had discontinued form the trial to get pregnant. The dates of conception range from 3.5 to 10 months after the last injection. 4 of the 7 pregnancies were ongoing at the time of the report, and the other 3 were terminated by therapeutic abortion.

In previous studies presented in the 1997 NDA, 83% of 90 women who discontinued Lunelle™ to become pregnant had conceived at one year. More than 50% had conceived in the first 6 months. 95% (55/58) of the pregnancies resulted in live births.

5.12 Intrauterine exposure

Previously submitted information on five neonates from unexpected pregnancies exposed to Lunelle™ reveals no evidence of congenital abnormalities or adverse events. One infant was followed for two years. Two pregnancies were lost to follow-up. One first trimester spontaneous abortion and two induced abortions were reported.

5.13 Adverse Events

Adverse events were reported by 89.0% of Lunelle™ users and 84.3% of Ortho-Novum 7/7/7 users. Serious adverse events were reported by 1.9% of Lunelle™ users and 1.3% of Ortho-Novum 7/7/7 users. A higher proportion of Lunelle™ users (19.6%) discontinued due to adverse events compared with Ortho-Novum 7/7/7 users (7.5%). 52.8% of adverse events in Lunelle™ users were judged to be drug-related, compared to 27.4% in the Ortho-Novum 7/7/7 users. With the open-label nonrandomized design of the trial, this could represent the potential bias of comparing an experimental drug with a well-known drug.

The adverse events recorded in this trial are consistent with those expected with the use of combined hormonal contraceptives. The most frequent adverse events reported by Lunelle™ users were the following:

- various infections (unrelated to the study drug, mostly upper respiratory infections)--32.3%
- headache----------17.2%
- breast pain----------14.1%
- weight gain----------13.9%
- sinusitis----------13.0%
- dysmenorrhea--------12.6%
- accidental injury------12.0%
- acne----------10.7%

The following adverse events were reported more frequently in Lunelle™ users than in Ortho-Novum 7/7/7 users:

	Lunelle™ users	Ortho-Novum 7/7/7 users
• breast pain	14.1 %	4.4 %
• weight gain	13.9 %	3.5 %
• acne	10.7 %	5.0 %
• abdominal pain	9.4 %	4.1%
• emotional lability	9.2 %	4.7 %
• metrorrhagia	6.8 %	1.6 %
• menorrhagia	6.6 %	0.3 %
• decreased libido	4.6 %	1.6 %
• dyspepsia	3.0 %	0.6 %
• enlarged abdomen	3.1 %	0.9 %
• amenorrhea	2.6 %	0.6 %
• vaginal hemorrhage	2.6 %	0.3 %
• nervousness	2.6 %	0.6 %
• syncope	1.4 %	0.0 %
furunculosis	1.3 %	0.0 %

Drug-Related Adverse Events

The most frequent drug-related adverse events reported by Lunelle™ users were the following:

- breast pain----------11.9%
- weight gain---------10.8%
- acne----------8.9%
- emotional lability----6.8%
- dysmenorrhea--------6.5%
- metrorrhagia---------6.5%
- menorrhagia----------6.5%
- headache----------4.8%
- depression----------2.7%
- nausea----------2.7%
- amenorrhea----------2.5%
- abdominal pain---------2.3%
- nervousness----------2.1%
- abdomen enlarged------1.9%
- vaginal hemorrhage----1.8%
- vulvovaginal disorder--1.7%
- vaginal moniliasis------1.2%
- dizziness----------1.2%
- alopecia----------1.2%
- asthenia----------1.0%

Reviewer's comment:

The incidence of these adverse events is somewhat different than in the WHO trials of Lunelle™. Integrated data from the previous trials revealed a lower incidence of breast pain, weight gain, acne, emotional liability and dysmenorrhea, and a higher incidence of amenorrhea, hypomenorrhea, menorrhagia, and metrorrhagia. Differences in reporting of these adverse events may reflect cultural differences among the subjects in the various trials.

The following adverse reactions or effects may be associated with the use of combined hormonal contraceptives:

- thromboembolic disorders and other vascular problems
- benign hepatic adenomas
- ocular lesions
- changes in carbohydrate and lipid metabolism
- elevated blood pressure
- gall bladder disease

Of these, only events related to the gall bladder were reported as serious adverse events in Lunelle™ users. Several of the adverse reactions included in the class labeling for combined oral contraceptives were not observed in more than 1% of women in this study.

Serious Adverse Events

Serious adverse events were reported in 15 (1.9%) of 775 Lunelle™ users. No serious adverse event resulted in a patient discontinuing the investigational medication.

Two serious adverse events were judged to be possibly related to the study drug.

- One subject, a 21-year-old —— obese subject with no previous history of gall bladder disease, developed cholelithiasis that was judged to be drug-related after her 4th injection and required hospitalization. ——————

- The other, a 23-year-old —— obese subject with a prior history of gastrointestinal symptoms and lower abdominal pain associated with oral contraceptive use required hospitalization ——— ——— gall bladder inflammation (coded cholecystitis)before her 4th injection, felt to be exacerbated by Lunelle™. Both women continued on Lunelle™ ——————

A third case (cholelithiasis) was judged to be unrelated to the drug. In this case, a 27-year-old —— obese subject with a history of back pain developed acute cholelithiasis after her 13th injection of Lunelle™. ——————— were performed and the woman discontinued from the trial.

Cholecystitis was reported as an adverse event in two additional Lunelle™ subjects. One 36-year-old subject reported cholecystitis after her 12th injection. She received general anesthesia for an unreported procedure. The episode lasted only one day, and she completed the study. The event was considered non-serious and not drug-related. Another 39-year-old subject reported cholecystitis after her 13th injection. It was considered a non-serious adverse event of moderate intensity, lasting 3 days and treated with ciprofloxacin and compazine for 7 days. The subject completed the study.

Reviewer's comment:
Adverse events related to the gallbladder were reported in 5 of 782 participants (0.6%). This is consistent with the known association between combined hormonal contraceptives and gallbladder disease. These adverse events were also reported by 2 0f 321 (0.6%) Ortho-Novum-7/7/7 users.

Adverse events related to depression can also be a concern with combined hormonal contraceptives. 51 Lunelle™ users in this trial reported depression and 72 reported emotional lability. Three serious adverse events related to depression and/or situational stress occurred in Lunelle™ users: an overdose of lorazepam, a suicide attempt, and depression requiring hospitalization. These were all considered to be unrelated to treatment.

- One subject was a 35 year old —— who started Lunelle™ on ——————— for depression. She had marital problems (husband infidelity) and two autistic children under the age of 5 years to care for.

- Another 35 year old, ——— reported at her week 8 visit that she had been evaluated in the emergency room after ——————— ——— The event was precipitated by marital stress. She took the overdose in front of her husband, hoping to elicit a response. She did not feel suicidal. She had a history of clinical depression and had at one time been treated with ——— . She had been started on —— —— daily. The subject later discontinued from the trial due to irregular bleeding and weight gain.

- A 19-year-old — ingested ——————— — She had been under significant stress due to a previous abusive boyfriend who was recently released from prison and was threatening to take her child. She

had no history of depression or use of antidepressants (the ——— was a friend's prescription). She later admitted to a history of substance abuse including "

Reviewer's comment:
These serious adverse events related to depression do not appear to be related to Lunelle use.

Adverse Events Leading to Discontinuation
The most common adverse event leading to discontinuation of treatment was weight gain (5.7%).

The following events leading to discontinuation were classified as cardiovascular events:

- Hypertension led to discontinuation in 3 Ortho-Novum 7/7/7 users and no Lunelle™ users.
- One Lunelle™ user and one Ortho-Novum 7/7/7 user discontinued because of migraines.
- One Lunelle™ user discontinued because of vasodilatation (hot flashes).
- One Lunelle™ user discontinued because of superficial thrombophlebitis. This 20-year-old patient was treated with indomethacin and cefadroxil and discontinued from the study, having completed 12 cycles of treatment. No other information is available.

One Lunelle™ user discontinued due to anemia and leukopenia, and one due to multiple sclerosis that was diagnosed during the study.

Adverse Events by Race
Emotional lability and depression were reported most frequently by white women (11.1% and 7.6%) compared with Hispanic (5.8% and 4.1%) or black women (3.8% and 3.8%). Fewer Hispanic women (0.8%) reported anxiety than white (3.2%) or black women (3.8%). More Hispanic women (9.9%) reported decreased libido than white (4.4%) or black women (0.9%).

Breast-related adverse events were more frequent in white subjects than in black or Hispanic subjects. Breast pain was reported by 15.1% of white subjects, 11.6% of Hispanic subjects, and 11.3 % of Black subjects. Breast enlargement was reported by 1.5%, 0.8%, and 0%, respectively.

Hispanic subjects were less likely to discontinue for breast-related or bleeding-related adverse events , and black subjects were less likely to discontinue for acne or nausea.

Acne was reported by 12.2% of white subjects vs. 11.6% of Hispanics and only 1.9% of black subjects. Abdominal pain was reported by more Hispanic patients (13.2% vs. 9.0% for white and 8.5% for black patients). White patients experienced weight gain more frequently (15.5% vs. 9.9% for Hispanic and 12.3% for black patients).

5.14 Safety analyses stratified by BMI

FDA specification: Analysis of safety data stratified by body mass index should be provided.

Sponsor's Response:
"Adverse event data are stratified by baseline BMI (27.3 kg/m^2 or less vs. over 27.3 kg/m$^{2)}$. No consistent effect of BMI was apparent in the reporting of adverse events. Women with a BMI of 27.3 kg/m^2 or less had a higher incidence of metrorrhagia (7.6% vs. 5.1%), breast pain (15.2% vs. 11.4%), and acne (11.9% vs. 8.0%), and a lower incidence of vulvovaginal disorder (5.8% vs. 8.0%), emotional lability (8.7% vs. 10.1%), and amenorrhea (1.7% vs. 4.6%). There was no obvious influence of baseline BMI on change in body weight."

Median weight gain to week 60 was 8 pounds for women with BMI >27.3 kg/m^2 and 4 pounds for those with BMI $\leq$ 27.3 kg/m^2 .

6.0 EFFICACY ASSESSMENT

Following recommendations made by FDA in July, 1998, changes were initiated in this protocol such that minimum requirements for 200 women completing 13 cycles of product use were met.

Data from protocols 0004 and 0006 demonstrate that Lunelle™ was a highly effective contraceptive in eligible subjects participating in this trial. Data previously submitted from the multicountry —— and ——— trials and other supportive controlled and uncontrolled trials revealed a total of 11 pregnancies. These data are from over 18,000 women representing over 155,500 woman-months of exposure to Lunelle™. Life table pregnancy rates were from 0 to 0.2%, but multiple deficiencies in these studies made accurate assessment of efficacy impossible.

The sample size for the US trial was sufficient to demonstrate efficacy but was limited with regard to extensive drug exposure. In addition, efficacy data is lacking for 72 women (approximately 10% of the trial participants) who discontinued the trial without a final pregnancy test at discontinuation and were not successfully contacted for follow-up.

7.0 SAFETY ASSESSMENT

Adverse events—

The adverse events reported in this trial were consistent with those expected with the use of combined hormonal contraceptives. The most frequent drug-related adverse events (reported by more than 5% of participants) were breast pain, weight gain, acne, dysmenorrhea metrorrhagia, menorrhagia, and emotional lability.

The only serious adverse events judged to be possibly related to Lunelle™ were events related to the gall bladder. Three patients underwent cholecystectomy during the trial, two for cholelithiasis and one for cholecystitis. Two additional patients experienced cholecystitis but did not require surgery.

There were three serious adverse events related to depression and/or situational stress. None of these was considered to be related to treatment.

There were no reports of serious cardiovascular adverse events.

Weight gain—

Changes in weight ranged from 62 pounds lost to 54 pounds gained. The median weight gain was 4 pounds from screen to visit 8. However, 31% of participants gained more than 10 pounds and 7.2% gained more than 20 pounds during participation in this trial. Weight gain was the most common adverse event leading to discontinuation (5.7%).

Bleeding pattern changes—

Although the mean and median number and duration of bleeding episodes are suggestive of normal menstrual cycles, 58.6% of Lunelle™ users reported clinically undesirable bleeding patterns in the fourth (final) 90-day reference period. 4.1% reported amenorrhea in the fourth reference period. The incidence of anemia was at most 5%, considering that 3.7% of participants took concomitant treatment with iron. Therefore, the preponderance of undesirable bleeding patterns represents a nuisance factor instead of a safety concern.

Anemia—

There was no clinically significant change in hemoglobin or hematocrit in Lunelle™ users in this trial. Anemia was reported as an adverse event in 1.3% of participants. Most of them experienced no significant change in hemoglobin and hematocrit from screen to the final visit. Only two subjects had clinically significant abnormal hematocrit ($\leq$25%) or hemoglobin ($\leq$8 g/dL).

Coagulation factors—

This portion of the trial could not be analyzed because of problems with sample handling and validity of coagulation assays. Previous studies showed no rise in procoagulant factors as seen with combined oral contraceptives, indicating that Lunelle™ would be expected to have less effect than combined oral contraceptives on hemostasis.

Blood pressure—

There is no indication of a statistically or clinically significant effect on systolic or diastolic blood pressure.

Lipid and carbohydrate metabolism—

This study shows a decrease in total cholesterol, LDL-cholesterol, HDL-cholesterol, apolipoproteins A-I, A-II, and B, and triglycerides and no change in the total cholesterol/HDL ratio. There is no evidence that Lunelle™ affects carbohydrate metabolism.

Hepatic function—

Four subjects experienced clinically significant abnormal hepatic functions more than 3 times the upper limit of normal. Two of these returned to normal by the end of the study, and there is no follow-up information available for the other two. No clinical or laboratory investigations were conducted to determine the etiology of the abnormality. There were no reports of clinically significant bilirubin elevations. These findings are not sufficient to suggest a significant risk of hepatic damage related to Lunelle™ use.

Cervical cytology—

Given that SIL is not an uncommon finding among sexually active women and that the false-negative rate for a single Pap test (e.g., the cytology result at screen)is 10-25% , the finding of SIL in approximately 2.4% of cytology results at the final visit probably does not suggest any significant effect of Lunelle™ use on cervical cytology.

Return to ovulation—

Return of ovulation was demonstrated between 63 and 112 days following the final injection in 11 of 14 women who participated in a pharmacodynamic trial. Previous studies had reported that 52% of participants ovulated in the first post-treatment month and 71% in the second month. After 2 years of treatment, 60% ovulated by the third follow-up month. This is a significantly shorter time for return of ovulation than with use of DMPA.

Return of fertility—

A previous study of 90 women who discontinued Lunelle™ to become pregnant reported that 83% conceived in the first year after discontinuation. Over 50% conceived in the first 6 months. There is no evidence of any long-term effect of Lunelle™ on fertility after discontinuation.

Intrauterine exposure—

5 neonates exposed to Lunelle™ during unexpected pregnancies were previously reported. One was followed for two years. None showed evidence of congenital malformations or adverse events. Two additional exposed pregnancies were lost to follow-up, one resulted in a first trimester spontaneous abortion, and two were terminated by vacuum aspiration.

Effect on lactation—

No information available

Anaphylaxis/Allergic reactions—

Although anaphylaxis and anaphylactoid reactions have been reported with DMPA use, none have been reported with Lunelle™. Only a few mild dermatologic reactions have been judged to possibly represent an allergic response to Lunelle™.

8.0 SAFETY UPDATE

A safety update was presented August 18, 1999 and included safety data from three US trials. No new safety concerns were identified.

M/5415/0011 is an ongoing extension of M/5415/004 to collect long-term safety data for women wishing to continue using Lunelle™ for up to 104 weeks. The trial began in December 1997. 196 patients were in the database at the cut-off date (May 31, 1999). These 196 women received 1340 injections. Over 90% of injections were given within 23 to 33 days of the previous injection. 61 participants (31.1%) discontinued before June 1, 1999, mostly for personal request. 11 women (5.6%) discontinued for a medical reason, all non-serious adverse events.

One pregnancy was reported in this trial and was not considered a method failure. This 21-year-old woman received her third injection [redacted] and failed to keep her next appointment because she was stranded in another country. She returned [redacted] and had a positive pregnancy test at that visit. Her last menses was [redacted] No pregnancy was seen on ultrasound on [redacted] Beta-HCG was 46 IU/L on [redacted] and 166 IU/L on [redacted] On March 18, a gestational sac was seen on ultrasound. The probable date of conception was [redacted] The patient elected to terminate the pregnancy.

Two serious adverse events were reported, neither of them related to the study drug. One was a psychiatric hospitalization for an explosive outburst, the other a hospitalization for treatment of tuberculosis.

9 subjects reported adverse events leading to discontinuation of Lunelle™ use:

- One subject discontinued due to anemia and episodes of disorientation. Her Hgb was 12.7 g/dL and Hct 37.2% at screen. At discontinuation, her Hgb was 10.3 g/dL. Her serum iron was 41µg/dL (normal 37-145 µg/dL), TIBC 452 µg/dL (normal 250-450 µg/dL), and ferritin 5.7 ng/ml (normal 7-283 ng/ml).
- One subject discontinued due to abnormal liver function tests. Her liver function test results were normal at screen. At week 60, ALT was 48 U/L, AST 32 U/L, GGT 94 U/L. These levels reached a maximum at week 95 with ALT 95 U/L, AST 83 U/L, and GGT 180 U/L. At discontinuation (week 103), all values had returned to normal with ALT 35 U/L, AST 31 U/L, and GGT 63 U/L. Bilirubin remained normal throughout the trial. There is no indication that further clinical or laboratory evaluation was conducted to evaluate this adverse event.
- Another subject discontinued because of hypertension. Her only two recorded blood pressures were normal, 110/80 and 120/80. She was treated with Maxide, and later switched to Norvasc.
- Two subjects discontinued due to weight gain
- Two subjects discontinued due to acne
- One discontinued due to amenorrhea
- One discontinued because of decreased libido and difficulty losing weight.

No patient in this study had liver function test results elevated to 3 time the upper limit of normal, and there was no further increase in the mean values for these results after the end of study M/5415/0004.

Hypertension was reported in 5 patients, but only one report was substantiated by recorded blood pressure values. This patient had a blood pressure of 130/90 at screen and 140/100 at visit 5. She took various antihypertensive medications. Her final blood pressure was 130/90 at visit 8.

One patient had a laparoscopic cholecystectomy during the trial.

M/5415/0009 was an efficacy and safety trial in adolescents that closed less than 1 month after initiation due to changing priorities within the sponsor business group.

[redacted]

9.0 FINAL CONCLUSIONS AND RECOMMENDATIONS

The data presented from this study indicate that Lunelle™ is safe and effective in preventing pregnancy. However, due to the absence of any reported pregnancies in the current trial, incomplete pregnancy assessments and follow-up for all participants in the current trial, and the poor quality of data from previous trials, it is not possible to calculate an accurate Life Table Failure Rate for this method of contraception.

The data do not support the sponsor's goal of providing a contraceptive option that included the benefits of Depo-Provera (DMPA) with the added benefit of an estrogen, which would also promote a more normal menstrual bleeding pattern. In fact, aside from a significantly lower incidence of amenorrhea, the data reveal a higher incidence of

unacceptable bleeding patterns with Lunelle than with the currently available progestogen-only injectable contraceptive.

The sponsor suggests that the combination of MPA and E_2C in Lunelle™ reduces the risk of breakthrough ovulation and allows the use of a lower monthly dose of MPA. However, earlier studies demonstrated that MPA alone in doses of 12.5 or 25 mg effectively suppressed ovulation for at least a month and that either dose of MPA combined with a lower dose (2.5 mg) of estradiol cypionate resulted in an unacceptable rate of ovulation.

However, Lunelle ™ does allow a more rapid return of ovulation and fertility after discontinuation than DMPA and may have a less negative effect on bone mineral density.

The sponsor also suggests that Lunelle™ users can share in the benefits afforded by combination estrogen-progestin oral contraceptives, e.g., reduced incidence of ovarian and endometrial carcinomas, reduced uterine fibroids, ectopic pregnancies, benign breast disease, and probably, some protective effect on bone mineral density, compared to non-users. To date, there are no data to support such claims. Data from this study do not show other non-contraceptive benefits similar to those of oral contraceptives such as less painful menstrual periods and less loss of menstrual blood. The possibility of a lower risk of anemia and fewer pelvic infections also have not been studied.

It is recommended that Lunelle™ Monthly Contraceptive Injection be approved for marketing with the requirement that the sponsor conduct Phase IV postmarketing studies, one to confirm a beneficial effect on bone mineral density compared to Depo-Provera.

10.0 LABELING

Extensive revisions to the sponsor's proposed labeling are recommended so as to reflect the findings of the clinical trials and to provide labeling consistent with other injectable contraceptives as well as combined oral hormonal contraceptives. These recommendations were communicated to the sponsor on September 20, 1999.

/S/

Dena R. Hixon, MD, FACOG
Medical Officer, DRUDP

I concur.

S

Susan S. Allen, MD, MPH
Team Leader, DRUDP

9/23/99

APPEARS THIS WAY
ON ORIGINAL

Cc: HFD-580/L. Rarick/M. Mann/S. Allen/D. Hixon
Cc: NDA 20,874/Division File

/S/

Joint Medical Officer's Original Summary

SEP 3 1998

NDA 20-774

Original submission date:	9/26/97
Review completed:	9/1/98

Applicant: Pharmacia & Upjohn
7000 Portage Road
Kalamazoo MI 49001

1. General Information:

   a. Name of Drug

      (1) Generic: Medroxyprogesterone acetate and estradiol cypionate
      (2) Proposed Trade Name: ———

   b. Pharmacologic Category: Estrogen and progestin
   c. Proposed Clinical Indication: Prevention of pregnancy
   d. Dosages and route of administration: 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate given as a 0.5 ml intramuscular injection q 28-30 days
   e. Related Drugs: Depo-Provera, Mesigyna

2. Manufacturing Control Data: See Chemist Review

3. Pharmacologic Review: See Pharmacologist Review

4. Biopharmaceutics Review: See Biopharmaceutics Review

Table of Contents

1.0 Resume

This application contains data from a total of 41 clinical trials evaluating the safety, efficacy and pharmacokinetics of a monthly injectable contraceptive product, Cyclo-Provera, consisting of 25 mg of Medroxyprogesterone Acetate (MPA)combined with 5 mg of Estradiol Cypionate (E_2C). The product was developed as an injectable contraceptive that combined progesterone with estrogen in an attempt to reduce the disturbances of menstrual cycle and bleeding patterns noted with injectable progestin-only contraceptives.

Three large, randomized, controlled clinical trials (the Multicountry, Egypt and China studies) comprise the pivotal trials providing safety and efficacy data. Two of these trials (the Multicountry and the Egypt studies) were designed to compare the safety and efficacy of Cyclo-Provera and a second monthly injectable contraceptive (Mesigyna) containing 50 mg of Norethisterone Enanthate combined with 5 mg of Estradiol Valerate. The third trial (the China study) compared Cyclo-Provera to two other injectable contraceptive products—Mesigyna and Chinese Injectable No.1 (containing 250 mg of 17-Hydroxy-Progesterone Caproate combined with 5 mg of Estradiol Valerate). From these three pivotal trials, data from over 4,200 women with an exposure of > 41,000 woman-months were analyzed and submitted in support of the proposed use of Cyclo-Provera as a monthly injectable contraceptive.

2.0 Background

2.1 Regulatory History

Cyclo-Provera was developed by The Upjohn Company over 30 years ago and was first tested in a large scale safety and efficacy trial conducted by the World Health Organization (WHO) in 1984. In 1990, Upjohn turned over the development rights for this product to WHO which subsequently licensed the product to the Program for Appropriate Technology in Health (PATH) and its associated nonprofit organization, the Concept Foundation. PATH/Concept has licensed Cyclo-Provera to several companies in Asia and Latin America. As of mid-1997, ——— units of Cyclo-Provera had been sold worldwide, with no withdrawals from marketing in any country for safety reasons.

On September 26, 1997, the current sponsor (Pharmacia Upjohn) submitted an original New Drug Application for Cyclo-Provera, seeking FDA-approval for marketing the product in the United States.

The following meetings were held with the sponsor or with investigators participating in clinical trials of Cyclo-Provera throughout the product development period up to the date of NDA submission:

February 8, 1993:

A Pre-IND meeting was held with ——————— to discuss the expected approval of Cyclofem for use in —— later in the year and requirements for approval of this product in the US.

November 15, 1993:

A Pre-IND meeting was held with ——————— and PATH. At this meeting, it was noted that pharmacological studies that had been performed on Cyclo-Provera were conducted in the 1970s outside the US with no teratology or pharmacokinetic studies having been completed. It was noted that toxicological requirements might be abbreviated in this case, but that bridging studies between the older formulation and the formulation proposed for marketing would be needed.

The sponsor noted that the supplies used in the historical studies could not be reproduced due to the length of time that had passed since manufacturing of these supplies with information regarding the manufacture of supplies for the early clinical trials no longer being available. Required biopharmaceutical data and studies were discussed.

June 6, 1995:

A Pre-NDA meeting was held with Pharmacia & UpJohn and limitations of the data base were noted and discussed including:

-The lack of comments from investigators on study reports
-The fact that study reports contained coded information only
-The lack of determinations of relatedness or seriousness of medical events noted during the studies
-The lack of availability of safety data beyond one year of use
-The lack of CRFs available for either the Egypt or China studies
-The discrepancy between the formulation reported as having been used in the Egypt study and that described in the sponsor's records

The sponsor was informed that the data to be submitted in the application was weak and that the lack of CRFs was a serious concern. The possibility of performing several phase IV studies to address these concerns was discussed.

2.2 Clinical Background and Proposed Mechanism of Action:

Injectable contraceptives have been available in some countries for many years. The most widely used injectable contraceptives are the progestin-only methods, depot-medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN). Currently, DMPA is the only injectable contraceptive approved for use in the U.S.

The most common reason for discontinuation of both oral and injectable progestin-only contraceptives is disruption of menstrual bleeding patterns which result in unsatisfactory acceptability profiles for these products. Cyclo-Provera was designed to provide low, stable serum concentrations of MPA for ovulation suppression in addition to providing serum levels of estradiol (administered as E_2C) that mimic a normal preovulatory estradiol surge, thereby creating more regular monthly bleeding patterns. If approved, Cyclo-Provera would be the first monthly injectable contraceptive available in the U.S. and the first such contraceptive containing estrogen in addition to a progestin.

Medroxyprogesterone acetate and estradiol have been used in products for the treatment of gynecologic conditions as well as in contraceptive products for decades. The contraceptive mechanism of action of the combination product Cyclo-Provera is based upon the actions of its component products. MPA is a derivative of progesterone which has little androgenic or anabolic activity and no estrogenic activity. Exogenous administration of MPA suppresses LH secretion, thereby preventing ovulation. Estradiol cypionate is an ester of 17-B-estradiol that is [redacted] to E_2 and cyclopentane [redacted] upon entering the systemic circulation. This component of Cyclo-Provera suppresses FSH secretion, thereby preventing emergence of a dominant follicle, stabilizes the endometrium, and potentiates the action of progesterone via increasing the concentration of intracellular P-receptors.

2.3 Human Pharmacology, Pharmacokinetics, Pharmacodynamics:

Seven studies were performed to evaluate the pharmacokinetics of Cyclo-Provera, three of which calculated pharmacokinetic parameters. High intersubject variability in serum concentrations of MPA and E_2C were noted in these studies after Cyclo-Provera administration.

Following monthly injections of Cyclo-Provera, peak MPA concentrations were achieved in 7 to 10 days. The mean maximum concentration after three injections was 1.12 (0.93-1.43) ng/mL and ranged from 1.45-2.15 mg/mL after repeated monthly injections for one year. At the end of the monthly injection interval, MPA concentrations are usually below 0.05 ng/mL which is consistent with a half-life of 10-14 days. Accumulation of MPA is observed after repeated monthly injections for the first six injections. Thereafter, no further accumulation is seen. MPA is detectable for approximately 60 days after the last Cyclo-Provera injection.

Serum estradiol concentrations peak approximately 4 days postinjection of Cyclo-Provera and range from 200 to 400 pg/mL. The peak estradiol concentration levels decline to basal levels (typically < 100 pg/mL) by day 14, consistent with a half-life of 4-7 days. Estradiol does not accumulate after repeated injections.

Two of the 7 studies performed evaluated the pharmacokinetics of MPA and E_2C in women from different countries, demonstrating similar serum concentrations of both drugs in women from all countries studied excluding Thailand. Thai women showed a higher C_{max} and shorter T_{max} for both MPA and E_2C, indicating faster drug absorption as compared to women from other countries. In addition, ovulation returned earlier after discontinuation of Cyclo-Provera in Thai women, as would be expected with faster drug absorption.

Reviewer's comments:

Although the sponsor stated that the pharmacokinetic differences with regard to contraception observed in Thai women were not clinically relevant, differences in hormone levels and possibly in steroid metabolism are known to occur in Asian, as compared to non-Asian, populations. The pharmacokinetic differences in drug metabolism have been demonstrated in both women and men in Asia, although reasons for this are unclear.

While the contraceptive efficacy of Cyclo-Provera in Thai women was noted to be similar to that of other populations, data contained in the current submission reveal differences in bleeding patterns and in the incidence of discontinuation due to bleeding related problems for Asian women as compared to women of other ethnic groups, as detailed in Section 7.1. The differences in bleeding related events experienced by Asian women could be related to ethnic differences in drug metabolism or could be indicative of differences in cultural acceptability of menstrual bleeding in these patient populations.

The fact that metabolism of Cyclo-Provera was shown to be different in one ethnic group studied raises concerns that the drug could be metabolized differently by other ethnic groups that were not included in three pivotal trials, particularly African-American and Native-American women.

The pharmacodynamics of Cyclo-Provera are related to the actions of its individual steroid components. Progesterone-mediated suppression of LH secretion and subsequent ovulation combined with estrogen-mediated suppression of FSH and stabilization of the endometrium provide the primary contraceptive mechanisms of action of Cyclo-Provera.

Several studies demonstrated effective and consistent suppression of ovulation following Cyclo-Provera injection as determined by serum levels of estrogen and progesterone and urinary levels of pregnanediol and pituitary gonadotropins.

After three months of Cyclo-Provera administration, endometrial biopsy specimens showed regressed, non-functioning endometrium in nine of ten studies performed. The endometrial suppression associated with Cyclo-Provera use was reversible after treatment discontinuation. No abnormal endometrial glands or stromal changes suggestive of neoplasia were reported in any of the studies performed.

Two lower-dose formulations of Cyclo-Provera, one containing 12.5 mg of medroxyprogesterone acetate with 5 mg of estradiol cypionate and the other containing 12.5 mg medroxyprogesterone acetate with 2.5 mg of estradiol cypionate did not consistently suppress ovulation. Of the patients using the former formulation, 1 in 20 (5%) ovulated after 3 months of product use. Ten of 24 patients (42%) using the latter formulation ovulated after 3 months of product use.

2.4 International Marketing Experience

Human experience with Cyclo-Provera includes both comparative and introductory studies that have been conducted in over twenty countries. Cyclo-Provera (also known as CYCLOFEM™, CYCLOFEMINA™, CycloGeston or Novafem) is currently marketed in several Latin American and Asian countries. Approximately ——— units were sold worldwide during 1996, primarily in Indonesia and Mexico. During the first six months of 1997, ——— units had been sold worldwide, with no withdrawal from marketing in any country for safety reasons.

3.0 Description of Clinical Data Sources

The Three Pivotal Studies:

The pivotal trials which provide safety and efficacy data for this submission were initiated as early as 1984, and one trial (the Multicountry study) was conducted prior to the development of most international GCP guidelines. As a result, information collected on case record forms (CRFs) during the studies was not all inclusive, and CRFs from two of the three pivotal trials (Egypt and China) as well as from several sites of the third pivotal trial were not available for review and auditing. Because of these facts, the current sponsor conducted a reanalysis of data from available CRFs for the Multicountry study and from raw data files for the Egypt and China studies to prepare integrated safety and efficacy data bases for the three pivotal trials.

3.1 Summary of the Three Pivotal Studies

The three major controlled trials (the pivotal studies) include:

Multicountry Study, WHO Project 83913—This was a large phase III, randomized, controlled study conducted at 18 sites in 13 countries. The study was initiated in 1984 and compared the efficacy and safety of Cyclo-Provera and another monthly injectable contraceptive, Mesigyna. Two-thousand, three-hundred ninety-six women were enrolled in the Multicountry Study, 1202 of whom were randomized to the Cyclo-Provera treatment group and 1194 of whom were randomized to the Mesigyna treatment group. All volunteers enrolled were of one of three ethnic groups—White, Hispanic or Asian. Of the women in the Cyclo-Provera treatment group, 572 were of white, 480 were of Hispanic and 150 were of Asian ethnic groups, respectively.

The Egypt Study, WHO Project 88911—This was a multicenter, randomized, controlled study comparing the safety and efficacy of Cyclo-Provera and Mesigyna. The trial was conducted from November 1, 1989 to July 31, 1992. Two-thousand-four women had data analyzed, 1111 in the Cyclo-Provera treatment group and 1093 in the Mesigyna treatment group. All volunteers enrolled were classified as of white race.

The —— Study, WHO Project 87903—This was a multicenter, randomized, controlled study comparing the safety and efficacy of Cyclo-Provera, Mesigyna and Chinese Injectable No.1 (250 mg 17-hydroxy-progesterone caproate and 5 mg estradiol valerate). The study was conducted from October 10, 1988 to July 12, 1991. Data from a total of 3918 patients were analyzed: 1955 in the Cyclo-Provera treatment group and 1960 in the Mesigyna group. An analysis of data for volunteers receiving Chinese injectable No.1 was not provided with the current submission.

Other Supportive Studies--Thirteen other supportive phase III studies were summarized in the NDA. Four of these studies were controlled studies which compared Cyclo-Provera to Mesigyna, DMPA and a 28-day combined oral contraceptive (COC) [Ortho-Novum 1/35]. A total of 667 women received Cyclo-Provera in these trials. Nine other phase III uncontrolled introductory studies provided supportive safety and efficacy data. In these trials, a total of 11,047 women received Cyclo-Provera to evaluate the safety, efficacy, acceptability and service delivery issues related to product administration in a wider community setting.

Supportive safety and efficacy data were also provided by 21 phase II dose-selection and proof-of-concept studies conducted in 1305 women receiving Cyclo-Provera.

4.0 Pivotal Study #1: The Multicountry Study (WHO Project 83913)

4.1 Study Objective

The primary objective of this study was to compare the efficacy and safety of Cyclo-Provera and Mesigyna administered monthly for 12 treatment months.

4.2 Study Design

This was a one year, randomized, active-controlled, parallel, 18 center study conducted in 13 countries (Hungary, Egypt, Thailand, Philippines, USSR, UK, Indonesia, Pakistan, Italy, Cuba, Mexico, Chile and Guatemala). Women enrolled in the study were randomized to receive a 1.0 ml intramuscular injection of either Cyclo-Provera or Mesigyna in the gluteal area every 30 +/- 3 days for a period of one year.

Reviewer's comments:

(1) As noted in Section 3.1 of this review, all of the pivotal trials failed to include volunteers that could be considered representative of the African-American population (other than possibly the Cuban centers in the Multicountry trial). This exclusion could be of significance due to the fact that pharmacokinetic parameter differences were noted in women of different ethnic groups who received Cyclo-Provera in the studies.

(2) The formulation of Cyclo-Provera used in this study was different than that used in both the Egypt and China studies. The latter formulation is proposed for marketing in the U.S. The Multicountry trial used a Cyclo-Provera formulation that contained 1.0 ml of saline diluent, as opposed to 0.5 ml of saline diluent which was used in the other two pivotal trials.

A bridging study demonstrating the bioequivalence of the two formulations was initially requested of the sponsor. However, in the NDA submission provided, the sponsor states that due to the long development process for Cyclo-Provera, information regarding the manufacture of clinical supplies for the early clinical trials (one of which was the Multicountry trial) is no longer available. This fact would preclude performance of a

bridging pharmacokinetic study designed to demonstrate bioequivalence of the two formulations. Per the biopharmaceutical review, the additional volume of diluent is unlikely to have resulted in substantial differences in bioavailability. Therefore, a bridging study is not be required.

4.3 Study population

Patient characteristics for participants enrolled in the Multicountry trial, other than ethnic group classification, are summarized in table 1 below. Both treatment groups were noted to be very similar for all evaluated characteristics.

Table 1. Admission characteristics of subjects (modified from volume 29 page 8/15/87, Revised NDA)

	Cyclo-Provera	Mesigyna	All Women
Number of subjects	1168	1152	2320
Age (years) mean	26.6	26.7	26.6
SD	4.4	4.4	4.3
Weight (kg) mean	56.1	56.0	56.1
SD	11.3	11.2	11.2
Height (m) mean	1.56	1.56	1.56
SD	0.07	0.07	0.07
Quetelet mean	23.0	22.9	23.0
index (kg/m^2) SD	4.4	4.3	4.4
Systolic BP mean	111.7	111.2	111.5
(mm Hg) SD	9.9	10.0	10.0
Diastolic mean	72.0	71.8	71.9
BP (mm Hg) SD	8.4	8.6	8.5

4.4 Inclusion and Exclusion Criteria

Participants had to satisfy the following criteria for inclusion in the study:

- healthy, informed female volunteers;
- age between 18 and 34 years, inclusive and not post-menopausal;
- of proven fertility;
- willing to rely upon the treatment product as a method of fertility regulation;
- willing to abide by the protocol;
- willing and able to return at the prescribed intervals for follow-up;
- not be presently lactating and must have had at least one normal menstrual cycle prior to admission to the study;
- for post partum subjects, must have had one normal menstrual cycle since delivery and regular menstrual cycles for 6 months prior to pregnancy;
- for post-abortion subjects, must have menstruated regularly during the six months prior to the pregnancy terminating in abortion and could receive their first injection during any menstrual period after the abortion;
- for all other subjects, must have been menstruating regularly during the last 6 months with regular menstrual cycles of length 24-35 days. Subjects whose entry into the study was deferred would be provided with alternative methods of contraception;
- ability to keep a menstrual diary card.

Participants having any of the following conditions or satisfying any of the following criteria were excluded from the study:

- diabetes (known or suspected);
- Papanicolaou smear grades 3, 4 or 5;
- history of thromboembolism including cerebrovascular disorders or incapacitating migraine;
- vaginal bleeding of unknown etiology (i.e. other than attributable to menses);
- confirmed hypertension (systolic blood pressure greater than 140 or diastolic blood pressure greater than 90), with blood pressure taken in the sitting position;
- pregnancy;
- recent or severe liver disease, including recurrent pruritis of pregnancy;
- use of the following drugs: barbiturates, anti-convulsants, rifampicin, systemic steroids, drugs affecting the cardiovascular or hepatic systems, or any drug used prophylactically on a long-term basis;
- known or suspected malignancy;
- abnormal discharge from nipples;
- DMPA administered in the 6 months (180 days) prior to admission, or NET-EN administered 4 months prior to admission;

Reviewer's comments:

(1) Information regarding eligibility for participation in the trial based on the inclusion and exclusion criteria was collected on a CRF entitled the "Screening Form". These forms were not duplicate forms, and once completed, the screening form was to be kept with the patient's records and not sent to the sponsor. Since most of the source documents for this trial have been destroyed, it is not possible to ensure that all patients enrolled in the study met the entry criteria and were at risk of pregnancy at admission.

(2) The requirement that women in the post-partum period have only a single normal menstrual cycle after delivery in order to be eligible for enrollment in the trial, may not have been sufficient to ensure the return of ovulation (and hence risk of pregnancy). Only 30% of women in the post-partum period resume ovulation by 90 days post-delivery. Inclusion of these women in the trial could have resulted in a misleadingly low failure rate. No information was available on the number of women in the post-partum period who were enrolled in the trial nor time since delivery prior to admission and, hence, no conclusions about this effect on efficacy rate could be made.

(3) The administration of the first test product injection "during any menstrual period" after a pregnancy termination may have resulted in the inclusion of patients who had not reestablished regular menstrual cycles and thus might not have been at risk of pregnancy. Fifty percent of women in the post-abortion period resume ovulation by 3 weeks post-procedure; however, bleeding in the immediate post-abortion period can be irregular, can indicate an incomplete procedure, and (unless regular cyclic bleeding patterns have resumed) does not necessarily represent return of ovulatory function. Inclusion of these patients could also have resulted in a misleadingly low failure rate. Information on the number of women in the immediate post-abortion period who were enrolled in the trial was not collected in this study; therefore no conclusions about this effect on efficacy rate could be made.

(4) Women who had received DMPA injections within 6 months prior to enrollment were excluded from study participation. However, clinical studies have demonstrated that ovulation does not resume post-DMPA injection until MPA levels fall below 0.1 ng/ml or become undetectable.

These serum levels occur approximately 7.5-9 months after DMPA administration[1,2]. It has also been noted that fertility resumes on average 10 months following the last DMPA injection, but ovulation suppression may persist for as long as 22 months post-administration[3]. Inclusion of previous DMPA users whose last injection was less than 10 months prior to enrollment could have resulted in fewer contraceptive failures if these women were not at risk of pregnancy at the time of admission to the study. Although the percent of prior DMPA-users in this study was stated to be 2.3%, a review of the raw data reveals that 71.4% of prior injectable users were admitted to this study with their last injection occurring less than 10 months prior to entry. In addition, data documenting that DMPA users had 6 months of regular menstrual cycles prior to admission to the study was not available.

(5) Women using COCs were not required to undergo a wash-out period prior to enrollment in the study. Inclusion of former COC-users who had not resumed regular menstrual cycles after discontinuation of COCs could also have resulted in a misleadingly low failure rate if these women were not ovulating (and hence not at risk of pregnancy) at enrollment. In this study, 26.5% of women enrolled used "the pill" as their last contraceptive method prior to enrollment. A review of raw data reveals that 60.0% of prior OC users were admitted to the study with last OC use occurring less than three months prior to enrollment. Since the average time for return to ovulation post COC use is 2-3 months[4], these women may not have resumed ovulation (and hence might not have been at risk of pregnancy) at enrollment.

(6) While the requirement that a woman admitted to the study have a history of 6 months of regular menstrual cycles prior to enrollment should have ensured that women admitted (whether former DMPA users or not) were ovulating and at risk of pregnancy, the information related to menstrual cycle history prior to enrollment (other than LMP) was collected on the "Screening Visit Form" that was kept in the patient's source document at the trial site and not returned to the sponsor. As discussed in Section 4.9 below, a majority of the sites participating in this trial had no source documents or CRFs available for review and audit. Thus, verification that patients met the entry criteria for admission to the trial (and were at risk of pregnancy) was not possible.

(7) Due to the above concerns, the number and percentage of patients admitted to the trial who had not resumed regular, ovulatory menstrual cycles (and hence, may not have been at risk of pregnancy) at entry is unknown; therefore, pregnancy rates from this trial can not be accurately determined.

4.5 Screening period

During the screening period informed consent was obtained from trial participants, and a physical examination, including gynecological examination, was performed to assess patient eligibility to participate in the trial. Pap smears were obtained on all patients screened. Patients were then given a menstrual diary card and instructed regarding its use.

4.6 Treatment period

Each patient enrolled in the trial was seen monthly (defined as every 30 +/- 3 days) for Cyclo-Provera injections and every third month for follow-up. At each monthly visit menstrual history was reviewed and details of the menstrual diary form verified. Safety monitoring included measurements of blood pressure

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[1] Ortiz A et al. J Clin Endo Metab. 1977. Jan, 44(1): 32-38.
[2] Mishell DR et al. J Repro Med. 1996. May, 41(5): 381-390.
[3] Kaunitz AM. Intl J Fert Womens Med. 1998. Mar, 43(2): 73-83.
[4] ACOG Technical Bulletin. October, 1994. Number 198: 1-10.

and weight, as well as performance of breast and vaginal examinations every three months. A complete physical examination including a Pap smear was repeated at study termination.

During the trial, patients were discontinued for any of the following reasons:

1. Medical reasons

    a. pregnancy;
    b. any condition which the physician in charge considered a contraindication to the patient continuing the contraceptive method or the study.

2. Personal reasons

    a. desire for pregnancy;
    b. inability to continue;
    c. patient wished to drop out.

4.7 **Statistical Procedures:**

The duration of use of the two study products was compared for each discontinuation reason by means of the logrank test as recommended by —— All logrank statistics quoted have one degree of freedom.

The following censoring convention was used in the analysis: A woman who returned late for a particular injection was credited with protection for the whole injection interval provided she actually received the next injection. If she refused the injection, she was credited with protection to 33 days from her last injection. If a woman received an injection and was subsequently lost to follow-up she was not credited with any post injection protection.

4.8 **Evaluation criteria:**

The primary study endpoint and criterion for measurement of efficacy was pregnancy rate calculated as both a Life Table pregnancy rate and a Pearl index. Pregnancy was assessed by performance of a urine pregnancy test on subjects with amenorrhea lasting for more than 45 days, if clinically indicated.

Reviewer's comments:

(1) As described by the sponsor, the criteria for performing a pregnancy test to assess contraceptive failure may have resulted in a lack of detection of some pregnancies and an aberrantly low failure rate. All study patients with amenorrhea should have had a pregnancy test performed. Although not required in the study protocol, patients should have had a pregnancy test performed at the final study visit to ensure non-pregnant status at study discontinuation. In contraceptive trials, pregnancy testing is typically performed at each follow-up visit and at early discontinuation and study completion.

The degree to which the lack of appropriate performance of pregnancy testing affected efficacy rates for Cyclo-Provera cannot be determined from the data provided.

(2) Review of the CRFs revealed that the only CRF which contained a field for pregnancy testing was the "Pregnancy Report Form". The absence of this field on follow-up, unscheduled visit and discontinuation forms could have decreased the likelihood of pregnancy testing and result recording when testing was done.

4.9 Withdrawal and Compliance

Of 2320 women admitted to the study (1168 who received Cyclo-Provera and 1152 who received Mesigyna), 1487 women completed the study. The number of patients who completed the study from each of the two treatment groups was comparable with 756 of the Cyclo-Provera-users and 731 of the Mesigyna-users completing the study.

Four-hundred-twelve patients receiving Cyclo-Provera and 421 patients receiving Mesigyna discontinued the study prior to completion of all visits. The reasons for these discontinuations and life-table cumulative discontinuation rates are listed in table 2.

Table 2: Reasons given for terminating study by number of women and by cumulative life-table discontinuation rate at 12 months

Reason given for terminating study	Number of women		Cumulative life-table discontinuation rates	
	Cyclo-Provera	Mesigyna	Cyclo-Provera	Mesigyna
Pregnancy	0	2	0	0.2
Amenorrhea	21	16	2.1	1.6
Bleeding-heavy	6	10	0.5	1.0
Bleeding-prolonged	26	18	2.5	1.8
Bleeding-heavy/prolonged	13	17	1.2	1.9
Bleeding-irregular	8	13	0.8	1.3
Spotting	4	7	0.4	0.8
Other bleeding problems	7	7	0.7	0.7
Other medical reasons	62	63	6.3	6.6
Desired pregnancy	26	30	2.8	3.2
No longer needed	18	29	1.9	3.2
Other personal reasons	55	62	3.8	3.3
Late for injection	33	29	3.5	3.1
Received medication	14	10	1.4	1.0
Lack of supplies	5	5	0.5	0.5
Lost to follow-up	110	103	11.4	10.5
Total termination	412	421	35.5	36.8
Total completing the study	756	731	64.5	63.2

Other medical reasons for termination included weight gain, hypertension, headache and dizziness, with the most common of these reasons being headache and dizziness which occurred in 29/125 of study participants using either product. Seventeen of the 125 women who discontinued for other medical reasons did so for weight gain, with 10 of these 17 having received Cyclo-Provera . Thus, ten of 412 discontinuations (2.4%) in the Cyclo-Provera-treatment group were for weight gain.

Discontinuation rates varied widely from center to center. Overall cumulative discontinuation rates for patients receiving Cyclo-Provera varied from a low of 9.0% in Jakarta to 60.3% in Rome. Discontinuation

rates specifically for bleeding-related problems also varied considerably among centers, and the differences were thought to be reflective of cultural differences in tolerance to menstrual cycle disturbances as well as to differences in the quality of medical counseling at various study centers.

Reviewer's comments:

(1) One-hundred-ten patients in the Cyclo-Provera treatment group were lost to follow-up. These patients accounted for 9.4% of women in this treatment group, and compared to a similar number and percentage of women lost-to-follow-up in the Mesigyna treatment group (8.9%). These lost-to-follow-up rates are comparable to the lost-to-follow-up rates seen in a large scale, phase III WHO-sponsored clinical trial of DMPA (lost-to-follow-up rate = 7.6 %) [5]. Clinical conditions that may have contributed to or may have been associated with loss to follow-up can not be determined for any patient in this study.

(2) Large site-by-site variations in discontinuation rates were noted. An attempt was made to audit the Jakarta and Rome study sites; however, all records had been destroyed from Jakarta site and no source documents were available for Rome; therefore, an explanation for these large variations in discontinuation rates could not be determined.

4.10 Efficacy analysis

No pregnancies occurred in the Cyclo-Provera treatment group. Two pregnancies occurred in the Mesigyna treatment group and were attributed to method failure. In one Russian patient receiving Mesigyna, contraception was estimated to have occurred 7 days after the third injection; the other pregnancy in this treatment group was reported in Pakistan and was estimated to have occurred 3 days before the second Mesigyna injection.

4.11 Safety analysis

In the Multicountry trial, a maximum of two medical events per visit and two reasons for discontinuation were coded, with no classification of these events by body system or seriousness. Because of the manner in which medical events and discontinuations from this trial were recorded, the sponsor performed a reanalysis of the Multicountry safety data. From this reanalysis of safety data, five serious medical events were identified from the Multicountry study. Two of these events occurred in women treated with Cyclo-Provera, while three occurred in women treated with Mesigyna. Additionally, two women treated with Cyclo-Provera developed diabetes mellitus and subsequently discontinued their participation in the trial.

Serious medical events:

Of the 1202[6] patients receiving Cyclo-Provera in this trial, two experienced serious medical events. One patient, a 29 year-old woman, experienced chest pain requiring hospitalization 4 days after a single

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[5] WHO Task Force on Long-Acting Systemic Agents for Fertility Regulation. Contraception. 1986. 34(3): 224-235.

6 The total number of women enrolled was reported to be 2320 in the WHO publication of results from the Multicountry trial. Of these 2320 women, 1168 received Cyclo-Provera and 1152 received Mesigyna. The reanalysis of the data by the sponsor showed that a total of 2396 women were enrolled in the Multicountry study, with 1202 women receiving Cyclo-Provera and 1194 women receiving Mesigyna. The discrepancy in the number of women who received Cyclo-Provera in this trial (a total of 34 additional patients for the reanalysis performed by the sponsor) was attributed to the facts that (1) the reanalysis included all intent-to-treat patients and (2) WHO's cut-off date for analysis occurred prior to receipt of all CRFs for the study.

injection of Cyclo-Provera. Upon examination, she was noted to have a blood pressure of 150/90 mm Hg and was hospitalized with a diagnosis of angina pectoris. She was treated with Betoloc (a beta-blocker) and Sedatrium (an anxiolitic) and was discontinued from the study on day 33. No other information on this patient's outcome was available. A second patient, a 24 year-old woman, died as a result of an accident, the date and cause of which are unknown.

Additionally, two other patients receiving Cyclo-Provera were discontinued from the study with a diagnosis of diabetes mellitus. In one patient glucosuria was found with a corresponding serum glucose of 8.3 mmole/L. A second patient discontinued at visit 8 because of changes noted in blood pressure and serum glucose level. No further information was available on either patient. Direct causality could not be determined for either of these cases.

Only 1 patient discontinued her participation in this trial due to development of anemia; however, routine monitoring of Hg and Hct was not performed throughout the study.

Frequent Medical Events:

Medical events reported by $\geq$ 1% of study participants were similar in the Cyclo-Provera-treatment and Mesigyna-treatment groups. In the Cyclo-Provera-treatment group, the highest frequency of medical events occurred in the urogenital system (47.2%), the body as a whole (18.9%) and the nervous system (7.7%). Medical events related to the urogenital system included bleeding-related events, with > 5% of women receiving Cyclo-Provera reporting menorrhagia, amenorrhea, vaginal spotting, metrorrhagia and hypomenorrhea. (The frequency of these events was similar to that seen in the Mesigyna treatment group of this study as well as in the other two pivotal trials as described below.) Headache was also reported by >5% of patients receiving Cyclo-Provera in this study.

The number of women reporting events of potential clinical significance in the Multicountry study as categorized by COSTART body system are included in table 5.

Table 5: Number of Women Reporting Medical Events of Potential Clinical Significance (table modified from Table 3.G-20 page 3/1/135, Revised NDA)

COSTART Body System and Preferred Term	N (N=1202)	%
CARDIOVASCULAR		
Hypertension	6	0.5
Syncope	3	0.3
Palpitations	1	0.1
Angina Pectoris	1	0.1
BODY AS A WHOLE		
Chest pain	10	0.8
Allergic reaction	3	0.3
Injection site-reaction pain	2	0.2
DIGESTIVE		
liver function test abnormality	1	0.1
ENDOCRINE		
diabetes mellitus	2	0.2
RESPIRATORY		
dyspnea	8	0.7
SKIN/APPENDAGES		
rash	6	0.5
maculopapular rash	1	0.1
urticaria	0	0.1

Evaluation of bleeding patterns:

Evaluation of bleeding patterns was based on data obtained from menstrual diaries using the approach suggested by Rodriguez et al.[7] The menstrual diary was divided into four reference periods of 90 days each, starting on the day of first injection and ending 360 days later at the approximate anniversary of the first injection.

Bleeding was defined as any bloody vaginal discharge which required the use of pads or tampons for protection. Spotting was defined as any bloody vaginal discharge not sufficient to require protection. For each woman, the following six summary statistics of bleeding events were calculated for each reference period:

- number of bleeding/spotting days
- number of bleeding/spotting episodes
- mean length of bleeding/spotting episodes
- mean length of bleeding/spotting free intervals
- number of spotting days
- number of spotting-only episodes

[7] Rodriquez G, Faundes-Latham A and Atkinson LE. An approach to the analysis of menstrual patterns in the critical evaluation of contraceptives. Stud. Fam. Plann. 7:42-51 (1976)

Bleeding patterns were determined in each successive 90 day reference period. Women were classified into one of seven clinical groups of bleeding patterns per the Rodriguez criteria, six of which were labeled "clinically unacceptable" and are listed below:

- no bleeding throughout the reference period;
- prolonged bleeding: at least one bleeding/spotting episode lasting more than 14 days;
- frequent bleeding: more than 5 bleeding/spotting episodes;
- infrequent bleeding: 1 or 2 bleeding/spotting episodes;
- irregular bleeding: 3 to 5 bleeding/spotting episodes and less than 3 bleeding/spotting-free intervals of 14 days or more;
- combinations of the above categories;

Bleeding patterns classified as "clinically acceptable" were those described by none of the above criteria (for example, a pattern with 3 to 5 bleeding/spotting episodes, none longer than 14 days and at least 3 bleeding/spotting-free intervals of 14 days or more).

Table 6 compares the summary statistics regarding bleeding events for each reference period of use of Cyclo-Provera.

Table 6: Comparison of Summary Statistics Regarding Bleeding Events for each 90-day Reference Period of Cyclo-Provera use in the Multicountry Study (modification of Table 1, Volume 29, page 8/15/106, Revised NDA)

	Reference period							
	I days 1-90		II days 90-180		III days 180-270		IV days 270-360	
	Median	Interquartile Range*	Median	Interquartile Range*	Median	Interquartile Range*	Median	Interquartile Range*
# bleeding/spotting days	18.0	11.0	16.0	7.8	15.0	9.0	15.0	9.0
# bleeding/spotting episodes	4.0	2.0	3.0	1.0	3.0	1.0	3.0	1.0
# of spotting days	7.0	9.0	6.0	7.0	6.0	7.0	5.9	7.0
# of spotting only episodes	1.0	1.0	0.0	1.0	0.0	1.0	0.0	1.0
mean length of bleeding/spotting episode	4.5	2.1	5.0	2.3	4.5	2.1	4.5	2.0
mean length of bleeding/spotting-free intervals	18.0	8.3	19.1	7.0	19.5	7.6	19.5	7.8
# diaries for analysis	1001		885		802		730	

*interquartile range represents the interval between the 25th and 75th percentile

Review of bleeding-related data for this trial revealed that 84 Cyclo-Provera patients (7.2%) at a variety of the study sites received various treatments for bleeding during the study. These patients received at least one treatment for bleeding disturbances. Treatments included supplemental ethinyl estradiol (oral and injectable), supplemental progesterone (oral and injectable), uterotonics, ascorbic acid and vitamin K. No mention was made of how data for these patients were handled in the analysis of bleeding-related events for this trial.

Reviewer's comments:

(1) **The fact that 7.2% of women in this trial required treatment for bleeding related to Cyclo-Provera use is of concern for several reasons: (a) since assessment of bleeding pattern changes was one of the primary safety endpoints in this trial, treatment of bleeding throughout the trial was inappropriate and confounds the data on bleeding pattern changes. The degree to which these results influenced the overall bleeding-related safety assessment of Cyclo-Provera is uncertain because no description of data management (either by truncation or exclusion) is provided; (b) treatments for bleeding disturbances were quite variable and included products that could treat anemia (iron, "hemostatics", vitamins) or could influence efficacy (supplemental estrogen and progesterone); (c) Because irregular bleeding can be a symptom of more serious medical conditions (uterine cancer, cervical cancer, pregnancy), the possibility that multiple treatments occurred without adequate work-up for other serious problems is of concern.**

(2) **The mean length of bleeding and spotting episodes throughout all reference periods was approximately 4-5 days.**

(3) **Although the bleeding patterns described were not associated with development of anemia requiring discontinuation, patient and provider education regarding expected bleeding patterns with Cyclo-Provera use will be important for product use and acceptability as well as for the identification of pathologic conditions associated with abnormal vaginal bleeding.**

Table 7 compares bleeding patterns noted across reference periods for Cyclo-Provera use.

Table 7: Number (and percentage) of Women Experiencing Different types of Bleeding Patterns in each Reference Period of Cyclo-Provera Treatment for the Multicountry Study.
[Modified from Table 2, Volume 29, page 8/15/109, Revised NDA]

	Reference period			
Bleeding patterns	I days 1-90	II days 91-180	III days 181-270	IV days 271-360
Infrequent	53 (5.3)	122 (13.8)	136 (17.0)	87 (11.9)
Frequent	92 (9.2)	22 (2.5)	19 (2.4)	22 (3.0)
Irregular	235 (23.5)	102 (11.5)	64 (8.4)	118 (16.2)
Prolonged and Irregular	34 (3.4)	6 (0.7)	2 (0.2)	4 (0.5)
Prolonged and Infrequent	5 (0.5)	0 (0.0)	2 (0.2)	0 (0.0)
Prolonged and Frequent	8 (0.8)	3 (0.3)	0 (0.0)	0 (0.0)
No Bleeding	3 (0.3)	2 (0.2)	9 (1.1)	17 (2.3)
Unacceptable patterns	433 (43.3)	263 (29.7)	233 (29.1)	249 (34.1)
Acceptable patterns	568 (56.7)	622 (70.3)	569 (70.9)	481 (65.9)

Reviewer's comments:

(1) The data presented show that certain types of bleeding patterns improve with increasing duration of Cyclo-Provera use in this trial. Bleeding disturbances were most frequent during the first 3 months of product use (i.e., first reference period). Compared to the first reference period, the decrease in the incidence of prolonged and frequent bleeding patterns with continued product use is one of the more clinically significant findings related to bleeding pattern changes during the trial. However, the degree to which treatment for bleeding disturbances influenced these results is unknown.

(2) Although the study reports that only 1 volunteer developed anemia and discontinued her participation in the trial, routine monitoring of Hg or Hct was not performed during the study. Therefore, the true incidence of anemia can not be verified.

(3) The incidence of amenorrhea after 12 months of Cyclo-Provera use was low at 2.3%.

5.0 Pivotal Trial #2: The Egypt Study (WHO Project #88911)

5.1 Study Objective

The primary objective of this study was to compare the efficacy and safety of Cyclo-Provera and Mesigyna administered monthly for 12 treatment months. An additional study objective was the determination of product acceptability for both Cyclo-Provera and Mesigyna.

5.2 Study Design

This was a randomized, controlled , parallel group study performed at 11 Egyptian research centers involving 2400 women, 1111 of whom received Cyclo-Provera and 1093 of whom received Mesigyna. Women enrolled in the study were randomized to receive a 1.0 ml injection of either Cyclo-Provera or Mesigyna in the gluteal area every 30 +/- 3 days.

Reviewer's comment:

Although published study reports state that the formulation used in this trial differed from that proposed for marketing in the U.S. in that a 1.0 ml (as opposed to a 0.5 ml) suspension was administered, the documentation provided by the sponsor showed that the formulation used in this study was the 0.5 ml suspension.

5.3 Study population

Patient characteristics for participants enrolled in the Egypt study, other than ethnic group classification, are summarized in Table 8 below. Both treatment groups were noted to be very similar for all evaluated characteristics.

Table 8: Admission characteristics of subjects
(modified from Tables 7 and 8, Volume 30, pages 8/16/32-33, Revised NDA)

	Cyclo-Provera		Mesigyna		All Women	
Number of subjects	1111		1093		2204	
Age (years) mean	28.9		29.2		29.0	
SD	3.7		3.7		3.7	
Weight (kg) mean	65.6		66.9		66.3	
SD	13.0		13.0		13.0	
Height (m) mean	1.58		1.58		1.58	
SD	6.0		6.0		6.0	
Quetelet Index mean	26.3		26.8		26.6	
SD	5.3		5.5		5.4	
Systolic BP mean	113.8		113.9		113.8	
(mm/Hg) SD	9.1		9.2		9.2	
Diastolic BP mean	73.6		73.6		73.8	
(mm/Hg) SD	7.0		6.8		6.9	
Last contraceptive used	n	%	n	%	n	%
Pills	566	50.9	550	50.3	1116	50.6
IUD	242	21.8	239	21.9	481	21.8
injectables	44	4.0	39	3.6	83	3.8
others	29	2.6	33	3.0	62	2.8
none	230	20.7	232	21.2	462	21.0
Abortion within the past six months	n=46	4.1%	n=47	4.3%	n=93	4.2%

5.4 Inclusion and Exclusion Criteria

Inclusion criteria were identical to those for the Multicountry trial with the following differences:

-the age range for inclusion was 20-35 years;
-proven fertility was defined as having had at least two children;

Exclusion criteria were identical to those from the Multicountry trial.

Reviewer's comments:

(1) Inclusion and exclusion criteria for this study are very similar to those for the Multicountry study and are limited by the same characteristics as those noted in the "Reviewer's comments" in section 4.4 of this review.

(2) Information on the number and percentage of women who had undergone an abortion prior to enrollment was available for this study.

5.5 Screening and Treatment Periods

Procedures performed during the screening and treatment periods were essentially the same as those for the Multicountry study. Changes in weight, quetelet index, systolic and diastolic blood pressure were calculated between admission and each of the follow-up visits at months 3, 6, 9, 12 and at discontinuation.

5.6 Statistical Analysis

Two factors repeated measurement (ANOVA) were used to test the significance of changes over time in the characteristics noted above. Differences in changes in these characteristics were also calculated between the Cyclo-Provera and Mesigyna treatment groups. Reason-specific discontinuation rates for each treatment group was calculated using the lifetable analysis technique.

5.7 Evaluation Criteria

The primary study endpoint and criterion for measurement of efficacy was pregnancy rate, as described in Section 4.8 above. Pregnancy testing was not performed at admission nor at termination of the study. In addition, no parameters for evaluation of amenorrhea were provided for this study.

Reviewer's Comment:

The lack of routine pregnancy testing at admission, at study termination and in response to complaints of amenorrhea throughout the trial could have resulted in failure to detect several pregnancies during Cyclo-Provera use. The extent to which the efficacy rate was influenced by these omissions cannot be determined.

5.8 Withdrawals and Compliance

Of 2252 patients admitted to the study (1137 who received Cyclo-Provera and 1115 who received Mesigyna), 1375 women completed the study. The number of patients who completed the study from each of the two treatment groups was comparable with 702 of the Cyclo-Provera-users and 673 of the Mesigyna-users completing the study.

Of the 1137 patients recruited for the Cyclo-Provera arm of the study, 26 women were noted to have protocol violations and were excluded from the safety and efficacy analyses. A total of 1111 patients were included in final efficacy and safety analyses for Cyclo-Provera.

Four-hundred-nine patients receiving Cyclo-Provera and 420 patients receiving Mesigyna discontinued the study prior to completion of all visits. The reasons for these discontinuations and life-table cumulative discontinuation rates are listed in Table 9.

Table 9: Reasons given for terminating study by number of women and by cumulative life-table discontinuation rate at 12 months
(Modified from Table 14, Volume 30, Revised NDA)

Reason given for terminating study	Number of Women		Cumulative Life-Table Discontinuation Rate	
	Cyclo-Provera	Mesigyna	Cyclo-Provera	Mesigyna
Pregnancy	2	4	0.19	0.41
Amenorrhea	24	12	2.74	1.38
Bleeding-heavy	11	18	1.26	1.92
Bleeding-prolonged	14	17	1.48	1.98
Bleeding-heavy/prolonged	21	40	2.46	4.70
Bleeding-irregular	14	22	1.60	2.40
Spotting	4	8	0.43	0.97
Other bleeding problems	3	1	0.38	0.11
Other medical reasons	37	41	7.79	4.72
Desired pregnancy	17	23	1.87	2.86
No longer needed	37	28	4.25	3.19
Other personal reasons	115	117	12.42	12.79
Late for follow-up	101	94	11.08	10.67
Method switching	7	7	0.79	0.81
Missed injection	5	3	0.60	0.18
Lost to follow-up	51	36	4.10	2.71
All other reasons	164	140	15.91	14.04
Total termination	409	420	38.94	37.98
Total completing the study	702	673	61.06	62.02

The lost-to-follow-up rate was almost 40% higher in Mesigyna group (51/1111 = 4.6%) than in the Cyclo-Provera group (36/1093 = 3.3%). The lost-to-follow-up rate for Cyclo-Provera-users in this study was one-half that seen in the Multicountry study.

Discontinuation rates varied widely from center to center. Overall cumulative discontinuation rates for patients receiving Cyclo-Provera varied from a low of 13.1% in Alexandria to 91.7% in Zagazig. Variations in the proportions of women discontinuing their participation for bleeding related problems by study site were noted, ranging from 1.1% in Al Ashar to 18.1% in El Galaa.

Reviewer's comment:

The lost-to-follow-up rate for both treatment groups was significantly lower in this study as compared to the Multicountry study. In addition, the loss-to-follow-up rate for the Cyclo-Provera treatment group was lower than that for the Mesigyna treatment group in this trial. No explanation for these differences was provided.

5.9 Efficacy Analysis

Ten pregnancies were identified after study initiation, four of which were due to inadvertent admission of patients pregnant prior to enrollment. Of the remaining six pregnancies, all were classified as method failures, and two occurred in the Cyclo-Provera treatment group. These two pregnancies are described as follows:

1. Patient # 436 - At admission, this patient was 26 years old, weighed 87 kg and was 160 cm tall. She had used oral contraceptives until [redacted] and received her first injection of Cyclo-Provera on [redacted]. On the date of her second injection [redacted] the patient reported no menstrual period since her first Cyclo-Provera injection. The patient received her second injection as scheduled. She remained amenorrheic, and at the scheduled visit for her third injection, a pelvic exam was performed, revealing an enlarged uterus. The patient's last menstrual period (LMP) was [redacted] giving her an estimated date of conception based on LMP of 12 days after the first Cyclo-Provera injection. At delivery of a full-term, healthy infant, the patient's estimated date of conception was calculated as 8 days after the first Cyclo-Provera injection.

2. Patient # 107 - At admission, this patient was 32 years old, weighed [redacted] and was [redacted] tall with a normal pelvic and breast exam. She had used an IUD until the date of the first Cyclo-Provera injection [redacted]. The patient received a second and third Cyclo-Provera injection, the former given on [redacted] and the latter on [redacted] (36 days from the previous injection). The patient's menstrual diary showed a menstrual flow of 6 days on the 18th day of the cycle of her first injection, followed by one normal menstrual period 29 days later that lasted 5 days. On [redacted] the patient was noted to have a 6 to 8 week sized uterus on pelvic examination. The patient's LMP was [redacted] and her estimated date of conception based on LMP was [redacted] (day 30 of the second injection interval or 57 days from the first injection). The patient was lost to follow-up.

Reviewer's comments:

(1) Pelvic exam alone was used to assess pregnancy status at enrollment to the study. This process is not adequate to identify pregnancies as demonstrated by the fact that four women were admitted to the study already pregnant.

(2) Patient complaints and changes in menstrual cycle patterns unaccompanied by pregnancy testing is not an acceptable procedure for detecting pregnancies. In this study, patients received up to three injections while pregnant, confirming the potential for missing pregnancies throughout the trial.

(3) Not all pregnant patients had ultrasound examinations for determination of fetal age. Pediatric evaluation of gestational age (Dubawitz scoring) was not reported in this study.

5.10 Safety Analysis

Potentially Significant Medical Events:

No CRFs were available for either the Egypt or China studies. As a result, a monitor for the sponsor reviewed the data listings of medical events from these two trials and classified events as having "potential clinical relevance". There were no narratives for medical events judged to be potentially significant per the Pharmacia & Upjohn monitor.

Reviewer's comments:

Safety information for medical events of potential clinical significance in this trial was obtained after reanalysis of safety data by the sponsor as described in Section 8 below. Detailed information on specific medical problems experienced by study participants using Cyclo-Provera was not available.

The safety data provided for review from this clinical trial are insufficient to draw conclusions about overall safety of Cyclo-Provera.

Evaluation of bleeding patterns:

The evaluation of bleeding patterns was similar to that used in the Multicountry study; however, the definitions of clinically acceptable bleeding patterns were different for this study. For the Egyptian study, the definitions of clinically acceptable bleeding patterns were:

- amenorrhea- no bleeding throughout the reference period;
- prolonged bleeding- at least one bleeding/spotting episode lasting 10 days or more;
- frequent bleeding- more than 4 bleeding/spotting episodes within the same reference period;
- infrequent bleeding- less than 2 bleeding/spotting episodes in the same reference period;
- irregular bleeding- a range of bleeding/spotting-free intervals greater than 17 days.

Table 10 compares the summary statistics regarding bleeding events for each reference period of use of Cyclo-Provera.

Table 10: Comparison of Summary Statistics Regarding Bleeding Events for each 90-day Reference Period of Cyclo-Provera use in the Egypt Study (modified from Table 1, Volume 30, page 8/16/139, Revised NDA)

	Reference period							
	I days 1-90		II days 90-180		III days 180-270		IV days 270-360	
	Median	Interquartile Range*	Median	Interquartile Range*	Median	Interquartile Range*	Median	Interquartile Range*
# bleeding/spotting days	15.0	7.7	13.8	6.0	13.7	6.0	14.1	6.8
# bleeding/spotting episodes	3.0	0.0	3.0	0.5	3.0	0.7	3.0	1.0
mean length of bleeding/spotting episodes	5.0	2.0	4.7	1.7	4.7	1.7	4.5	1.8
# of bleeding/spotting free intervals	4.0	1.0	3.0	0.5	3.0	0.8	3.0	1.2
mean length of bleeding/spotting free intervals	23.7	5.7	25.2	4.8	24.6	5.2	20.3	7.0
# diaries for analysis	955		825		725		625	

Approximately eight percent of patients in this study were treated with medication for bleeding-related problems associated with Cyclo-Provera use. The most common treatments administered were ebolics (prostaglandins) and anti-fibrinolytics. As soon as treatment for bleeding was initiated, menstrual diaries of treated patients were truncated as of the first day of treatment.

Reviewer's comments:

(1) Although truncation of menstrual diary data was performed as soon as treatment for bleeding related problems was initiated (thereby effectively eliminating further data contributions by these patients), these women could have had the worst bleeding-related responses to Cyclo-Provera and their removal from the analysis could have biased the bleeding-related results for the trial. Elimination of data for treated women will skew the total data available for evaluation of bleeding-related problems due to Cyclo-Provera use.

(2) Bleeding events were similar for Cyclo-Provera users in both the Egypt and Multicountry trials.

Table 11 compares bleeding patterns noted across reference periods for Cyclo-Provera use.

Table 11: Number (and percentage) of Women Experiencing Different Types of Bleeding Patterns in each Reference Period of Cyclo-Provera Treatment for the Egypt Study.
[Modified from Table 34, Volume 30, page 8/16/79]

	Reference period			
Bleeding patterns	I days 1-90	II days 91-180	III days 181-270	IV days 271-360
Infrequent	34 (3.6)	17 (2.1)	23 (3.2)	47 (7.5)
Frequent	9 (0.9)	3 (0.4)	3 (0.4)	19 (3.0)
Irregular	251 (26.3)	238 (28.8)	203 (28.0)	201 (32.2)
Prolonged and Irregular	25 (2.6)	47 (5.7)	33 (4.6)	6 (1.0)
Prolonged and Infrequent	3 (0.3)	1 (0.1)	2 (0.3)	6 (1.0)
Prolonged and Frequent	2 (0.2)	0 (0.0)	1 (0.1)	2 (0.3)
No Bleeding	6 (0.6)	10 (1.2)	13 (1.8)	20 (3.2)
Unacceptable patterns	391 (40.9)	349(42.3)	302 (41.8)	317 (50.7)
Acceptable patterns	564 (59.1)	476 (57.7)	423 (58.3)	308 (49.3)

Reviewer's comments:

(1) The bleeding patterns seen in Egypt study differ from those seen in the Multicountry study. In the Egypt study, no improvement in bleeding patterns was noted with increasing duration of Cyclo-Provera use.

(2) The incidence of amenorrhea with Cyclo-Provera use increased over time from 0.6% after 3 months of product use to 3.2% after 12 months of product use. Notably, the rate of amenorrhea at 12 months was quite low in comparison to that typically seen with DMPA (55% at 12 months) and slightly higher than that seen with COCs (approximately 1%).

6.0 Pivotal Study #3: The China Study

6.1 Study Objectives

The objectives of this study were to compare the efficacy, safety, and bleeding patterns of Cyclo-Provera, Mesigyna and Injectable #1 (250 mg 17-hydroxyprogesterone caproate and 5 mg estradiol valerate) given by monthly injections for 12 months.

6.2 Study Design

Part 1

This was a one year, randomized, active-controlled parallel study conducted in 15 Chinese centers initially involving 2710 women, 965 of whom received Cyclo-Provera, 972 of whom received Mesigyna, and 770 of whom received Chinese Injectable No.1. (Three patients were excluded from the analysis as protocol violations.) Women enrolled in the study were randomized to receive a 0.5 ml injection of Cyclo-Provera or a 1.0 ml injection of either of the other two study products in the gluteal area every 30 +/- 3 days.

Because of an unexpectedly high failure rate in the Chinese injectable No.1 arm of the study, recruitment to the study was stopped between March, 1989 and May, 1989 in various participating centers. The injection schedule for Chinese injectable No.1 was modified, and the study was restarted as "Part 2", enrolling an additional 2970 subjects. Data from parts 1 and 2 of the study were combined for the Cyclo-Provera and the Mesigyna treatment groups.

Parts 1 and 2 Combined

A total of 3915 women were admitted to both parts of this study, with 1955 enrolled in the Cyclo-Provera treatment group and 1960 enrolled in the Mesigyna treatment group. Of the women enrolled in the Cyclo-Provera treatment group, approximately one-third (n = 665) were enrolled in the Hangzhou region, one-third (n = 654) in the Shanghai region and one-third (n = 636) in the Sichuan region.

6.3 Study Population

In both parts 1 and 2 of this study, all 3 treatment groups were comparable for age, weight and height. Classification of patients by last contraceptive use and prior abortion history are summarized in Table 12 below.

Table 12: Patient Classification by Last Contraceptive Use and Previous Abortion History (modified from Table 13, Volume 30, page 8/16/252, Revised NDA)

	Cyclo-Provera		Mesigyna	
Last contraceptive used	n	%	n	%
Pill	95	4.9	112	5.7
IUD	404	20.7	443	22.6
Injectable	17	0.9	14	0.7
Other	739	37.8	719	36.7
None	700	35.8	672	34.3
Abortion	n	%	n	%
Yes	719	36.8	694	35.4
No	1236	63.2	1266	64.6

6.4 Inclusion and Exclusion Criteria

Inclusion criteria were identical to those for the Multicountry trial with the following differences:

-there was no requirement that women be "of proven fertility" as in the Multicountry and trials.

Exclusion criteria were identical to those from the Multicountry trial.

The published report by Sang[8] summarizing the results from this study indicates differences in inclusion and exclusion criteria that are not documented in the protocol for this study. These differences are:

-participants could not have used long-acting oral contraceptive pills in the 4 months prior to admission;

-postabortion women were required to have had one normal menstrual cycle since abortion

Reviewer's comment:

(1) The discrepancy in inclusion and exclusion criteria between the protocol for the study and the published study report is of concern. If the criteria listed in the published report had truly been adhered to, women enrolled in this trial would have been more likely to be at risk of pregnancy at admission than women in the Egypt and Multicountry trials. However, if these criteria were adhered to, they are not those described in the original study protocol. This raises serious doubts about the quality of the data base for this study.

6.5 Screening and Treatment Periods

Procedures performed during the screening and treatment periods were essentially the same as those for the Multicountry study. Changes in weight, Quetelet index, systolic and diastolic blood pressure were calculated between admission and each of the follow-up visits at months 3, 6, 9, 12 and at discontinuation.

Reviewer's comments:

(1) Inclusion and exclusion criteria for this study are very similar to those for the Multicountry study and are limited by the same characteristics as those noted in the "Reviewer's comments" in section 4.4 of this review.

(2) Information on the number and percentage of women who had undergone an abortion prior to enrollment was available for this study.

6.6 Evaluation Criteria

The primary study endpoint and criterion for measurement of efficacy was pregnancy rate, as described in Section 4.8 above. Pregnancy testing was not performed at admission nor at termination of the study. In

[8] Sang GW et al. A Multicenter Phase 3 Comparative Clinical Trial of Mesigyna, Cyclofem and Injectable No.1 given Monthly by Intramuscular Injection to Chinese Women. Contraception. 1995. 51: 167-183.

addition, parameters for evaluation of amenorrhea were provided in the protocol and were the same as those for the other two pivotal trials.

Reviewer's Comment:

As described for the two other pivotal trials, the lack of pregnancy testing at admission, at study termination and in response to complaints of amenorrhea throughout the trial could have resulted in failure to detect several pregnancies during Cyclo-Provera use. The extent to which the efficacy rate was influenced by these omissions cannot be determined for this study.

6.7 Withdrawals and Compliance

Part 1

Two-thousand-seven-hundred-seven patients were admitted to this part of the study, 965 of whom received Cyclo-Provera, 972 of whom received Mesigyna, and 770 of whom received Chinese Injectable No.1. The number of patients who completed this part of the study from the Cyclo-Provera and Mesigyna treatment groups was comparable with 66.1% of the Cyclo-Provera-users, 76.1% of the Mesigyna-users completing the study. Due to the high failure rate with Chinese injectable No. 1 and resultant change in injection schedule, only 25.5% of women in this treatment arm completed this part of the study.

Three-hundred-twenty-seven patients receiving Cyclo-Provera and 232 patients receiving Mesigyna discontinued the study prior to completion of all visits. The most common reasons for discontinuation for the Cyclo-Provera-treated patients were bleeding problems (47.1%) including 16.5% for amenorrhea, personal reasons (16.0%) and other medical reasons (11.6%).

Significant inter-center differences in cumulative life table discontinuation rates were found for Cyclo-Provera users ranging from a low of 0% in —— center — to a high of 65.5% at other centers not specifically named. Significant variations in the proportions of women discontinuing their participation for bleeding related problems by study site were also noted; however, specific information in this regard was not provided.

The lost-to-follow-up rate was extremely low (0.89%) for all three treatment groups combined. The lost-to-follow-up rate for Cyclo-Provera-users in this study (1.08%) was significantly lower than that seen in the Multicountry or Egypt studies.

Part 2

A total of 2970 subjects entered this part of the study, with 990 enrolled in the Cyclo-Provera treatment arm, 988 in the Mesigyna treatment arm and 992 in the Chinese injectable No.1 treatment arm.

A total of 2441 women completed the study, with 801 (80.9%) of Cyclo-Provera users and 850 (86.1%) of Mesigyna users completing their participation. One year cumulative discontinuation rates for all reasons including loss-to-follow-up was 19.1% and 13.9% for Cyclo-Provera and Mesigyna, respectively. The most common reasons for discontinuation in the Cyclo-Provera treated group were bleeding related problems (41.8%) including 17.5% for amenorrhea, other personal reasons (11.1%) and other medical reasons (10.6%).

Significant and unexplained inter-center differences in discontinuation rates were noted for Part 2 of the study, with the lowest rates again noted for the Sichuan center —— As in Part 1 of the study, no patients discontinued Cyclo-Provera use at this Sichuan study site.

Significant inter-center variations in discontinuation rates for bleeding-related problems were again noted in this part of the study; however, specific rates for each center were not provided for review.

The lost-to-follow-up rate for this part of the study was again noted to be significantly lower (0.88%) than that of either the Multicountry or the Egypt study.

Parts 1 and 2 Combined

Of 3915 women admitted to both parts of this study, 1955 were enrolled in the Cyclo-Provera treatment arm and 1960 in the Mesigyna treatment arm. A total of 3029 women completed the study, 1439 (73.6%) using Cyclo-Provera and 1590 (81.1%) using Mesigyna. Of the women enrolled in the Cyclo-Provera treatment group, approximately one-third (n = 665) were enrolled in the Hangzhou region, one-third (n = 654) in the Shanghai region and one-third (n = 636) in the Sichuan region.

When parts 1&2 of this trial are combined, a total of 516 women (26.4%) who received Cyclo-Provera discontinued their participation in the trial for all reasons, including loss-to-follow-up. Of these, 233 women (45.2%) discontinued their participation in the trial for bleeding related reasons. Eighty-seven women (16.9%) receiving Cyclo-Provera discontinued their participation due to development of amenorrhea. Eighteen patients (0.92%) using Cyclo-Provera were lost to follow-up.

Significant variations in total and reason-specific discontinuation rates were noted among centers as stated above, with lowest rates found in Sichuan center, [redacted] where no women using Cyclo-Provera discontinued study participation. Significant variations in the proportions of women discontinuing their participation for bleeding related problems by study site were noted again, ranging from 0.4% in Chengdu to 32.2% in Hangzhou.

The explanations provided for these differences include:

1. Cultural factors
2. Different pharmacokinetic profiles in different populations
3. Differences in counseling related to method use

Reviewer's comments:

(1) While explanations for the marked variations in discontinuation rates for all reasons and for bleeding specific reasons are provided in the study reports, two of three explanations are worrisome. Pharmacokinetic differences in metabolism of steroids have been proposed for individuals of different ethnic groups (such as those of Asian descent) but have not been proposed for individuals of the same ethnic group who merely live in different regions of a single country. In addition, if counseling was thought to affect bleeding patterns, this should have been standardized at the onset of the trial and examined as a possible confounding factor in analysis of bleeding patterns.

(2) The fact that none of the Cyclo-Provera users at Sichuan site [redacted] discontinued for any reason in either Part 1 or 2 of the trial is extremely unusual. The credibility of data from this site is therefore questioned. A total of 636 volunteers, accounting for 32.5% of all Cyclo-Provera users in the trial participated at the Sichuan site. A formal evaluation of this and other sites participating in the trial that might provide an explanation for the regional differences in discontinuation rates seen was not possible due to a lack of CRFs for this trial.

6.8 Efficacy Analysis

Three patients receiving Cyclo-Provera became pregnant during their participation in the China study. A summary is provided below:

(1) At admission, this patient weighed — and received her first Cyclo-Provera injection on . — — (menstrual cycle day 6). She received 4 Cyclo-Provera injections, the last of which occurred on — The summary information provided in the submission states that the patient returned to the clinic on . — for a visit during which a pregnancy test was performed for presumed amenorrhea. It is unknown whether the patient received another injection of Cyclo-Provera at that visit. The patient returned to the clinic on — complaining of prolonged vaginal bleeding and was diagnosed with a partial spontaneous abortion for which a vacuum aspiration was performed. Although not possible to confirm, pregnancy most likely occurred after the third or fourth Cyclo-Provera injection.

(2) At admission, this patient weighed — and her LMP prior to treatment began on — She received her first Cyclo-Provera injection on menstrual cycle day 4. There was no recorded Cyclo-Provera injection in —. At her next visit (—), a pregnancy test was performed with a negative result, although a pelvic examination revealed an 8-week sized uterus. A vacuum aspiration was performed at the — visit. This pregnancy could have been either a method failure, a user failure or a pregnancy prior to admission.

(3) This patient weighed — at admission and her LMP prior to treatment was March 13, 1989. She received her first Cyclo-Provera injection on menstrual cycle day 5. She received scheduled Cyclo-Provera injections in —. Per the pregnancy report form, a fourth injection was administered in — However, the data set states that the patient was discontinued in — The pregnancy was confirmed on — with an estimated date of conception of — Based upon this information, the duration of gestation was estimated to be 50 days and a vacuum aspiration was performed.

Reviewer's comments:

(1) As in the Egypt study, pelvic exam alone was used to assess pregnancy status at enrollment to this study. As noted in Section 5.9, this process is not adequate to identify pregnancies.

(2) It is clear from the descriptions of pregnancies provided that accurate and adequate record keeping and pregnancy monitoring was not performed throughout this trial. This, along with comments noted in items #1 and 3 of this section, lead to a lack of confidence in the quality of the data obtained from this (as well as the other) trials.

(3) As noted for the two other pivotal trials, patient complaints of amenorrhea and changes in menstrual cycle patterns unaccompanied by pregnancy testing are not acceptable procedures for detecting pregnancies.

6.9 Safety Analysis

As noted in Section 5.10 above, no CRFs were available for this study. As a result, a monitor for the sponsor reviewed the data listings of medical events from these two trials and classified events as having "potential clinical relevance". There were no narratives for medical events judged to be potentially significant per the Pharmacia & Upjohn monitor.

Reviewer's comments:

Safety information for medical events of potential clinical significance in this trial was obtained after reanalysis of safety data by the sponsor as described in Section 8 below. Detailed information of specific medical problems experienced by study participants using Cyclo-Provera was not available.

The safety data provided for review from this clinical trial are insufficient to draw conclusions about overall safety of Cyclo-Provera.

Bleeding pattern changes

Unlike the Multicountry and Egypt studies in which study participants had menstrual diaries reviewed by clinic staff at their monthly visits, there is no evidence of routine review of diaries for participants in the China trial. The only descriptive information regarding diary completion states that participants in this trial were asked to return the diary to the investigator at the end of the study, despite the fact that, per the protocol, menstrual diaries were to have been collected at each monthly visit and new ones issued concurrently.

The same definitions for acceptable and unacceptable bleeding patterns as those in the Egypt study were used in this study. Differences in bleeding pattern results were noted between Cyclo-Provera and Mesigyna, unlike the two other pivotal trials. These differences included:

-Cyclo-Provera users experienced significantly more unacceptable bleeding patterns than Mesigyna users;
-Cyclo-Provera users had much greater inter-individual variability in bleeding patterns than Mesigyna users;
-The predictability of onset of the next bleeding/spotting episode improved only slightly in Cyclo-Provera users as compared to Mesigyna users in which predictability improved markedly with treatment time;
-Cyclo-Provera users experienced more infrequent, prolonged, prolonged and irregular, and prolonged and infrequent bleeding patterns than Mesigyna users.

Data provided in volume 40, page 8/26/386 (unrevised NDA) reveal that 254 women receiving Cyclo-Provera during this trial (13% of those participating) were treated for bleeding problems during the study. No information is available on the specific patients treated, type of treatment received or number of total treatments received per patient. In addition, while information on treatment for bleeding problems during unscheduled visits was available for the Egypt study (and partial information was available from the Multicountry study), this information was not available for the China study.

Reviewer's comments:

(1) The lack of review of menstrual diaries on a routine basis to assure compliance with diary recording could have resulted in diary results that were subject to recall bias if they were completed retrospectively and returned to the study investigator at the end of the trial.

(2) As previously noted, treatment of bleeding during these trials should not have been permitted due to the potential for confounding safety results. Ideally, patients who require treatment for bleeding should have been discontinued from the study due to s serious adverse event. An objective cut-off for significant anemia should have been pre-specified. Since no information on specific treatments administered is available for this trial, the effects such treatments may have had on both safety and efficacy cannot be determined. Although the Egypt trial did not administer hormonal treatments for bleeding, this was done in the Multicountry trial. If

supplemental E and P compounds were given for days or weeks at a time in the — trial to control bleeding and for multiple bleeding episodes, efficacy could have been significantly impacted.

7.0 Reviewers Assessment of Safety and Efficacy

7.1 Safety Assessment

As described in Section 4.11 of this review, coding of medical events from the Multicountry trial was performed for a maximum of two medical events per visit and two reasons for discontinuation, with no classification of these events by body system or seriousness. Because of the manner in which medical events and discontinuations from this trial were recorded, the sponsor performed a reanalysis of the Multicountry safety data as previously described. From this reanalysis, five serious medical events were identified, none of which were thought to be related to use of either product. Because no CRFs (other than pregnancy report forms) were available for either the Egypt or China studies, the sponsor performed a reanalysis of raw data files for these studies, retrospectively recoding medical events and reasons for discontinuations into COSTART terms. The sponsor then integrated all demographic and safety data from these reanalyses of the three pivotal trials.

From the data provided and the reanalyses performed, medical events resulting in discontinuations were similar for both treatment groups (i.e., Cyclo-Provera or Mesigyna treatment) in all of the three pivotal trials, although no formal statistical analyses of these differences were performed by the sponsor for individual studies. A higher frequency of discontinuation for at least one medical event was noted in the Cyclo-Provera treated groups (16.2%) as compared to the Mesigyna treated groups (13.4%). Most medical events resulting in discontinuation of treatment occurred in the urogenital system, followed by body as a whole and the nervous system, with 12.9%, 2.0% and 0.8% of the Cyclo-Provera treated patients discontinuing treatment for these reasons, respectively.

Regarding bleeding related events, from the reanalysis and integration of data from the 3 pivotal trials, when compared to untreated women, Cyclo-Provera users had similar incidences of amenorrhea and infrequent bleeding but significantly increased incidences of frequent, irregular and prolonged bleeding during one year of product use. These latter three clinical bleeding patterns did not appear to be associated with health risks as demonstrated by the fact that only 2 women (one in the Multicountry study and one in the Egypt study) [0.05%] reportedly experienced anemia and were subsequently discontinued from the trial for that reason. Notably, however, since some women were treated for bleeding disturbances, the incidence of anemia is probably under-reported.

As noted above, several patients in the Cyclo-Provera-treatment group in each pivotal trial received treatment for bleeding-related problems during the trial. The percentages of women who received this treatment is compared across the three pivotal studies as outlined in Table 13 below:

Table 13: Number and Percentage of Cyclo-Provera-users Receiving Treatment for Bleeding-Related Problems During the Pivotal Trials
(Adapted from Table 5, Volume 18, page 8/4/22 of Unrevised NDA)

Treatment for Bleeding	Multicountry (N = 1202)		Egypt (N = 1111)		China (N = 1955)		Total (N = 4268)	
	n	%	n	%	n	%	n	%
No Treatment given	1065	91.03	968	92.10	1697	86.85	3730	89.34
	n	%	n	%	n	%	n	%
Treatment given	84	7.18	81	7.71	254	13.00	419	10.04
	n	%	n	%	n	%	n	%
Unknown/No treatment	21	1.75	2	0.19	3	0.15	25	5.86

N = number of patients in study population
n = number of patients for whom data was available

Reviewer's comments:

(1) Although bleeding disturbances resulting in discontinuation for anemia were reported in a very low percentage of patients (0.05%), no data on actual changes in Hg and HCT were available for review and evaluation for any pivotal trial; therefore, the true incidence of anemia cannot be calculated.

(2) The percentage of patients requiring treatment for Cyclo-Provera-induced bleeding problems for each individual trial and for the three pivotal studies combined confounded the analysis of safety data related to bleeding pattern changes throughout the trial as noted above. As described in Sections 4. 11 and 5.10, products used in the Multicountry and Egypt studies for the treatment of bleeding disturbances included supplemental estrogens and progesterone, ebolics, antifibrinoloytics, iron, "hemostatics" and vitamins. Because several of the treatments provided could have affected the incidence other safety events (i.e., anemia) and of efficacy, definitive conclusions regarding bleeding pattern changes with Cyclo-Provera use cannot be made with confidence.

Menstrual Cycle and Bleeding Pattern Changes

Bleeding patterns were assessed by analysis of menstrual diaries in which patients recorded the days on which bleeding or spotting events occurred. As noted in Section 6.10 above, it is unclear whether menstrual diaries were retrospectively completed at the end of trial participation by volunteers in the China study, as opposed to the monthly completion and review required in the study protocol and performed in the Egypt and Multicountry trials.

In the Multicountry study, bleeding disturbances were most common during the first reference period (first 3 months) of Cyclo-Provera use, then normalized during the last 3 reference periods. During this first reference period, women were noted to have a higher median number of bleeding and spotting days as well as a shorter length of any bleeding-spotting-free interval. The mean length of bleeding-spotting episodes was approximately constant throughout all reference periods, averaging 4-5 days. No differences in bleeding pattern changes were noted between treatment groups.

In the Egypt study, bleeding disturbances did not normalize with Cyclo-Provera use after the first reference period. The median number of bleeding-spotting days was slightly greater in the first reference period and the mean length of any bleeding-spotting-free interval was slightly shorter in this reference period. The mean length of bleeding-spotting episodes was constant over all reference periods and ranged from 4.5-5 days. Differences in bleeding pattern changes were noted between treatment groups for the first reference period only.

In the China study, differences in bleeding pattern changes were noted between treatment groups for all 4 reference periods studied. The percent of women experiencing metrorrhagia, hypomenorrhea and amenorrhea was higher the Cyclo-Provera, as compared to the Mesigyna, treatment group. There was more between-women variability in bleeding patterns noted in the Cyclo-Provera treatment group, and the percentage of women with "normal" bleeding patterns was lower in the Cyclo-Provera treatment group.

When compared to untreated women, long-term Cyclo-Provera users had similar incidences of amenorrhea and infrequent bleeding but significantly increased incidences of frequent, irregular and prolonged bleeding.

Reviewer's comments:

As discussed previously, bleeding pattern disturbances were treated with a variety of products, some of which could have affected efficacy results. Complete information on which patients were treated, what products they were treated with and how often they received treatment is available only for the Egypt study. In addition, only the Egypt study describes how safety data was analyzed for patients that received treatment for bleeding disturbances. Although the Egypt study contained the best data base from which to assess bleeding, it is not possible to draw definitive conclusions about the safety effects of Cyclo-Provera which are related to bleeding pattern changes.

Frequent Medical Events

The profile of Medical Events Summary for the China study was noted to be different from that of the Egypt and Multicountry studies in the following ways:

a) Unlike the Egypt and Multicountry studies, differences in the frequency profile of medical events between the treatment groups were noted in the China study;
b) The number and percentage of "urogenital" (particularly bleeding-related) events resulting in discontinuation in the China study was noted to be almost twice that seen in either the Egypt or the Multicountry study;
c) While headache occurred in > 5% of patients in both the Egypt and the Multicountry studies, no medical events other than bleeding-related problems were reported by > 5% of women in the China study;
d) The types of bleeding events reported with highest frequency were site specific, with women participating in the China study reporting a higher percentage of menorrhagia and hypomenorrhea than women in the either of the other two pivotal trials.

Reviewer's comments:

(1) The sponsor noted two issues unique to the safety data analysis of this NDA that impact the extent and quality of results, namely that (1) due to an initial lack of classification of medical events by body system or seriousness, safety data obtained from the Multicountry trial was retrospectively classified into these categories and subsequently reanalyzed by the sponsor; (2) no CRFs (other than pregnancy report forms) detailing safety data were available from the Egypt and China studies. As a result of the latter issue, the sponsor retrospectively identified

events "with potential clinical relevance or significance", as compared to standard classification of "serious" or "nonserious" events during conduct of the trial.

Because of the lack of CRFs available from two of the three pivotal trials and from several sites of the third pivotal trial, comprehensive information on medical events (serious, nonserious and "of potential clinical significance") occurring with Cyclo-Provera use was not available for review and audit. In addition, retrospective classification of such medical events several years after event occurrence could have resulted in biased data.

Volume 16, page 8/2/322 of the Revised NDA lists medical events resulting in discontinuation from the pivotal trials. Several of these events could have been serious if further information was available; for instance: "abdomen enlarged", "allergic reaction", "chest pain", "generalized edema", "reaction unevaluable", "syncope", coma", "endometrial disorder". No further information is available for specifying whether these events were serious or not.

Although the reported incidence of patients who experienced more than 2 medical events was low, the fact that the investigators were only required to record 2 medical events regardless of how many actually occurred could have resulted in significant underreporting of such events, some of which could have been serious in nature.

(2) The differences in medical event experiences and discontinuations noted for the China study when compared to the Egypt and Multicountry studies could represent cultural differences in menstrual bleeding pattern characterization and acceptance by this population. These differences in medical event experiences could also indicate differences in Cyclo-Provera metabolism in women of Asian descent, and hence support further evaluation of pharmacokinetic parameters of Cyclo-Provera metabolism in patient populations representative of the US population as described in Section 2.3 above.

(3) Large variations in total and reason-specific discontinuation rates among study sites and across studies that cannot be explained by review and audit of study sites is of concern. Although explanations for these differences are provided in the China study (see Section 6.7 above), the explanations provided raise more questions about the quality of the pivotal trials instead of alleviating concerns. While such variations could be due to cultural or local factors on the part of either the patients or the providers participating in the studies, it could also reflect individual differences in the patient populations studied at each site.

(4) The fact that Cyclo-Provera-induced bleeding disturbances were treated with various medications throughout the pivotal trials confounded bleeding-related results and, therefore, definitive conclusions regarding Cyclo-Provera's effect on menstrual pattern changes can not be made. Since bleeding pattern changes were a primary safety endpoint in this trial, no treatment for bleeding should have been permitted during the trial.

(5) Despite an improvement in bleeding patterns with increased duration of Cyclo-Provera use, 30-51% of women reported bleeding pattern disturbances after one year of treatment. The most common bleeding pattern disturbances noted in Cyclo-Provera-users were irregular, prolonged or frequent bleeding. These findings do not support the claim that Cyclo-Provera creates a regular monthly bleeding patterns in users.

7.2 Efficacy Assessment

A total of five pregnancies occurred in women using Cyclo-Provera throughout the pivotal trials. Two of these pregnancies occurred in the Egypt study and three in the China study. The timing of these pregnancies was as follows:

-1 occurred after the first Cyclo-Provera injection;
-1 occurred after the second Cyclo-Provera injection;
-2 occurred after the third Cyclo-Provera injection;
-1 occurred prior to admission to the study.

After reanalysis of all data available by the sponsor, these events resulted in a Pearl Index of 0.15 (95% confidence interval = 0.03-0.26). A life-table pregnancy rate was not calculated for reanalyzed data.

The table below lists characteristics of Cyclo-Provera users at enrollment for each of the three pivotal trials.

Table 14: Characteristics of Cyclo-Provera users at Enrollment to each of the Three Pivotal Trials (Modified from Table 2B, Volume 18, page 8/4/10-11, Unrevised NDA)

Characteristic	Multicountry trial (total N = 1202)		Egypt Trial (total N = 1111)		China trial (total N = 1955)	
Last contraceptive used:	n	%	n	%	n	%
Pill	319	26.5	566	50.9	95	4.9
IUD	337	28.0	242	21.8	388	19.8
Injectable	28	2.3	44	4.0	17	0.9
Other	75	6.2	29	2.6	739	37.8
None	----	----	230	20.7	700	35.8
Condom	86	7.2	---	----	---	----
Undefined	357	29.7	0	0.0	16	0.8
Abortion within the past 6 months	n ---*	% ---*	n 46	% 4.1	n 719	% 36.8
Post-partum	n NA	%	n NA	%	n NA	%

N = number of patients in study population
n = number of patients for whom data were available
*Information on whether a volunteer had had an abortion in the 6 months prior to enrollment was not collected in the Multicountry study.

Specific individual listings of last contraceptive used and time between last use and enrollment are listed in Volume 26, pages 8/12/63-131 of the Revised NDA. This information is only available for the Multicountry study and does not correlate completely with information found in the table above. A summary of pertinent positive information is as follows:

-Of 302 women who used OCs prior to entry to the Multicountry trial, 181 of them (60.0%) were enrolled before being off OCs for a minimum of 3 months.

-Of 21 women who used injectables prior to entry in the Multicountry trial, 15 of them (71.4%) had received their last injection within the last 10 months.

-CRFs proving that women enrolled had 6 regular cycles prior to admission are not available for any of the three pivotal studies.

-Comparable information on specific times since last contraceptive use and enrollment are not available for the Egypt and China studies.

Reviewer's comments:

(1) While the total number of pregnancies reported for both the pivotal and the supportive trials was small, several factors were noted and have been described above that could not be controlled for in statistical analyses and could have significantly influenced the efficacy rates obtained. These include:

1. **Inclusion of women in the immediate post-partum or post-abortion periods who had not resumed regular menstrual cycles and therefore were not at risk of pregnancy;**
2. **Inclusion of women with an incomplete wash-out period after COC use;**
3. **Lack of performance of pregnancy testing at study admission, in women with amenorrhea and at trial discontinuation.**

Because of the lack of data available on these specific patient populations, it is not possible to determine what percentage of the patients enrolled in the study were actually at risk of pregnancy upon admission. The degree to which this impacted the efficacy rates for the individual pivotal trials as well as for the integrated data from the 3 pivotal studies cannot be determined.

(2) Although the data reanalysis performed by the sponsor showed that 2% of women enrolled in the 3 pivotal trials were prior "injectable contraceptive users", there was no data available regarding:

(a) the number and percent of such women who used DMPA as opposed to NET-EN;
(b) the amount of time (in months) that had elapsed since last DMPA or NET-EN injection prior to enrollment (available for Multicountry study only);
(c) documentation of regular menses for 6 months prior to enrollment in previous DMPA users.

8.0 Safety Update

On July 16, 1998, an additional submission to this NDA was received. That submission contained safety information on a subset of volunteers in an ongoing US clinical trial (M/5415/0004). This clinical trial is an open label, non-randomized study comparing the safety effects of Cyclo-Provera to those of ON 777. Safety effects were primary endpoints of this trial, with efficacy noted to be a secondary study endpoint. Recruitment for the study was done in an 8-to-3 ratio, with plans for 800 women choosing Cyclo-Provera and 300 women choosing ON 777 to be enrolled.

The cut-off date for the analysis of data contained in this submission was March 31, 1998. As of that date, the study was fully enrolled with 782 patients in the Cyclo-Provera group and 320 patients in the ON 777 group. One-hundred-ninety-eight patients (25.3%) enrolled in the Cyclo-Provera treatment arm of this trial had discontinued treatment, leaving 584 women still enrolled in this arm of the study. The average number of weeks of drug exposure as of the cut-off date was 26.5 out of a planned total of 60 weeks.

With regard to data quality, several concerns from the pivotal trials should be addressed by the ongoing US trial including: (1) adequate ethnic diversity of the study population; (2) CRFs and source documents available for review and audit; (3) collection of comprehensive information on specific safety issues such as Hg, HCT, lipids, coagulation factors and carbohydrate metabolism. Thus the U.S. trial should address some of the data quality concerns noted in the pivotal trials described in the current NDA. Although pregnancy testing was performed at entry to the US trial, monthly pregnancy testing and testing at study discontinuation was not part of the study protocol. Monthly pregnancy testing in this trial had been recommended to the sponsor in February, 1997 as a component of the Agency's review of the protocol for this study, but the sponsor had not implemented this testing as of July 10, 1998. During a telephone conference on July 10, 1998, the sponsor was informed that adequate pregnancy testing would be necessary in the US trial to demonstrate product efficacy. Urine pregnancy testing at study discontinuation and at monthly study visits was therefore implemented on July 22, 1998.

CRFs for 122 women who had discontinued their participation in the US trial as of March 31, 1998 were included in the Safety Update. No information was available on patients who had completed one year of Cyclo-Provera use. In addition, although changes in bleeding patterns with Cyclo-Provera use was the primary safety endpoint for this trial, no information was provided in the Safety Update on bleeding pattern changes with Cyclo-Provera use. From review of the limited CRFs available, inappropriate treatment of bleeding pattern disturbances with hormonal or other compounds was not evident; however, no specific information was provided on treatment for bleeding disturbances in the Update.

Reviewer's comment:

No information was available in the U.S. Safety Update on patients who had completed one-year of Cyclo-Provera use. In addition, the only CRFs that were provided for review were for subjects who had discontinued their trial participation as of March 31, 1998. Thus, complete safety data was not contained in this submission. In addition, because routine pregnancy testing and pregnancy testing at discontinuation was not implemented until July 22, 1998, reliable information on product efficacy was not contained in the Safety Update.

Although the information contained in the U.S. Safety Update does address many concerns regarding data quality (i.e., sufficient ethnic diversity of study population, adequate CRFs and source documents for review and audit, collection of comprehensive information on specific safety issues, no hormonal treatment for bleeding disturbances) and provides some safety data related to Cyclo-Provera use, the information is based upon limited product exposure in a subset of the study population.

9.0 Final conclusions and Recommendations

Although Cyclo-Provera has been used extensively by women worldwide, the poor quality of the data contained in the NDA submission makes it difficult to have confidence in either the efficacy rates or the safety profile for the product as described in the NDA. Of a total of 44 study sites from the pivotal trials, only 2 were deemed auditable, making verification of data collection, verification of adherence to the study protocol, and provision of explanations for variability in study results among sites impossible to accomplish.

As described above, the quality of the data obtained from the pivotal trials was compromised by many components of the study protocol used in those trials. The lack of information available on specific patient populations who might not have been at risk of pregnancy at enrollment as well as the lack of adequate pregnancy testing for method failure assessment made interpretation of the efficacy data difficult. No CRFs were available for 2 of the 3 pivotal trials, accounting for 75% of the data base. Data collection for safety assessments was inadequate, and treatment of bleeding related events during the pivotal trials confounded the results obtained for menstrual bleeding pattern changes associated with Cyclo-Provera use. In addition, the products used for treatment of bleeding disturbances could have affected efficacy results.

The lack of withdrawal of Cyclo-Provera for safety reasons from any country in which it is currently marketed would imply that serious safety or efficacy concerns with the product are not common. However, the pivotal trials in this NDA do not allow a confident assessment of safety or efficacy.

Data provided in the current NDA are insufficient to permit approval for marketing in the US.; however, in light of the fact that a large scale, U.S. trial is currently ongoing with efficacy as a secondary endpoint, evaluation of the data from this study may support the efficacy and safety claims in the current NDA. In a teleconference with the sponsor on July 30, 1998, it was clarified that data from a minimum of 200 patients completing 13 treatment cycles of Cyclo-Provera use with pregnancy testing at study discontinuation must be provided in order to assess efficacy. The issues of appropriate inclusion of patients at risk of pregnancy, appropriate performance of pregnancy testing, and avoidance of treatment of bleeding disturbances must be addressed in the ongoing US trial. A review of the results from this trial and demonstration of efficacy in a suitable patient population will be necessary prior to approval of Cyclo-Provera for marketing in the U.S.

/S/ 9/3/98

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~~Concurrences~~:
cc: HFD-580/Division Director

cc: NDA 20,8[illegible]/Division File

APPEARS THIS WAY
ON ORIGINAL

NDA 20-874
Lunelle™ Monthly Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate)
Pharmacia & Upjohn

Safety Update Review

The safety update is included in Medical Officer review dated September 27, 2000, pages 3-8.

Medical Officer's Review
NDA # 20-874 Complete Response to Approvable Letter

Date of Submission	April 6, 2000
Date Received	April 7, 2000
Date Review Completed	September 27, 2000
Applicant	Pharmacia & Upjohn
Drug (generic name)	Medroxyprogesterone Acetate and Estradiol Cypionate Injection
Proposed Trade Name	**Lunelle™ Monthly Contraceptive Injection**
Pharmacologic Category	Progestin and estrogen combination
Proposed Clinical Indication	Prevention of pregnancy
Dosage and route of Administration	25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate given as a 0.5 ml intramuscular injection q 28-30 days (not to exceed 33 days)
Manufacturing Control Data	See Chemistry Review
Pharmacologic Data	See Pharmacology Review
Biopharmaceutics Data	See Biopharmaceutics Review
Reviewer	Dena R. Hixon, MD, FACOG Medical Officer, DRUDP

1.0 RESUME

This submission is the sponsor's complete response to an Approvable Letter from the US Food and Drug Administration (FDA) October 15, 1999 following review of NDA 20-874 submitted April 15, 1999.

The current submission contains an ——— regarding the manufacturing deficiencies at the ——— plant, revised physician and patient labeling, draft summaries of the proposed Phase IV commitment study proposals, and a safety update. The safety update includes an integrated summary of the data from Protocols 0004 and 0011 and safety gleaned from published sources over the period May 31, 1999 through February 8, 2000. Since Protocols M/5415/0009 and Z/5415/0012 provided no new data, they have not been discussed further. However, final study reports are provided.

2.0 BACKGROUND

Lunelle™ Monthly Contraceptive Injection (Lunelle™), also known by the previously submitted name CYCLO-PROVERA®, was developed by The Upjohn Company over 30 years ago and was first tested in a large scale safety and efficacy trial conducted by the World Health Organization (WHO) in 1984. In 1990, Upjohn turned over the development rights for this product to WHO which subsequently licensed the product to the Program for Appropriate Technology in Health (PATH) and its associated nonprofit organization, the Concept Foundation (Concept). PATH/Concept has licensed CYCLO-PROVERA® to several companies in Asia and Latin America. As of mid-1997, ——— units of CYCLO-PROVERA® had been sold worldwide, with no withdrawals from marketing in any country for safety reasons.

Pharmacia & Upjohn (P&U) submitted a New Drug Application, NDA 20-874, for CYCLO-PROVERA® for the prevention of pregnancy September 26, 1997, based on published data, including data from 3 studies sponsored by the World Health Organization (WHO).

Clinical review of the September 26, 1997 submission revealed deficiencies that resulted in a Non-Approvable decision by the FDA. Of a total of 44 study sites worldwide, only 2 were deemed auditable, making it impossible to verify data collection and adherence to the study protocol or to explain variability in results between study sites.

The quality of the data from the pivotal trials was compromised by many components of the study protocol. Information was lacking on specific patient populations who might not have been at risk for pregnancy at enrollment. Adequate pregnancy testing for method failure was not done, compromising interpretation of efficacy data. Safety data was inadequate. Treatment of bleeding during the pivotal trials confounded the observations of menstrual bleeding patterns associated with the drug and could have confounded efficacy results.

The lack of withdrawal from marketing in any country would imply that serious safety or efficacy concerns with Lunelle™ are not common. However, the pivotal trials presented for the original NDA were not sufficient for a confident assessment of safety or efficacy, and a Non-Approvable letter was issued on September 25, 1998.

In light of the fact that a large scale U.S. trial, #M/5415/0004, was ongoing at the time of the original review with efficacy as a secondary endpoint, the agency agreed to review the data from this study to assess efficacy and safety and determine approvability based upon this data. The sponsor was advised that a minimum of 200 patients must complete 13 treatment cycles of Lunelle™ with pregnancy testing at discontinuation in order to assess efficacy. Appropriate inclusion of patients at risk of pregnancy, appropriate pregnancy testing, and avoidance of treatment of bleeding disturbances were specified for the trial in telephone conferences on July 10, 1998 and August 4, 1998.

Amendment 001 was submitted to NDA 20-874 in April 1999 to address the deficiencies. This amendment included data from protocol M/5415/0004, a 60-week study conducted in the United States to evaluate the

safety, patient acceptability, and efficacy of treatment with Lunelle™ compared with Ortho-Novum 7/7/7. Protocol 0004 was completed in February 1999. Based on review of the final report of Protocol 0004, Lunelle™ was found to be safe and effective for the prevention of pregnancy. However, an October 1, 1999 FDA inspection of the Kalamazoo manufacturing site found manufacturing deficiencies of such a magnitude or nature that the Office of Compliance recommended withholding approval, and the decision was to send an approvable letter.

Another significant review issue was the application of the combination drug regulation, 21 CFR 300.50. This regulation requires each component to make a contribution to the claimed effects to enhance safety or effectiveness. The company's response to questions about estrogen's contribution to the product, however, were not substantive. Therefore, the non-approval letter of September 1998 called for appropriate studies to establish safety and efficacy for this combination drug product. The Division has recommended studies to investigate the theoretical advantages of the estrogen component.

An ongoing extension study, protocol M/5415/0011 is being conducted to allow for continued use of Lunelle™ and to collect additional data related to long-term safety of the product. Available data from this extension study as of the February 8, 2000 cutoff date is included with the safety update for the current submission.

3.0 MANUFACTURING DEFICIENCIES AT THE —— PLANT

See Chemistry review.

4.0 SAFETY UPDATE

Of the 782 patients treated with Lunelle™ at the 42 sites participating in protocol 0004, 477 were enrolled at the 25 sites that elected to participate in the continuation protocol 0011. Of those 477 patients, 269 completed treatment under protocol 0004, and 200 of these elected to continue under protocol 0011. As of the data cutoff date for this report, February 8, 2000, 87 patients were continuing to receive treatment under the protocol.

56.5% of subjects discontinued from Protocol 0011, compared to 44.5% from Protocol 0004. Those who discontinued for a medical reason decreased from 19.1% in 0004 to 7.5% in 0011, and all were nonserious adverse events. Discontinuations for nonmedical reasons increased from 25.4% in protocol 0004 to 49.0% in 0011. The most frequent nonmedical reason for discontinuation was "personal request", cited by 23.0% of subjects in 0011.

8920 woman-cycles of treatment with Lunelle™ had been collected at the completion of 0004, and as of the cutoff date for this update, the total exposure was 11,144 cycles. A total of 128 subjects received treatment for at least 24 cycles, with a maximum duration of 37 cycles. 89.2% of injections were given within 23-33 days of the previous injection, as directed in the protocols.

Collectively, the data show that the additional exposure of patients in protocol 0011 did not change the safety profile for Lunelle™ that was presented in NDA 20-874 and in the subsequent amendments. No new safety concerns have been identified as a result of long-term exposure to the product. Published literature also raised no new safety concerns.

In addition, no patients with appropriate follow-up and pregnancy testing became pregnant during treatment with Lunelle™ in protocols 0004 and 0011.

- One patient (# 2819) had a positive pregnancy test 2-3 months after her last injection, and was described in the previous safety update. She received her third injection ——— and failed to keep her next appointment because she was stranded in another country. She returned ——— ——— and had a positive pregnancy test at that visit. Her last menses was ——— No pregnancy

was seen on ultrasound on —— Beta HCG was 46 IU/L on —— and 166 IU/L on ——
On —— a gestational sac was seen on ultrasound. The probable date of conception was ——
—— The patient elected to terminate the pregnancy.

Adverse Events

Listing of occurrence and initial onset of adverse events by quarter reveals that for the most frequently reported drug-related AEs (breast pain, weight gain, acne, emotional lability, dysmenorrhea, metrorrhagia, and menorrhagia), the initial onset was usually reported in the first or second quarter of use. Occurrence of breast pain and emotional lability subsided after the first quarter, while the occurrence of weight gain and acne tended to increase with duration of use.

The most frequent serious adverse event was cholelithiasis, which was reported in 0.4% of patients in both protocols, including 1 subject that was designated as having a SAE after the previous safety update report. Overall, 6 subjects were identified in both protocols combined who developed signs and symptoms of cholecystitis with or without stones. This rate is consistent with the expected rate in this patient population, but an association with the use of hormonal contraception cannot be excluded.

The two subjects in protocol 0011 who experienced SAEs after the previous safety update report were the following:

- A 28-year-old with a family history of cholelithiasis ——— t ——— Treatment was not stopped.
- A 20-year-old who was hospitalized for 2 days ——— . This was deemed unrelated to treatment, and treatment was not stopped.

The AE that led to discontinuation of treatment most often was weight gain (46/776, or 5.9%). Only 4 subjects discontinued for AEs after the previous safety update, and all were consistent with previous reports. One subject reported bleeding and fluctuations in emotions, one prolonged menses, one weight gain and amenorrhea, and another bilateral breast discharge and elevated prolactin.

One subject (#1328) in the combined protocols 0004 and 0011 experienced a superficial thrombophlebitis, discussed in the previous review. She was 20 years old and experienced the AE after completing 12 cycles of Lunelle™ use. She was treated with indomethacin and cefadroxil and discontinued from the study.

Reviewer's comment

These adverse events are consistent with those previously reported and reflect the adverse events expected with combined hormonal contraceptives.

Blood Pressure

There was no change from screen in median systolic blood pressure at cycles 15, 24 and last observation. For median diastolic blood pressure there was a 1 mm Hg increase at cycle 24. This small change in a group of 112 subjects does not indicate any consistent increase in blood pressure or risk. No women had consistently elevated blood pressures in protocol 0011. Some had diastolic readings of $\leq$ 50 mm Hg but this was not considered clinically significant in this group of healthy young women.

Hypertension was reported as an adverse event in 1.5% (12/776) of subjects in protocols 0004 and 0011 combined. 5 of these 12 cases (0.6% of 776 subjects) were reported during protocol 0004 and 4 new cases were reported during the previous safety update report from protocol 0011. 3 new cases were reported from 0011 subsequent to the data cutoff date for the previous safety update. All but one of these cases were sporadic blood pressure elevations.

- One subject (#4523) discussed in the previous review had a blood pressure of 98/64 at screen (8/97) and had elevated blood pressures of 160/118 in 5/99, 138/92 in 6/99, and 137/98 in 7/99.

Three subjects reported treatment for hypertension as concomitant medications:

- Subject #807 was on antihypertensives at the start of the trial (5/21/97). An adverse event of "uncontrolled hypertension" was reported on [redacted] and the trial medication was not discontinued.
- Subject # 3105 was also on antihypertensives at the start of the trial [redacted] and reported an exacerbation of hypertension on [redacted]
- Subject #1509 was not on antihypertensives at the start of the trial [redacted]. Hypertension was reported on [redacted]

Weight Change

The median weight gain experienced by Lunelle users was 5 pounds at the end of Protocol 0004 and remained the same after 30 cycles of treatment. Wide variability of weight gain or loss was observed in both protocols. The maximum weight loss after 12 cycles of use, as previously reported, was 48 pounds, and the maximum weight gain was 49 pounds. During the combined protocols 0004 and 0011 up to the cutoff date, the maximum weight loss was 80 pounds, occurring after 30 cycles of use, and the maximum gain was 56 pounds, after 27 cycles. The maximum gain to last observation was 60 pounds. The following extremes of weight gain were noted over time:

Weight Change	12 Cycles (n=469)	15 Cycles (n=433)	24 Cycles (n=111)
Lost > 20 pounds	1.5%	2%	5%
Lost > 10 pounds	7.5%	7%	16%
Gained >10 pounds	24%	31%	37%
Gained >20 pounds	5%	7%	22%

Reviewer's comment

- **These data show an increasing percentage of Lunelle™ subjects with weight change in excess of 10 and 20 pounds from 12 to 15 to 24 cycles of use.**
- **A number of subjects in this study took concomitant medications for weight control, possibly explaining the maximum weight loss observed.**

Cervical cytology

2 patients in protocol 0011 revealed possible low-grade squamous intraepithelial lesion (LGSIL) on cervical cytology. No cases of high-grade lesions (HGSIL) or carcinoma in situ were reported.

Reviewer's comment

These findings are consistent with those previously reported for protocol 0004 in which 9.2% of Lunelle™ subjects had abnormal cervical cytology at screen and 9.1% at the final visit. Given that SIL is not uncommon among sexually active women and that the false-negative rate for a single Pap test (e.g., the cytology result at screen) is 10-25%, this finding does not suggest any significant effect of Lunelle™ on cervical cytology.

Clinical Chemistry

Statistically significant changes from screen (beginning of protocol 0004) occurred but were generally small and not clinically relevant. The majority of patients had chemistry assay values that were normal at screen and remained normal at the last observation. Subsequent to the data cutoff date (31 May, 1999) for the previous safety update report, no patients reported adverse events of glucose intolerance, renal dysfunction, or abnormal liver function tests.

Hepatic function

As of the data cutoff date for this report, no clinically significant abnormal values (defined as $\geq$ 3 times upper limit of normal for ALT, AST, GGT, and ALP and $\geq$ 2 times upper limit of normal for bilirubin) were observed for patients in protocol 0011.

- Alkaline phosphatase (ALP) (normal range 30-150 U/L) showed a median value of 74 U/L at cycle 15 (Median change from baseline 8.0 U/L), 74.5 U/L at cycle 24 (median change from baseline 7.5 U/L), and 71.0 U/L at last observation (median change from baseline 5.0 U/L). 14 subjects (3.4%) who had

normal values at baseline had values exceeding normal limits at cycle 15, 2 (2.1%) at cycle 24, and 17 (2.4%) at last observation.

- ALT/SGPT (normal range 0-45 U/L) showed a median value of 15.0 U/L at cycle 15 (median change from baseline of 1.0 U/L), 17.0 U/L at cycle 24 (median change 1.5 U/L) and 16.0 U/L at last observation (median change 2.0 U/L). 5 subjects (1.2%) who had normal values at baseline had values exceeding normal limits at cycle 15, 2 (2.1%) at cycle 24, and 15 (2.1%) at last observation.
- AST/SGOT (normal range 0-41 U/L) showed a median value of 18 U/L at cycle 15 (median change 0.0 U/L), 17.0 U/L at cycle 12 (median change 1.0 U/L), and 17.0 U/L at last observation (median change 0.0 U/L). 4 subjects (1.0%) who had normal values at baseline had values exceeding normal limits at cycle 15, 2 (2.1%) at cycle 24, and 7 (1.0%) at last observation.
- Total bilirubin (0.1-1.2 mg/dL) showed a median value of 0.5 mg/dL at cycle 15 (median change 0.1 mg/dL), 0.4 mg/dL at cycle 24 (median change 0.0 mg/dL), and 0.5 mg/dL at last observation (median change 0.0 mg/dL). 13 subjects (3.1%) who had normal values at baseline had values exceeding normal limits at cycle 15, 2 (2.0%) at cycle 24, and 15 (2.1%) at last observation.

  The maximum observed bilirubin level was 2.2 mg/dL at cycle 27. This subject started the trial with a slightly elevated ALT of 53 U/L and a normal bilirubin of 1.2 mg/dL. Subsequent bilirubin values were 1.8 mg/dL at wk 19, 1.3 mg/dL at wk 38, 1.5 mg/dL at wk 57, 1.7 mg/dL at wk 61, 1.9 mg/dL at wk 73, 1.5 mg/dL at wk 90, 2.2 mg/dL at wk 101, 1.7 mg/dL at wk 112, and 0.9 mg/dL (normal) at wk 123. She had no other elevations of liver enzymes.
- GGT (2-65 U/L) showed a median value of 18 U/L at cycle 15 (median change 2.5 U/L), 16.0 U/L at cycle 24 (median change 0.0 U/L), and 17.0 U/L at last observation (median change 1.0 U/L). 2 subjects (0.5%) who had normal values at baseline had values exceeding normal limits at cycle 15, 1 (1.0%) at cycle 24, and 4 (0.6%) at last observation.

One subject (#820) discontinued the study for elevated liver function tests. At week 60, her ALT was mildly elevated at 48 U/L and GGT was 94 U/L. At week 83, all liver function tests were normal. At week 95, ALT was 83 U/L, AST 54 U/L and GGT 180 U/L. At week 103, all liver function tests were again normal. Her concomitant medications included topical nystatin and mycolog for fungal dermatitis, clarithromycin, methylprednisolone and prednisone, albuterol inhaler, ——— . nasal decongestant, amoxicillin, hepatitis vaccine, tetanus vaccine, measles/mumps/rubella vaccine, acetominophen, ——— cough syrup, and ——— cough syrup.

Reviewer's comment
In the previous review of study 0004, 4 subjects experienced clinically significant abnormal hepatic functions more than 3 times the upper limit of normal. Two of these returned to normal by the end of the study, and there is no follow-up information available for the other two, No clinical or laboratory investigations were conducted to determine the etiology of the abnormality. There were no reports of clinically significant bilirubin elevations. These findings were not sufficient to suggest a significant risk of hepatic damage related to Lunelle™ use.

Renal function

Serum creatinine (0.6-1.5 mg/dL) showed a median value of 0.9 mg/dL at cycle 15 (median change –0.1 mg/dL), 1.0 mg/dL at cycle 24 (median change 0.0 mg/dL), and 0.9 mg/dL at last observation (median change –0.1 mg/dL). All subjects in Protocol 0011 had normal values at baseline and at cycles 15, 24, and last observation.

Reviewer's comment
There is no evidence that Lunelle™ affects renal function.

Serum glucose/Carbohydrate metabolism

Glucose (normal range 70-125 mg/dL) showed a median value of 85.0 mg/dL at cycle 15 (median change –2.0 mg/dL), 86.0 mg/dL at cycle 24 (median change –0.5 mg/dL), and 87.0 mg/dL at last observation (median change –1.0 mg/dL). 3 subjects (0.7%) who had normal values at baseline had values exceeding normal limits at cycle 15, 1 (1.1%) at cycle 24, and 14 (2.0%) at last observation. No subject had a clinically significant value of more than 2 times the upper limit of normal.

Reviewer's comment
There is no evidence that Lunelle™ affects carbohydrate metabolism.

Serum ferritin, iron, and TIBC

These data were not collected during protocol 0004 or the beginning of protocol 0011. Therefore only limited data are available at screen (start of 0011) (N=2). Median values were within the normal range at each time point. However, no meaningful comparison of changes from screen to subsequent time points can be made because of the limited data available at screen.

- Serum ferritin (normal range 6.0-232.5 ng/mL) showed a median value of 47.35 ng/mL at screen (n=2), 32.70 ng/mL at cycle 21 (n=105), 33.50 ng/mL at cycle 27 (n=86), 38.3 ng/mL at cycle 33 (n=20), and 32.80 ng/mL at last observation (n=159)
- Serum iron (normal range 37-145 µg/dL) showed a median value of 132.0 µg/dL at screen (n=2), 75.0 µg/dL at cycle 21 (n=105), 78.5 µg/dL at cycle 27 (n=86), 90 µg/dL at cycle 33 (n+20), and 88.0 µg/dL at last observation (n=159).
- TIBC (normal range 250-450 µg/dL) showed a median value of 257.5 µg/dL at screen (n=2), 307.0 µg/dL at cycle 21 (n=105), 306.5 µg/dL at cycle 27 (n=86), 303.5 µg/dL at cycle 33 (n=20), and 310.0 µg/dL at last observation (n=159).

Reviewer's comment
Despite median values in the normal range at each time point, no meaningful comparison can be made because of the limited data at screen.

Hematology

The median change from screen for the hematology assays was statistically significant, but the direction and magnitude of change were not considered to be clinically significant. The majority of patients had hematology assay values that were normal at screen and remained normal at the last observation in protocol 0011. No trends toward clinically significant anemia were apparent. Overall, anemia was reported as an AE in 1.7% (13/776) of subjects in protocols 0004 and 0011 combined. This includes 1 subject with anemia that was reported after the data cutoff date for the previous safety update report.

- Hematocrit (normal range 38-49%) median value at 15 cycles was 42.80% (median change from baseline of 0.50%, at cycle 24, 42.80% (median change 0.10%), and at last observation 41.80% (median change 0.06%). 11 subjects (2.9%) who had normal values at baseline had values below normal limits at cycle 15, 3 (3.6%) at cycle 24, and 40 (6.2%) at last observation.
- Hemoglobin (normal range 12.1-15.6 g/dL) median value was 13.10 g/dL at cycle 15 (median change 0.10 g/dL), 13.60 g/dL at cycle 24 (median change 0.30 g/dL), and 13.10 g/dL at last observation (median change 0.10 g/dL). 27 subjects (7.5%) who had normal values at baseline had values below normal limits at cycle 15, 5 (6.0%) at cycle 24 and 49 (7.9%) at last observation.
- WBC (normal range 4.0-10.5 x 10^3/mm^3) median value was 5.78 x 10^3/mm^3 at cycle 15 (median change –0.440 x 10^3/mm^3), 6.41 x 10^3/mm^3 at cycle 24 (median change –0.470 x 10^3/mm^3), and 5.990 x 10^3/mm^3 at last observation (median change –0.230 x 10^3/mm^3). 30 subjects (7.7%) who had normal values at baseline had values below normal limits at cycle 15, 4 (4.4%) at cycle 24, and 38 (5.7%) at last observation. Although a statistically significant decrease from screen WBC was noted through 24 cycles, a median increase was noted during subsequent cycles (27, 30, or 33 cycles), with a statistically significant median increase of 0.63 x 10^3/mm^3 at 33 cycles.

Subsequent to the data cutoff date for the previous safety update report, one subject in protocol 0011 had clinically significant low hemoglobin values, defined as ≤ 10 g/dL. Subject 404 is a 32-year-old black woman who entered protocol 0011 on [redacted], and continues in the study. An adverse event of anemia was reported in [redacted]. She began concomitant treatment with iron sulfate 300 mg twice daily in [redacted]. Other AEs include urinary tract infection, vaginitis, and infection (cold). Her baseline Hg for Protocol 0004 was 12 g/dL and Hct 37.7%. At cycle 15, Her Hg was 12.4 g/dL and Hct 42.4%. Subsequent values were as follows Hg 11 g/dL and Hct 34.3 % at wk 85, Hgb 11.8 g/dL and Hct 39.3 % at

wk 97, Hgb 11.1 g/dL and Hct 36 % at wk 109, Hgb 9.8 g/dL and Hct 31.4 % at wk 125, Hgb 11.4 g/dL and Hct 37.1% at wk 138.

Reviewer's comment
There was no clinically significant change in hemoglobin or hematocrit in Lunelle™ subjects throughout these trials. Anemia was reported as an adverse event in 1.7% of participants. Most of them experienced no significant change in hemoglobin and hematocrit from screen to the final visit. Only 2 subjects had clinically significant abnormal hematocrit (≤25%) or hemoglobin (≤8 g/dL). The findings do not suggest a significant effect of Lunelle™ on hematology parameters.

5.0 LUNELLE™ MONTHLY CONTRACEPTIVE INJECTION BRIEFING DOCUMENT ON BLEEDING PATTERNS

Bleeding data from Study 0004 were analyzed using a method that was considered suitable for drugs such as DEPO-PROVERA® (medroxyprogesterone acetate/DMPA), which are administered less frequently than monthly. This analysis method was used for the initial World Health Organization (WHO) sponsored studies of Lunelle™ and was therefore chosen for use in Study 0004 to allow for comparison of the bleeding patterns associated with Lunelle™ use in US women with those in women from other countries. This method of analysis arbitrarily sections data into 90-day segments and creates a system that the sponsor believes is not amenable to the clinical interpretation of bleeding patterns for a monthly administered contraceptive.

The sponsor's review of published literature and Summary Basis of Approval (SBA) for previously marketed oral contraceptives has revealed a significant difference in the methods of analysis of bleeding patterns between those which were performed for Lunelle™ and those which have been performed for other monthly administered cyclical contraceptives. The sponsor reports that prior submissions of data for oral contraceptives have sectioned the data into monthly segments, defining a "withdrawal" period during the time in which placebo is administered, and including days of bleeding or spotting starting within 3 days of the first placebo pill (day 18) and lasting until 3 days after the last placebo pill (day 31), as long as the bleeding episode included at least one of the placebo-administration days.

With OCs, the estrogen component is typically administered during the first 21 days, and, because rapid degradation results in a short half-life, removal of the exogenous estrogen leads ideally to "withdrawal bleeding" during the placebo-administration days. The sponsor proposes that Lunelle™ accomplishes the same effect with administration of estradiol cypionate but that the timing of its effective removal varies somewhat more than that of a daily-administered pill.

The sponsor concludes that the major difference between oral contraceptives and Lunelle™ lies in the specificity of control over the timing of withdrawal bleeding. Most cyclical oral contraceptives use a defined 28-day cycle. Since Lunelle™ is a once-monthly administered contraceptive, it is not tightly bound to the repetitive 28-day administration but can be administered a few days prior to or after 28 days from the last dose. Also, the levels of hormones seen after Lunelle™ administration are not abruptly interrupted. Therefore, the number of days in a given "cycle" can vary.

The sponsor believes that monthly, cyclical contraceptive agents are best reviewed for their effect on bleeding patterns using similar methods. Therefore they have reanalyzed the data on bleeding patterns from Study M/5415/0004 using methods that they believe are similar to those commonly used for other monthly contraceptives.

For the bleeding analyses described here, data were sectioned into one-cycle segments, defined by the time between injections for subjects receiving Lunelle™ and the time between pill packages for the Ortho-

Novum treated women. A bleeding episode was defined as one or more consecutive bleeding or spotting days, separated by no more than a single bleeding/spotting-free day.

The withdrawal period was defined based on the pharmacokinetics of the estrogen component of Lunelle™ which predict that basal levels of estrogen would be reached by day 18. If the injections were < 28 days apart, then the withdrawal period was from day 18 through day 31. If a bleeding episode began between day 15 and 18 and continued into the withdrawal period, it was classified as withdrawal bleeding. If the injections were ≥ 28 days apart, then the withdrawal period was from day 18 until 3 days after the next injection.

Breakthrough bleeding was defined as any bleeding or spotting episode that was not classified as withdrawal bleeding.

The bleeding variables that were examined for each cycle were the number of bleeding and/or spotting episodes, the duration of each bleeding or spotting episode, the number of breakthrough and withdrawal bleeding episodes, and the occurrence of amenorrhea.

Results of the sponsor's re-analysis of bleeding patterns

1. After cycle 1, 72-82% of Lunelle™ subjects (vs. 85-95% of Ortho-Novum subjects) experienced only withdrawal bleeding during a given cycle.

Reviewer's comment

This includes subjects with more than one withdrawal bleeding episode during the designated interval. The proposed definition of a withdrawal period encompasses 14 days, which is half of a 28-day cycle. By including bleeding episodes that begin within 3 days before the proposed withdrawal period and those that continue up to 3 days after the next injection, the withdrawal period is extended to a maximum of 22 days for a 33 day injection interval. The usual withdrawal period for oral contraceptives is the 7-day placebo interval.

2. During treatment cycle 6, 64% of Lunelle™ subjects had withdrawal bleeding that was between 3 and 9 days in length.

Reviewer's comments

- **16% of Lunelle™ subjects vs. 7.5% of Ortho-Novum subjects had no withdrawal bleeding in cycle 6.**
- **Only 48% of Lunelle™ subjects vs. 83% of Ortho-Novum subjects had a withdrawal bleed of 3 to 7 days, which is the generally expected range for oral contraceptives.**
- **29% of Lunelle™ subjects vs. 5% of Ortho-Novum subjects had a withdrawal bleed lasting more than 7 days.**
- **9% of Lunelle™ subjects vs. 0.4% of Ortho-Novum subjects had a withdrawal bleed lasting more than 10 days.**
- **In cycle 13, 24% of Lunelle™ subjects had a withdrawal bleed lasting more than 7 days, and 6% more than 10 days, compared to 4% and 0% of Ortho-Novum subjects, respectively.**

3. After cycle 1, 70-80% of Lunelle™ subjects had only one bleeding episode during a given cycle vs. 85-92% of Ortho-Novum subjects.

Reviewer's comment

The one bleeding episode could be withdrawal bleeding or breakthrough bleeding, depending on when it occurred.

4. After cycle 1, 4-8% of Lunelle™ subjects experienced one or more breakthrough bleeding episodes during a given cycle vs. 3-11% of Ortho-Novum subjects.

Reviewer's comment

The withdrawal period as defined by the sponsor for Lunelle™ is longer than that generally accepted for oral contraceptives, therefore, possibly reducing the number of bleeding days considered as breakthrough bleeding with Lunelle™ use.

Summary comments

The sponsor's proposal for reanalysis of the bleeding patterns observed with Lunelle™ use is not acceptable and does not support the proposed changes in the previously recommended labeling for this product with regard to the expected effect on bleeding patterns.

The sponsor proposes that these bleeding patterns are similar to those observed with oral contraceptives, but the data do not support this conclusion. The bleeding patterns are clearly more unpredictable with Lunelle™ than with oral contraceptives and vary widely between individuals, most likely reflecting more inter-individual variability in pharmacokinetics of the injectable preparation compared to the daily-administered oral contraceptives.

The sponsor proposes that the pharmacokinetics of the estrogen component of Lunelle™ lead to this variability in bleeding patterns. This proposal ignores the pharmacokinetics of the progestin component. However, no data have been presented to support this position.

6.0 CLINICAL RESEARCH TR# 1022-00-001 (Report Z/5415/0012)

Determination of Follicular Growth During Treatment by Cyclo-Provera (Lunelle™) or Alesse-28

The main mechanism of action of Lunelle™ is inhibition of ovulation. Previous studies have shown that the initial rise in endogenous progesterone levels occurs between 71 and 90 days after the last injection is given, indicating that ovulation is inhibited for at least 2 months.

Although ovulation rarely occurs during the 3 months after a depo-medroxyprogesterone acetate (DMPA) injection, it occurs frequently during use of oral and implant progestin-only contraceptives. With use of levonorgestrel implants, ovulatory rates of 32% have been observed. With use of progestin-only OCs, ovulatory rates of 29-40% have been reported. A low ovulatory rate of 1.7 per 100 cycles was observed with use of monophasic and multiphasic OCs containing 35 µg of ethinyl estradiol, and a rate of 2.7% with use of an OC containing 20 µg ethinyl estradiol.

Inhibition of ovulation is the principle mechanism by which progestins provide their contraceptive effect, primarily by suppressing luteinizing hormone (LH) secretion, therefore preventing the LH surge needed for ovulation. In contrast, estrogens act centrally to suppress FSH secretion and thereby prevent folliculogenesis.

Ovarian follicular development occurs during treatment with combined and progestin-only oral contraceptive pills and progestin-containing subdermal implants and can be associated with the development of persistent functional cysts that may require surgical removal. A randomized comparative study was undertaken to compare the effect of ovarian follicular activity associated with use of Lunelle™ and a low dose oral contraceptive.

The incidence of follicular activity with Lunelle™ has not been previously reported. This study was designed to evaluate ovarian follicular activity with Lunelle™ and compare it to what occurs with use of a low dose combination monophasic OC containing 20 µg ethinyl estradiol.

This was a prospective, randomized clinical trial. Thirty healthy women between the ages of 18 and 49 with regular cycles had pelvic sonography on cycle days 8, 10, 12, 14, and 16 prior to treatment to confirm the presence of gradual development and rapid disappearance of a dominant follicle, a pattern consistent with ovulation. They were then randomly assigned to receive 2 cycles of treatment with either Lunelle™ or Alesse-28, an oral contraceptive containing 20 µg of ethinyl estradiol and 0.1 mg of levonorgestrel. During the second cycle of treatment, pelvic sonography was performed on cycle days 4, 8, 12, 16, 20, 24, and 28

and the maximum follicle diameter was measured. Study endpoints were the presence of follicles ≥ 10, 20, and 30 mm.

13 of 15 Alesse-28 subjects and 14 of 15 Lunelle™ subjects completed the study. Follicles measuring ≥ 10 mm were present in 11/13 (84.6%) of the Alesse-28 subjects and 4/14 (28.6%) of Lunelle™ subjects. In the Alesse group, 6 of 13 (46.1%) developed follicles ≥ 20 mm and 1of 13 (7.7%) developed follicles ≥ 30 mm. No Lunelle™ subject developed a follicle ≥20 mm.

The sponsor reports that a 13 mm follicle is the minimum size of a dominant follicle (the size needed for ovulation). Ten of 13 (76.9%) Alesse subjects developed a follicle ≥ 13 mm compared with 1 of 14 (7.1%) Lunelle™ subjects. Of the 10 dominant follicles in the Alesse group, 8 (80%) resolved to a size less than 13 mm by day 28. The single dominant follicle in the Lunelle™ group persisted on day 28. Serum progesterone and estradiol were not measured in this study; therefore, conclusions on the rate of ovulation and incidence of luteinized unruptured follicles cannot be determined.

This study indicates that Lunelle™ is associated with a significantly lower incidence of ovarian follicular development compared to use of an oral contraceptive containing 20 µg of ethinyl estradiol and 0.1 mg of levonorgestrel. Whereas suppression of ovulation is thought to be the mechanism whereby long term use of OCs containing 30 µg of ethinyl estradiol or more is associated with a 50% decrease in development of epithelial ovarian cancer, the sponsor postulates that these results would suggest that long-term use of Lunelle™ would also achieve this important non-contraceptive health benefit.

The probable complete suppression of ovulation observed in this study is attributable to the MPA component of Lunelle™. The suppression of follicular activity and prevention of follicle formation ≥ 20 mm are most likely due to the elevated levels of estradiol observed after an injection of Lunelle™ which suppress FSH.

Reviewer's comment
Although this trial did not directly compare Lunelle™ with MPA alone or DMPA, the demonstrated inhibition of follicular activity is likely a result of the estrogen component of the product and may provide further justification for this combination product.

7.0 SAFETY DATA FROM PUBLISHED LITERATURE

Of 10 articles identified during the period from March 31, 1998 to February 8, 2000, only one contains new information relevant to the safety assessment of Lunelle™. This article, "Endometrial histology in long-term users of the once-a-month injectable contraceptive Cyclofem", discusses a study of endometrial histology in 17 women ages 21-32 who used Lunelle™ for 1 year or longer.

Endometrial biopsies were obtained 27 to 33 days after the last injection of Lunelle™. The pathologist was blinded to the subject's bleeding pattern and the number of injections received. Of the 17 biopsies, 4 were inadequate for diagnosis because they consisted of only blood and mucus (two of these women were bleeding regularly, and the other 2 had amenorrhea.), 8 revealed a proliferative pattern (3 had amenorrhea and 5 were bleeding regularly), and 5 were reported as secretory endometrium, 4 of them showing pseudodecidual reaction compatible with the administration of progestin (All of these women were bleeding regularly). No hyperplasia was seen.

No correlation was found between endometrial histology and bleeding patterns.

8.0 COMBINATION DRUG REGULATION (JUSTIFICATION OF ESTROGEN COMPONENT)

Estrogens and progestins have been used in combination as oral hormonal contraceptives for many years and have been found safe and effective.

The data presented in this NDA do not support the sponsor's goal of providing a contraceptive option that included the benefits of Depo-Provera (DMPA) with the added benefit of an estrogen to promote a more normal bleeding pattern. In fact, aside from a significantly lower incidence of amenorrhea, the data reveal a higher incidence of unacceptable bleeding patterns with Lunelle™ than with the currently available progestogen-only injectable contraceptive.

The sponsor has also suggested that the combination of MPA and estradiol cypionate (E_2C) in Lunelle™ reduces the risk of breakthrough ovulation and allows the use of a lower monthly dose of MPA. However, early studies demonstrated that MPA alone in doses of 12.5 or 25 mg effectively suppressed ovulation for at least a month and that either dose of MPA combined with a lower dose (2.5 mg) of E_2C resulted in an unacceptable rate of ovulation.

The clinical study report discussed in section 6.0 above suggests that the addition of estrogen in this product results in a lower incidence of ovarian follicular activity and cyst formation than what is found with use of available progestin-only contraceptives. The sponsor also suggests that this may provide the user with protection against ovarian cancer, a non-contraceptive benefit of combination oral contraceptives. However, this study does not directly compare Lunelle™ with the same dose of MPA alone or with DMPA.

Information presented in the original NDA from a 1987 WHO pharmacokinetics and pharmacodynamics study showed that ovulation returned earlier in women who received either Lunelle™ or a half-strength formulation of 12.5 mg MPA: 2.5 mg E_2C than in those who received the 25 mg or 12.5 mg dose of MPA alone.

Number of Women who Ovulated in the First and Second Post-Treatment Months

Treatment	N	First Month Post-Treatment	Second Month Post-Treatment
Lunelle™	21	11 (52.4%)	15 (71.4%)
25 mg DMPA	21	5 (23.8%)	10 (47.6%)
12.5 mg MPA: 2.5mg E_2C	20	12 (60.0%)	18 (90.0%)
12.5 mg DMPA	20	8 (40.0%)	15 (75.0%)

Reviewer's conclusions

- **The contraceptive effect of LUNELLE™ Monthly Contraceptive Injection is clearly attributable to the progestin (MPA) component.**
- **The demonstrated advantage of the added estrogen (E_2C) component is the earlier return of ovulation after discontinuing use of the product compared to the progestin alone in the same dose.**
- **Additional theoretical benefits of the estrogen component include the following:**
  - **Maintenance of bone mineral density compared to DMPA**
  - **Reduced incidence of ovarian follicular activity and ovarian cyst formation**
  - **Non-contraceptive benefits of other hormonal contraceptives, including protection from ovarian cancer.**

9.0 LABELING

Revisions to the sponsor's proposed labeling are recommended so as to reflect the expected clinical outcomes based on findings of the clinical trials and to provide labeling consistent with other injectable contraceptives as well as combined oral hormonal contraceptives.

10.0 PHASE IV PROPOSALS

The Approvable letter from FDA to the sponsor dated October 15, 1999 states, "As discussed on October 12, 1999 and subsequently agreed by you via October 15, 1999 facsimile, the Division requests that you develop and execute further clinical trials to determine the added benefit of the estrogen-component of this combination product. Studies would include a comparison of bone mineral density changes, ovulation rates and alterations in bleeding patterns between Lunelle™ Monthly Contraceptive Injection and your medroxyprogesterone acetate alone product."

A letter from the sponsor dated October 13, 1999 stated that P&U would commit to one or more Phase IV studies to assess potential benefits of the combination product (including the estrogen). P&U proposed the following three arenas as possibly useful to document the benefit of added estrogen.

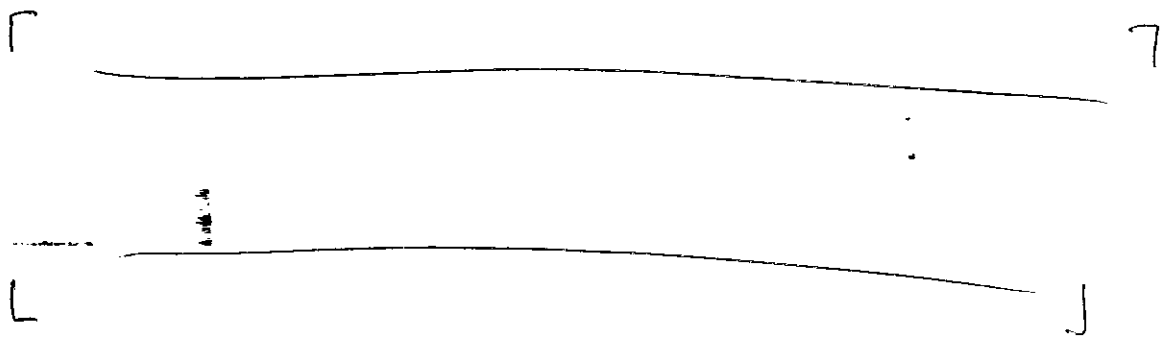
- Bleeding Pattern: A comparison of bleeding patterns in women receiving Lunelle™ versus those receiving MPA over a period of up to six months
- Return to Ovulation: A comparison of the time to return to ovulation following 3 monthly injections of Lunelle™ versus three months on MPA alone
- Bone Mineral Density: An evaluation of the effects of Lunelle™ on bone mineral density.

A subsequent letter, also dated October 13, 1999, modified the Phase IV commitment to change the above second arena to

- Ovulation Rates: A comparison of ovulation rates during product use following monthly injections of Lunelle™ versus MPA alone.

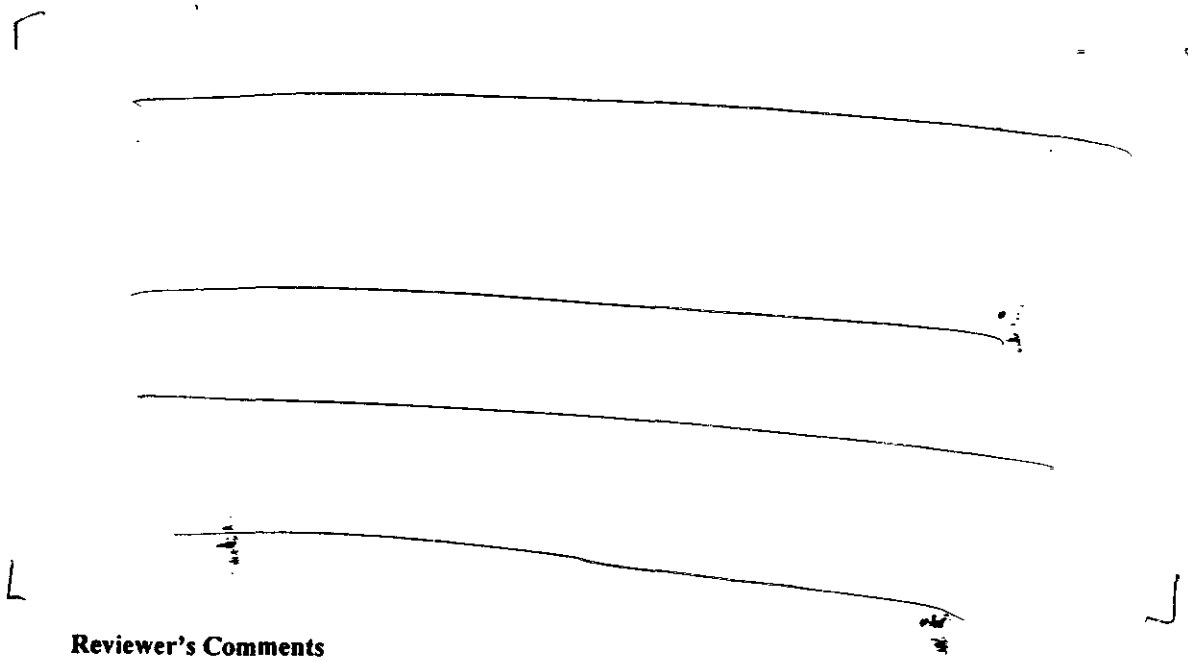
P&U committed to seek the Division's guidance by further discussion and finalization of specific protocol aspects within 6 months from the date of the 'approval' letter and to seek agreement with FDA on key studies/designs prior to initiation of these trials.

Draft summaries for two Phase IV protocols are presented with the current submission. The sponsor states a commitment to seek the Division's guidance within 6 months after approval prior to finalizing specific protocols and agreement before initiation of these studies.



Reviewer's comments

- **The October 15, 1999 letter clearly states that this study should compare the BMD changes between Lunelle™ and the MPA product alone.**
- **A revised protocol summary should be submitted for review prior to a final action on this current application.**
- **The size and duration of the proposed study are acceptable as long as a comparator arm (DMPA or both DMPA and MPA) is added.**
- **This study should take priority over the following study.**



Reviewer's Comments

- **The number of subjects for each study group should be designated.**
- **Additional analysis of ovulation should be planned between the first and final months of treatment, preferably with every cycle, but at the least after the third injection of MPA or Lunelle™ and in the third month of DMPA.**
- **Subjects over age 35 should be excluded because spontaneous ovulation becomes unpredictable after that age.**
- **This protocol is of secondary importance to the previous (BMD) protocol noted above.**
- **The clinical relevance of ovulation suppression is questionable since contraceptive efficacy has been demonstrated, and several different mechanisms of action contribute to the contraceptive effect.**

Bleeding patterns seen with Lunelle™ Monthly Contraceptive Injection have been extensively studied in M/5414/0004 using Belsey's criteria and re-analyzed for the current review based upon monthly injection intervals. Aside from a lower incidence of amenorrhea, these data show no improvement in bleeding patterns compared to those seen with the available injectable progestin-only contraceptive. However, no safety concern is associated with these bleeding patterns. It is unlikely that a further evaluation of bleeding patterns compared to Depo-Provera or to MPA alone would yield clinically important information. Therefore, the sponsor should not be required to perform such studies but could collect information on bleeding patterns in the proposed study of Bone Mineral Density if desired.

11.0 FINAL CONCLUSIONS AND RECOMMENDATIONS

As noted in the previous review, the data presented indicate that Lunelle™ is safe and effective in preventing pregnancy. However, due to the absence of any reported pregnancies in the current trial, incomplete pregnancy assessments and follow-up for all participants, and the poor quality of data from previous trials, it is not possible to calculate an accurate Life Table Failure Rate for this method of contraception.

The data do not support the sponsor's goal of providing a contraceptive option that included the benefits of Depo-Provera (DMPA) with the added benefit of a more normal menstrual bleeding pattern due to the estrogen component. In fact, aside from a significantly lower incidence of amenorrhea, the data reveal a higher incidence of unacceptable bleeding patterns with Lunelle™ than with the currently available progestogen-only injectable contraceptive. Whereas anemia or bleeding-related serious adverse events were

not commonly reported, the unacceptable bleeding patterns appear to be a nuisance and not a safety concern. Earlier studies also demonstrated that the combination of E_2C and MPA in Lunelle™ does not reduce the occurrence of breakthrough ovulation compared to MPA alone. However, Lunelle™ does allow a more rapid return of ovulation and fertility after discontinuation than DMPA or MPA alone in equal doses and may have a less negative effect on bone mineral density.

The sponsor has also presented data to demonstrate that Lunelle™ suppresses ovarian follicular activity, an effect most likely attributable to the estrogen component. This effect may provide the non-contraceptive benefit of protection from ovarian cancer seen with combined oral contraceptives.

The sponsor suggests that Lunelle™ users can share in other benefits afforded by combination estrogen-progestin oral contraceptives, e.g., reduced incidence of endometrial carcinomas, reduced uterine fibroids, ectopic pregnancies, benign breast disease, and probably, some protective effect on bone mineral density, compared to non-users. Data presented do not show other non-contraceptive benefits similar to those of oral contraceptives such as less painful menstrual periods and less loss of menstrual blood. The possibility of a lower risk of anemia and fewer pelvic infections also have not been studied.

It is recommended that Lunelle™ Monthly Contraceptive Injection be approved for marketing with the requirement that the sponsor conduct a Phase IV postmarketing study

/S/

9/27/00

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/S/

9/27/00

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CC: NDA 20,874/Division File

APPEARS THIS WAY
ON ORIGINAL

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

PROTOCOL SUMMARY – BONE MINERAL DENSITY

Project No/Name: 839-FEH-0034/Lunelle IM

Protocol No: 839-FEH-0034-009 **Indication: Contraception**

Title of Study: A comparison of LUNELLE™ and DEPO-PROVERA effect on BMD to document benefit of added Estrogen.

Rationale and Objectives: LUNELLE Monthly Contraceptive Injection is manufactured by the Pharmacia & Upjohn company as a sterile-aqueous suspension. It is a combination of medroxyprogesterone acetate (MPA, 50 mg/mL) and estradiol cypionate (E2C, 10 mg/mL). Each 0.5 mL dose contains 25 mg MPA and 5 mg E2C. The product is intended for deep intramuscular (IM) injection once every 28 days.

Reduction in bone density accompanies estrogen deficiencies in a number of populations. In younger women, estrogen deficiency has resulted from ovarian failure (after oophorectomy, after chemotherapy, or due to premature menopause) or from hypothalamo-pituitary dysfunction (anorexia nervosa, athletic amenorrhea, and use of long-acting gonadotrophic-releasing hormones). Postmenopausal estrogen deficiency is a major cause of bone loss in older women and contributes to substantial morbidity in this population. Maximum bone mineral density is achieved between the ages of 20 and 30 years and declines thereafter.

Bone formation and remodeling is a complex process involving the interaction of hormonal, physical, and nutritional factors. In addition to estrogens, progestogens promote bone formation and/or increase bone turnover. There have been some recent data that suggest there is a possible negative effect on bone mineral density by depot medroyxprogesterone acetate (Depo-Provera) in older premenopausal women and in adolescents using the drug for contraception. Cundy et al [1], in a cross-sectional study, used dual x-ray absorptiometry (DXA) measurements to compare DMPA users with pre- and postmenopausal controls. They found that DMPA users had a lower bone mineral density as compared to the premenopausal control individuals, but higher than that of postmenopausal control individuals. A randomized study by Naessen et al [2] compared single-photon absorptiometry (SPA) measurements of the forearm in subjects given either DMPA or levonorgestrel subdermal implants. DMPA users had a small but not statistically significant reduction in bone mineral density. Scholes et al [3] compared users and nonusers of DMPA and concluded that mean bone density levels were lower for users than for nonusers as measured by DXA.

The association between DEPO-PROVERA and bone mineral density has not been unanimous. Taneepanichskul et al [4], compared BMD in a cross-sectional study of women receiving DEPO-PROVERA and levonorgestrel subdermal implants. DXA measurements of the forearm found no significant differences between the groups. In a cross-sectional study by Gbolade et al [5], DXA measurements of the lumbar spine resulted in no relationship between the lumbar spine score and DMPA use.

The mainstay approach to the prevention of osteoporosis has been to prescribe estrogen therapy to women after the menopause, most commonly in combination with a progestogen.

The potential risk associated with the use of progestin-only contraceptives on bone should be lower since LUNELLE contains estradiol. The estradiol profile following LUNELLE injection showed peak levels that returned to nontreated baseline levels by about 10 to 16 days post-injection. It is possible that this estrogen profile could contribute to a positive effect on BMD. Data from postmenopausal women have shown a beneficial effect on BMD from the combination of MPA and estrogen.[6] In addition, studies with combination OCs have shown little or no effect on BMD.

Protocol 839-FEH-0034-009 is planned to fulfill FDA post-approval requirement to prove the benefit of adding estrogen to progestin. The primary objective is to evaluate BMD changes in women receiving Lunelle for up to two years as compared to women receiving **DEPO-PROVERA** with an interim analysis done at one year.

METHODOLOGY

Study Design: This is an open-label, multicenter study in adult women with regular menstrual cycles. Subjects will be randomized by age and prior use of hormonal contraceptive within one year into one of two treatment groups. Subjects will agree to participate for up to two years and will receive either LUNELLE Monthly Contraceptive Injection at 28 ± 5-day intervals, or DEPO-PROVERA contraceptive injection at 13 week intervals. Lumbar spine, hip, and total body BMD will be evaluated by DXA at a screening visit and at 6-month intervals. Physical and gynecologic exams and laboratory studies will be performed yearly.

Primary Endpoint: The primary endpoint will be whether or not a patient experienced bone mineral density loss after 2 years of treatment. A patient will be said to experience bone mineral density loss at the analysis time point if the DXA value at that time point is less than the baseline value. The endpoint will be analyzed by comparing the proportion in each treatment group experiencing BMD loss. An interim analysis on the proportion of patients experiencing bone mineral density loss after 1 year of treatment as measured by DXA will be done after all patients have been enrolled 1 year. If this interim analysis shows a significant difference in favor of Lunelle, the study may be stopped.

Other Endpoints: Percent change from baseline in bone mineral density at 1 year and 2 years after initiating treatment with Lunelle or Depo-Provera as measured by DXA will also be examined. Secondary endpoints include safety.

Statistical Methods: The primary efficacy analysis will be done for all patients receiving at least one dose of study treatment and with at least one DXA value after baseline. In the intent to treat analysis, an imputation of any missing DXA value at the analysis time point will be done by projecting linearly from baseline. An analysis will also be done on only the available data at the analysis time point. A chi-square test will be used to compare the percent of patients in each treatment group experiencing bone mineral density loss.

Analysis of safety endpoints will be performed for all patients receiving at least one dose of study treatment and having at least one safety assessment performed after treatment. Adverse events will be tabulated by treatment groups and by body system and listed for each subject.

Interim Analyses: An interim analysis will be performed 1 year after all patients have been enrolled in the study. It will be performed on safety and the percent of women experiencing a bone mineral density loss after 1 year as measured by DXA. Results of the analysis will be reviewed by an internal data monitoring committee. The significance level for the interim data analysis will be set at 0.01. To maintain an overall two-sided type I error rate of 0.05 the significance level for the final analysis will be set at 0.04. If the difference between the two treatment groups with respect to this endpoint is significant at the interim analysis, the study will be terminated.

Sample Size: The sample size is computed to support the testing of the hypothesis on the percent of women with BMD loss as measured by DXA after 2 years of treatment. The sample size is based on the assumption that 65% of the women in the Depo-Provera treatment group will experience some BMD loss after 2 years of treatment. The allocation to treatment groups will be 2:1 in favor of the Lunelle group. A sample size of 276 patients in the Lunelle treatment group and 138 in the Depo- Provera treatment group will give 80% power with an overall type I error <= 0.05 to detect a difference of 15% in the response rate in BMD loss between the two treatment groups. Assuming a drop out rate of 70% after 2 years, then 920 patients should be enrolled in the Lunelle treatment group and 460 in the Depo-Provera group. From the literature [1,7] a 1.1-1.5% decrease in bone density per year might be expected in women receiving Depo-Provera. The projected sample size would also give 80% power with an overall type I error <= 0.05 to detect a difference of 3% after 2 years with respect to percent change from baseline assuming a standard deviation of 10%. [8]

P/K Needed : No

TIMING	
Start Date: 4Q 2000 (trial supplies delivered)	**Finish Date:** 4Q 2003 (last patient complete)
Duration of Washout: None	**Duration of Enrollment Period:** 2 years
Duration of Run-In: None	**Duration of Treatment Period:** 2 years

MEDICATIONS

Tx Groups	Drug	Form	Route	Dose	Dosing Interval	# Evaluable Patients
1. Lunelle	Lunelle	Suspension	IM	25 MPA 5 E2C	28 d +/- 5 days	276

2. DEPO-PROVERA	DEPO-PROVERA	Suspension	IM	150mg DMPA	13 week +/-5 days	138

Inclusion Criteria:

1. Age 18-35.
2. Women of child bearing potential requiring contraception.
3. Negative urine pregnancy test at baseline.
4. Willing to enter study and comply with the study's specific procedures.
5. Willing and able to return at the prescribed intervals for follow-up visits.
6. Not presently breastfeeding
7. Signed, informed consent.

Exclusion Criteria:

1. Concomitant use of steroids including sex hormones, SERMS, bisphosphonates, growth hormone, PTH, aminoglutethimide, carbamazepine, rifampicin, griseofulvin, hydantoines, barbiturates, oxazepam, primidone, thyroid drugs, or GnRH agonists.
2. Cervical cytology: Any epithelial cell abnormality as reported in the Bethesda System except reactive and reparative changes such as atypical squamous cells of undetermined significance (ASCUS) in the past 6 months prior to entering the study.
3. Suspected, present or past history of cancer, except carcinoma-in-situ of the cervix which has been treated with subsequent normal Pap smears for 12 months and basal cell cancer of the skin.
4. History of mammary or ovarian carcinoma.
5. Thromboembolic disease, past or present, with the exception of superficial thrombophlebitis.
6. Active or history of cerebral vascular or coronary artery disease.
7. Undiagnosed abnormal genital bleeding.
8. History (within the last five years) of alcohol abuse (> 2-3 drinks/day) or other drug abuse.
9. Cholestatic jaundice of pregnancy or past history of jaundice with prior use of hormonal contraception including severe pruritis of pregnancy.
10. Current confirmed hypertension: defined as systolic > 160 mmHG or diastolic >90 mmHG. Hypertension stable on antihypertensives for previous 6 months is allowed.
11. Any use of DEPO-PROVERA or NORPLANT within the last 5 years
12. Active or history of clinically significant hepatic or renal disease. (Active hepatic disease is defined as having an AST/SGOT, ALT/SGPT, or GGPT 2.5 times upper limit of normal; total bilirubin > 1.5 mg/dL; Active renal disease is defined as having creatinine > 1.5 mg/dL).
13. Bone disease.
14. Abnormal serum calcium levels.
15. History of hyperparathyroidism or hypoparathyroidism. Current untreated hyperthyroidism

16. Hypersensitivity to study medications or subjects in whom estrogen and/or progestin are contraindicated.
17. Any subject incapable of understanding the necessary instructions or not reasonably expected to complete the study.
18. Concurrent use of other investigational medication(s).
19. Previous participation in this study.
20. Diabetes with vascular involvement.
21. Headaches with focal neurological symptoms.
22. Valvular heart disease with complications.
23. BMI <18 or >40.
24. Uncontrolled Diabetes.
25. Any use of investigational drug in the past 30 days.

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4. Taneepanichskul S, Intaraprasert S, Theppisai U, Chaturachinda K. Bone-mineral density in long-term depot medroxyprogesterone acetate acceptors. Contracept 1997;56:1-3.
5. Gbolade B, Ellis S, Murby B, Randall S, Kirkman R. Bone density in long-term users of depot medroxyprogesterone acetate. Br J Obstet Gynecol 1988;105:790-4.
6. Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA 1996;275(3):199-208.
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