CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-584

MEDICAL REVIEW(S)

Memo to the file

Date: 3-9-05

NDA #: 21-584

Date of submission: 12-17-2003

Sponsor: Pharmacia and Upjohn

Drug Product: Medroxyprogesterone acetate 104 mg/0.65 ml

Indication: Treatment to relieve pain symptoms caused by endometriosis

Subject: Labeling

Reviewer: Krishan L. Raheja, D.V.M., Ph.D.

Through P/T supervisor: Yangmee Shin, Ph.D.

Regulatory action: The preclinical toxicology section of the label for NDA 21-584 for the treatment of endometriosis is similar to that for NDA 21-583 for contraception and is acceptable to Pharmacology/Toxicology.

N21-584.label

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/s/

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DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

CLINICAL TEAM LEADER MEMORANDUM

NDA	NDA 21-584
Type of Application	Complete response to Approvable action
Applicant	Pharmacia & Upjohn Company, a subsidiary of Pfizer, Inc.
Proprietary Drug Name	depo-subQ provera 104™
Established Drug Name	Medroxyprogesterone acetate injectable suspension, USP
Dosage Form	Sterile aqueous suspension in prefilled syringe
Dosage Strength	160 mg/mL (delivered dose is 104 mg/0.65 mL per syringe)
Dosing Regimen	Subcutaneous injection once every 3 months
Indications (Proposed)	Management of endometriosis-associated pain Management of recurrence of symptoms
PDUFA Date	March 28, 2005
Date of Memorandum	March 25, 2005
Reviewer	Scott E Monroe, MD Clinical Team Leader, DRUDP

RECOMMENDATIONS

Recommendation regarding Approvability

I recommend approval for marketing of medroxyprogesterone acetate injectable suspension (depo-subQ provera 104) for "management of endometriosis-associated pain." I recommend that depo-subQ provera 104 not be approved for ' since the Applicant has not conducted studies to support this indication. The approved dosing regimen will be a subcutaneous injection once every 3 months (12-14 weeks), with a recommendation in labeling that treatment should not continue beyond 2 years due to effects on bone mineral density, unless there is recurrence of symptoms after discontinuation of treatment and bone mineral density (BMD) is evaluated prior to retreatment.

Recommendation for approval for the indication of management of endometriosis-associated pain is based on the data presented in the original NDA submission dated December 17, 2003 and additional information submitted during the original review cycle, the Applicant's complete response dated January 27, 2005 to the Approvable Letter of October 2004, and final revised product labeling submitted by e-mail on March 23, 2005 (PI) and March 25, 2005 (PPI). In 2 active-comparator Phase 3 clinical trials, depo-subQ provera 104 (hereafter referred to as DMPA-SC) was shown to be effective in reducing the severity of endometriosis-associated pain. The safety profile of DMPA-SC in these studies in women with endometriosis was acceptable and similar to that described for DMPA-SC in clinical trials for the prevention of pregnancy reported in

NDA 21-583. The Applicant has satisfactorily addressed all of the outstanding issues that were identified in the Approvable Letter of October 18, 2004.

Recommendation on Phase 4 Studies and/or Risk Management Steps

Phase 4 Studies. No Phase 4 studies are recommended. DMPA-SC for the management of endometriosis-associated pain should have a risk profile similar to (1) the presently marketed product (medroxyprogesterone acetate injectable suspension administered by intramuscular [IM] injection) that was approved in the U.S. in 1992 for prevention of pregnancy and (2) DMPA-SC used for prevention of pregnancy.

Risk Management Steps. The most significant risk associated with the use of DMPA-SC (i.e., a decrease in BMD) should be adequately managed by the approved Physician Label that includes (1) a Boxed Warning regarding the likely effect of long-term treatment with DMPA-SC on BMD and (2) the following statement under DOSAGE AND ADMINISTRATION:

> *"Treatment for longer than two years is not recommended, due to the impact of long-term depo-subQ provera 104 on bone mineral density. If symptoms return after discontinuation of treatment, bone mineral density should be evaluated prior to retreatment."*

The most common adverse events leading to premature discontinuation of treatment in the 6-month endometriosis clinical trials were related to abnormal uterine bleeding. The magnitude of the bleeding does not pose a safety concern but was the primary cause of premature discontinuation of treatment in 5 of 282 subjects. Bleeding patterns are well described in both physician and patient labeling.

BACKGROUND

Medroxyprogesterone acetate (MPA) is the synthetic 6-methyl analog of 17-hydroxy-progesterone. MPA has been marketed for many years as oral (Provera® Tablets) and intramuscular injection formulations (Depo-Provera® Sterile Aqueous Suspension [400 mg/mL; indication of palliative treatment of renal or endometrial cancer] and Depo-Provera® Contraceptive Injection [150 mg/mL]). A new formation of medroxyprogesterone acetate injectable suspension, which is administered by subcutaneous injection (SC) once every 3 months (depo-subQ provera 104 [DMPA-SC]; 104 mg/0.65 mL per injection) was approved for prevention of pregnancy in December, 2004. Depo-subQ provera 104 differs from the previously approved product (DMPA-IM) in that (1) it is to administered subcutaneously instead of intramuscularly and (2) the dose of MPA is lower (104 mg once every 3 months compared to 150 mg once every 3 months).

The present application (NDA 21-584) is for marketing approval of DMPA-SC for
(1) management of endometriosis-associated pain and
NDA 21-584
was originally submitted in December 2003 and received an Approvable action on October 18, 2004, subject to submission of acceptable labeling and agreement on a proprietary name.

ORIGINAL NDA SUBMISSION – CONCLUSIONS REGARDING EFFICACY AND SAFETY OF DMPA-SC FOR MANAGEMENT OF ENDOMETRIOSIS ASSOCIATED PAIN

The safety and efficacy of DMPA-SC for management of endometriosis-associated pain, based on the data provided in the Applicant's original NDA submission, are reviewed in detail in Dr. Soule's (the primary Medical Officer) review of October 12, 2004 and the clinical Team Leader's Memorandum of October 18, 2004.

The response to treatment with DMPA-SC, compared to the response to treatment with the approved active comparator (leuprolide acetate, Lupron) fully met all of the protocol defined criteria for statistical non-inferiority in one Phase 3 clinical trial (Study 270), but did not fully meet all criteria for statistical non-inferiority in the second Phase 3 clinical trial (Study 268). Consequently, several post hoc analyses were conducted to add clarity to the efficacy findings from Study 268. These latter analyses also supported the effectiveness of DMPA-SC. Based on the overall body of evidence from the two Phase 3 clinical trials, this reviewer concluded in his Memorandum of October 18, 2004 (and continues to believe) that DMPA-SC, 104 mg every 3 months by SC injection, is effective in reducing the painful symptoms of endometriosis.

Based on safety data provided in the original submission for NDA 21-584, this reviewer concluded in his Memorandum of October 18, 2004 that the safety profile of DMPA-SC was acceptable for a drug therapy for the management of endometriosis-associated pain. This conclusion was based on (1) clinical trial safety data for women with endometriosis who were treated with DMPA-SC for up to 6 months and reported in the original submission of NDA 21-584, (2) supportive clinical trial data for women treated with DMPA-SC for prevention of pregnancy for up to 2 years, and (3) many years of postmarketing safety data for DMPA-IM for prevention of pregnancy.

PRESENT SUBMISSION (COMPLETE RESPONSE TO APPROVABLE LETTER)

In the present submission, the Applicant submitted a safety update and revised drug labeling.

Safety Update

The Complete Response included a safety update that focused primarily on providing in an integrated format data that had already been submitted to the NDA since (1) no studies were ongoing with depo-subQ provera 104 for the endometriosis indication and (2) an integrated safety update for all studies with depo-subQ provera 104 was submitted in October 2004 in support of the prevention of pregnancy indication. Included in the current safety update were data integrated over both indications and formulations:

- Data integrated over the two completed endometriosis trials (Studies 268 and 270)
- Data integrated over 6 contraceptive trials (2 completed depo-subQ provera 104 contraceptive trials, 2 completed and one ongoing DMPA-IM contraceptive trials, and one ongoing contraception/BMD trial [Study 267BMD] that uses both depo-subQ provera 104 and DMPA-IM)

In addition, postmarketing safety data through June 30, 2004 for DMPA-IM were provided because the depo-subQ provera 104 formulation is not yet marketed anywhere in the world.

A thorough review of the data in the Safety Update is provided in Dr. Soule's review dated March 24, 2005. Dr. Soule made the following statements in her review:

> *"The information provided in the safety update does not raise safety concerns and the safety profile is expected to be similar to that of the approved contraceptive product, DMPA-IM. Given the previous demonstration of efficacy for depo-subQ provera 104 based on data in the original NDA submission of December 18, 2004, combined with updated safety information that raises no new concerns, the risk/benefit ratio continues to support approval for this indication."*

Medical Officer's Comment

- *I concur with Dr. Soule's assessment regarding the safety and efficacy of DMPA-SC for the management of endometriosis-associated pain.*

Revised Labeling

During the review of NDA 21-583 (DMPA-SC for the prevention of pregnancy indication), the Division requested, and the Applicant agreed to, extensive safety labeling changes pertaining to

- Impact of long-term treatment (e.g., for greater than 2 years) on BMD
- Delay in return to ovulation and fertility after discontinuation of treatment
- Increase in body weight with long-term treatment

The label proposed by the Applicant in the current submission was that approved by the Division in December 2004 for the prevention of pregnancy indication with additional information to support the endometriosis indication. Major revisions were requested by the Division for the endometriosis sections of the proposed label. These revisions included the following items to assist the physician and patient is assessing the relative benefits and disadvantages of treatment with DMPA-SC compared to treatment with a GnRH agonist (the active comparator used in the clinical trials) for pain-related symptoms of endometriosis:

- A figure that shows the relative response rates for each of the pain-related symptoms of endometriosis that were assessed in the Phase 3 clinical trials (point estimates for response rates were higher in GnRH agonist- [i.e., Lupron] treated patients)
- Comparative information about the percentages of patients experiencing moderate or severe hot flushes during treatment (percentages were higher in Lupron-treated patients)
- Comparative information about decreases in BMD during treatment (less loss of BMD was observed in DMPA-SC-treated patients).

At the completion of the first review cycle for NDA 21-584, this reviewer had recommended that the label prescribe that the duration of treatment with DMPA-SC be 6 months, with allowance for up to 3 additional 6-month courses of treatment, as warranted by recurrence of symptoms. This recommendation was based upon the fact that the efficacy and safety data submitted in support of the endometriosis indication was

limited to 6 months of treatment. This reviewer now recommends that labeling state the following regarding duration of treatment:

> *"Treatment for longer than two years is not recommended, due to the impact of long-term depo-subQ provera 104 on bone mineral density. If symptoms return after discontinuation of treatment, bone mineral density should be evaluated prior to retreatment."*

This recommendation is based on the following considerations:

- DMPA-SC, like other approved medical therapies for endometriosis, is not curative, and therefore, many women are likely to have recurrence of symptoms after 6 months of treatment.
- There is no basis to anticipate, based on the pharmacology of DMPA-SC, that the effectiveness of DMPA will diminish after 6-months of treatment.
- The safety of 2 years of treatment with DMPA-SC is well supported by the 2-year safety data obtained in women in the prevention of pregnancy clinical trials.

Medical Officer's Comment

- *Final physician and patient labeling submitted by the Applicant on March 23, 2005 (PI) and March 25, 2005 (PPI) are acceptable.*

OTHER ISSUES THAT WERE UNRESOLVED AT COMPLETION OF THE FIRST REVIEW CYCLE

Proprietary Drug Name

At the time of the Approvable action for DMPA-SC in October 2004, the Applicant wanted to use the proprietary name "Depo- ' or "Depo- ' Neither the Division of Reproductive and Urologic Drug Products (DRUDP) nor the Division of Medication Errors and Technical Support (DMETS) supported the use of these names. During the second review cycle for the prevention of pregnancy indication (NDA 21-583), the Division and the Applicant agreed to the proprietary name "depo-subQ provera 104." DMETS, however, had reservations about the name depo-subQ provera 104 largely because of the inclusion of the dosage route (subQ) and dosage (104) in the name.

Medical Officer's Comment

- *This proprietary name was accepted by the Division because it (1) does not suggest any clinical benefit for the SC formulation compared to the IM formulation and (2) clearly differentiated the new product from the IM formulation by inclusion of (a) the term "subQ" within the overall name (rather than at the end of the name) and (b) the mg dose of MPA (104), which differs from that of the IM formulation.*

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

DDMAC made many suggestions regarding the Applicant's proposed Package (Physician) Label during the original review cycle. Most of these comments were addressed during final labeling for the prevention of pregnancy indication. Those comments relevant to the endometriosis indication were all considered and addressed in the changes that the Division requested of the Applicant during labeling negotiations for this indication.

Division of Surveillance, Research, and Communication Support (DSRCS)

DSRCS made several recommendations regarding the format and simplification of language for the Patient Package Insert. All recommendations were considered and, for the most part, incorporated.

Chemistry

At the end of the first review cycle there were no outstanding chemistry issues other than agreement on acceptable labeling and an acceptable proprietary name. Both of these issues were resolved prior to approval of depo-subQ provera 104 for the prevention of pregnancy indication.

Other Disciplines

There are no preclinical toxicology deficiencies. Biopharmaceutical deficiencies related only to agreement on acceptable labeling. All biopharmaceutical labeling issues and deficiencies were resolved prior to approval of depo-subQ provera 104 for the prevention of pregnancy indication.

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/s/

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CLINICAL REVIEW

Application Type	21-584
Submission Number	000
Submission Code	AZ
Letter Date	January 27, 2005
Stamp Date	January 28, 2005
PDUFA Goal Date	March 28, 2005
Reviewer Name	Lisa Soule, M.D.
Review Completion Date	March 24 2005
Established Name	Medroxyprogesterone acetate
Trade Name	depo-subQ provera 104
Therapeutic Class	17-α hydroxyprogesterone analogue
Applicant	Pfizer
Priority Designation	S
Formulation	Subcutaneous injection
Dosing Regimen	104 mg in 0.65 ml every 3 months
Indication	Management of endometriosis-associated pain
Intended Population	Women with endometriosis-associated pain

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval of depot medroxyprogesterone acetate subcutaneous injection (depo-subQ provera 104) for management of endometriosis-associated pain. I recommend non-approval of the [redacted] since the Applicant has not conducted studies to support this indication. The approved dosing regimen will be a subcutaneous injection once every three months (12-14 weeks), with a recommendation that treatment should not continue beyond two years due to effects on bone mineral density (BMD), unless there is recurrence of symptoms after discontinuation of treatment and bone mineral density is evaluated prior to retreatment.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No post-marketing risk management plan is recommended. The safety profile is expected to approximate that of the currently marketed intramuscular formulation, which is indicated for prevention of pregnancy and has been marketed worldwide for more than 12 years. Completion of an ongoing study of the reversibility of BMD changes in adolescents may necessitate changes to the label when the final report is issued within the next two years.

1.3 Summary

On October 18, 2004, FDA issued an approvable action for NDA 21-584 because labeling had not been finalized. The Executive Summary of the original NDA 21-583 review is provided in the Appendix of this review as an overview of the issues that led to this action and to summarize the efficacy and safety findings in the original NDA submission.

The present submission included Pfizer's response to FDA's labeling recommendations, as well as a routine safety update. The submission addresses all items requested in FDA's approvable letter.

A related NDA, 21-583, for the same product for the indication of prevention of pregnancy received an Approval action on December 17, 2004. Labeling negotiated for this approval included FDA-requested changes relating to:

- Bone mineral density
- Return to ovulation and fertility
- Pregnancy and lactation
- Weight changes
- Injection site reactions
- Adverse events

The Applicant has proposed revised labeling to allow for a joint label to be used for both the pregnancy prevention and endometriosis indications. In response to requests from the Division, the Applicant submitted revised product and patient labeling on March 15, 2005 and March 23, 2005 that adequately addressed all of this reviewer's recommendations.

The safety update revealed no unexpected safety issues. In particular, there were

- No additional deaths or new serious adverse events
- No change in the profile of reasons for withdrawal from studies
- No significant changes or findings in the overall safety profile of depo-subQ provera 104

Overall, the data and the labeling support approval for the indication of "management of endometriosis-associated pain."

7 INTEGRATED REVIEW OF SAFETY

7.2.9 Safety Update

The Applicant has responded adequately to each of the items requested in the Approvable Letter of October 18. The Complete Response included a safety update that primarily focused on providing in integrated format data that had already been submitted to the NDA, since (1) no studies are ongoing with depo-subQ provera 104 for the endometriosis indication and (2) an integrated safety update for all studies with depo-subQ provera 104 was submitted on October 15, 2004 in support of the contraceptive indication. Included in the current safety update are data integrated over both indication and formulation, as follows:

- Data integrated over the two completed endometriosis trials
- Data integrated over six contraceptive trials (two completed depo-subQ provera 104 contraceptive trials, two completed and one ongoing Depo Provera intramuscular injection [DMPA-IM] contraceptive trials and the ongoing contraception/BMD trial [267BMD], which uses both depo-subQ provera 104 and DMPA-IM)
- Data integrated over the five depo-subQ provera 104 trials (three on contraception and two on endometriosis)

In addition, postmarketing safety data through June 30, 2004 for DMPA-IM are provided, as the depo-subQ provera 104 formulation is not yet marketed anywhere in the world.

APPEARS THIS WAY
ON ORIGINAL

7.2.9.1 Update of Clinical Studies

Table 1 summarizes the studies included in the safety update.

Table 1 Clinical Studies Involving depo-subQ provera 104 or DMPA-IM

Study Number	Objective	Treatment Group N	Comparator N	Planned Duration
Phase 3 Contraception Studies				
267	To establish the safety, efficacy of and subject satisfaction with depo-subQ provera 104 as a contraceptive	depo-subQ provera 104 mg every 3 months N=722	None	1 year (Completed)
269	To establish the safety, efficacy of and subject satisfaction with depo-subQ provera 104 as a contraceptive	depo-subQ provera 104 mg every 3 months N=1065	None	1 year (Completed)
267BMD	To evaluate BMD changes in women receiving either depo-subQ provera 104 or DMPA-IM as a contraceptive	depo-subQ provera 104 mg every 3 months n = 266	DMPA-IM 150 mg every 3 months n = 268	2 years, extended to 3 years (Ongoing)
Phase 3 Endometriosis Studies				
268	To establish that depo-subQ provera 104 and leuprolide offer equivalent efficacy for a reduction in endometriosis – associated pain.	depo-subQ provera 104 mg at 3 month intervals n = 136	Leuprolide IM 11.25 mg at 3 month intervals (2 injections) n = 138	6 month active treatment, 12 month follow-up (Completed)
270	To establish that depo-subQ provera 104 and leuprolide offer equivalent efficacy for a reduction in endometriosis -associated pain.	depo-subQ provera 104 mg at 3 month intervals n =153	Leuprolide SC 3.75 mg monthly for 6 injections n =146	6 month active treatment, 12 month follow-up (Completed)

Source: *2.7.4*, p 7, from January 27, 2005 submission

The analysis was integrated for treatment and indication. Table 2 shows the extent of the safety database from clinical trials for both the contraception and endometriosis indications.

Table 2 Exposure to depo-subQ provera 104 in the Safety Database

Exposure	Number of Subjects	Indication
Up to 6 months	282	Endometriosis
Up to one year	1,780	Contraception
Up to two years	263	Contraception
TOTAL	**2,325**	

Source: *2.7.4*, p 7, from January 27, 2005 submission

7.2.9.1.1 Data Integrated over the Endometriosis Indication

Comparing the data for the endometriosis indication in the original submission to the data in the present safety update, there were no changes in:

- demographic parameters (weight, mean age, and race) from the original submission to the safety update
- reasons for withdrawal from the study

A single additional subject was counted as having had an adverse event in the safety update; there were also minor changes in Preferred Term classification, none of which involved an event occurring at >5% frequency. There were no additional serious adverse events (SAEs) reported.

The net number of subjects who discontinued due to an adverse event increased by one in the safety update, with the addition of one discontinuation due to decreased libido and the reclassification of one discontinuation for "necrosis" to "injection site reaction NOS."

No deaths were reported in either the original submission or the safety update.

7.2.9.1.2 Data Integrated over the Contraception Indication

These data have been comprehensively discussed in the second-cycle review of NDA 21-583. (See review by Dr. Lesley Furlong, dated December 12, 2004)

7.2.9.1.3 Data Integrated over Both Indications

Deaths:
There were no new deaths reported in the safety update. Thus, the safety database for depo-subQ provera 104 reports two deaths, both occurring in the contraceptive trials – one in a motor vehicle crash, and one due to myocarditis-associated arrhythmia. Both were judged to be unrelated to treatment.

Adverse Events:
Of the 2,342 subjects included in the five trials, 41 (1.8%) reported SAEs, nine or 3.2% of endometriosis subjects and 32 or 1.6% of contraception subjects. The most common SAE in the contraception subjects was abdominal pain NOS, occurring in three subjects (0.15%). No SAE occurred in more than one subject among the endometriosis trials. A total of three subjects receiving DMPA experienced thromboembolic events during the five clinical trials: pulmonary emboli occurred in one DMPA-IM subject in a contraceptive trial and in one depo-subQ provera 104 in an endometriosis trial, and another DMPA-IM subject experienced a DVT in a contraceptive trial.

The rate of adverse events was greater for the endometriosis indication (77.7%) than in the contraceptive indication (58.9%). The endometriosis subjects reported a greater frequency of gastrointestinal complaints (42.2% vs. 13.4% in the contraceptive subjects), including nausea, diarrhea and constipation. Endometriosis subjects also more commonly reported musculoskeletal disorders (23.9% vs. 7.1% in the contraceptive subjects), with arthralgia and back pain the most frequent complaints.

Adverse events of particular interest include uterine/vaginal bleeding irregularities and weight gain. Vaginal bleeding was more common in the endometriosis subjects. Among subjects who received depo-subQ provera 104 for contraception, a higher proportion reported weight gain (6.8% vs. 2.5% in the endometriosis subjects).

Reviewer's comment:

- **While certain adverse events appeared to occur with greater frequency in the endometriosis subjects, the reviewer believes that the label's presentation of adverse events compiled over both indications, rather than for each indication separately, is appropriate. It is likely that the greater frequency of adverse events in the endometriosis subjects as compared to the**

contraceptive subjects is related to the underlying diagnosis, rather than to a different response to the drug. The contraception population comprised generally healthy women, while the endometriosis subjects had to demonstrate significant pain-related complaints in order to enroll in the trials. This is further borne out by data from the endometriosis subjects who received the active comparator; 75% of the subjects who received active comparator reported adverse events as compared to 77.7% of those who received depo-subQ provera 104.

- **It is likely that the prevalence of amenorrhea and of weight gain is related to duration of exposure, which was greater in the contraceptive trials than in the endometriosis trials.**

Adverse events reported in more than 5% of subjects receiving depo-subQ provera for either indication are listed in Table 3.

Table 3 Adverse Events occurring in >5% of depo-subQ provera Subjects

Preferred Term	Both Indications N=2342	
	N	%
Headache NOS*	199	8.6
Injection site reaction	121	5.2
Intermenstrual bleeding	169	7.3
Weight increased	145	6.2

Source: *2.7.4*, Table 3, pp 8-9, Table T3.1EC, p 221, from January 27, 2005 submission
* NOS = not otherwise specified

Discontinuations:
In the integrated data, the rate of withdrawal due to adverse events was greater in the contraceptive indication (9.9%) than in the endometriosis indication (3.5%) The most notable difference by indication in the events resulting in withdrawal was in withdrawals due to weight gain, which occurred exclusively in the contraceptive subjects. The most common reason for discontinuation due to adverse events in the endometriosis subjects was excessive uterine/vaginal bleeding, which occurred in five of the ten withdrawing subjects. Among the total of 202 contraceptive subjects and ten endometriosis subjects who stopped therapy for adverse events in the depo-subQ provera 104 group, the most common reasons were:

- Excessive uterine/vaginal bleeding (2.8% of all subjects – this category includes the terms genital hemorrhage, intermenstrual bleeding, menorrhagia, menometrorrhagia and uterine or vaginal hemorrhage)
- Increased weight (1.7%)
- Decreased/lost libido (1.1%)
- Acne (0.9%)
- Injection site reactions (0.5%)

Other safety parameters:
Regarding laboratory studies and vital signs, there were no significant changes noted in the safety update.

Reviewer's comment:

- **The information provided in the safety update does not raise safety concerns and the safety profile is expected to be similar to that of the approved contraceptive product, DMPA-IM. Given the previous demonstration of efficacy for depo-subQ provera 104 based on data in the original NDA submission of December 18, 2004, combined with updated safety information that raises no new concerns, the risk/benefit ratio continues to support approval for this indication.**

7.2.9.2 Update of Postmarketing Safety Reports for DMPA-IM

As depo-subQ provera 104 is not yet marketed anywhere, the Applicant provided a summary of the postmarketing database for the intramuscular product, which has indications for contraception in the U.S and for both contraception and treatment of endometriosis in foreign markets. Data was reported from the Applicant's early alert safety database for the period from September 30, 1999 to June 30, 2004, and from the Applicant's legacy safety database. Discussion here will focus on fatal outcomes and on events relating to fractures and decreased BMD.

Among 26,488 cases reported from sources other than clinical studies, 243 deaths were reported; of these, 204 were fetal or infant deaths following in utero exposure. One infant death from SIDS may have been associated with lactational exposure to DMPA-IM. Ten of the remaining 38 deaths were associated with underlying etiologies. The remaining 28 deaths involved:

- 4 with unknown, but typically sudden, cause of death
- 2 suicides
- 6 related to anaphylaxis
- 16 related to thromboembolic events
    - 5 of these had pre-existing risk factors
    - 10 had no known risk factors, and were associated with DMPA-IM exposures ranging from a single injection to six years of use

Reviewer's comment:

- **Although a true mortality rate cannot be calculated because the number of women using DMPA-IM over the period of reporting is not defined, an approximation can be made based on the U.S. usage from 1999-2001. In this time period, over — women-years of U.S. exposure occurred. If all the above reported deaths were confined to this population (and, in fact, they span a greater time period and include non-U.S. reports), the death rate would be 2.4 per 100,000. The U.S. mortality rates for women of reproductive age in 2002 ranged from 40 to 262 per 100,000.**
- **The Applicant has included thromboembolic disorders and anaphylaxis in the Warnings section of the label.**

In the early alert database, 23 reports concerned fracture-related events, six of which had no alternate etiology beyond DMPA-IM exposure. Women in this group had exposures ranging from 3 injections to 15 years of use and ranged in age from 25 to 45 years. An additional 34 cases reported events related to decreased bone mineral density without fractures. In the eight cases with sufficient information to evaluate causality and no alternate risk factors, DMPA-IM exposure ranged from "at least 2.5" to 15 years and the women ranged in age from 19 to 48 years. The Applicant provided a review of each case and concluded that DMPA-IM exposure could not be excluded as playing a contributory role in the decreased bone mineral density events or fracture events. The Applicant has included a postmarketing summary in the proposed label.

Reviewer's comment:

- **The Applicant has included BMD loss as a boxed warning on the label and there is a recommendation against using depo-subQ provera 104 for more than two years for treatment of endometriosis due to the effects of the drug on bone density unless there is recurrence of symptoms and bone mineral density has been evaluated.**
- **While studies comparing the rate of BMD loss between DMPA-IM and depo-subQ provera 104 showed no statistically significant difference, the endometriosis trials with Lupron as the active comparator did show statistically significantly lower BMD loss with depo-subQ provera 104.**

7.2.9.3 Reviewer's Conclusions

The safety update revealed no new or unexpected safety issues. The safety data do not raise safety concerns and the safety profile is expected to be similar to that of the approved contraceptive product, DMPA-IM.

9 OVERALL ASSESSMENT

9.1 Conclusions

The existing efficacy data support approval of the indication of management of endometriosis-associated pain, but do not provide support for the

There is adequate evidence demonstrating superiority of depo-subQ provera 104 over the active comparator Lupron® in minimizing loss of bone mineral density over a comparable duration of treatment, and showing that depo-subQ provera 104 provides a benefit relative to Lupron® in the frequency and severity of hot flushes resulting from treatment.

The safety update revealed no new or unexpected safety issues. The safety data do not raise safety concerns and the safety profile is expected to be similar to that of the approved contraceptive product, DMPA-IM. Thus, the overall risk/benefit ratio supports approval of the indication of management of endometriosis-associated pain. No risk management activity is needed.

9.4 Labeling Review

During the first-cycle review of the NDA for the contraceptive indication, FDA requested extensive changes throughout the labeling, including, text pertaining to

- Bone mineral density
- Return to ovulation and fertility
- Pregnancy and lactation
- Weight changes
- Injection site reactions
- Adverse events

These changes were accepted by the Applicant and labeling for the contraceptive indication was approved during the second-cycle review of the contraceptive indication.

The label currently proposed by the Applicant will be used for both contraceptive and endometriosis indications, and contains the language previously agreed upon, along with new sections pertaining to the endometriosis indication. The Applicant has proposed a

as the Applicant did not submit data to support this indication. Subjects were treated for a single six month period only

However, in the context of recommending against use of depo-subQ provera 104 for more than two years for treatment of endometriosis, the reviewer finds it acceptable to provide for retreatment if symptoms recur following cessation of treatment, if BMD is evaluated prior to restarting the drug.

During the first-cycle review of the endometriosis NDA, the reviewer had recommended that the label prescribe the duration of treatment as six months, with allowance for up to three additional courses of treatment, as warranted by recurrent symptoms. This recommendation was based upon the fact that the majority of efficacy and safety data submitted at that time was limited to six months of treatment. Upon review of the ongoing contraceptive trials relating to BMD changes with two years of treatment, the reviewer is in favor of the currently proposed labeling.

> "Treatment for longer than two years is not recommended, due to the impact of long-term depo-subQ provera 104 on bone mineral density. If symptoms return after discontinuation of treatment, bone mineral density should be evaluated prior to retreatment."

FDA's Division of Drug Marketing, Advertising, and Communications provided comments about the package insert. In addition, FDA's Division of Division of Surveillance, Research, and Communication Support provided comments about the proposed Patient Package Insert. Most of these comments were addressed during the contraceptive labeling review and those relevant to the endometriosis indication were addressed in the changes that the Division requested of the Applicant . The Chemistry Reviewer found the currently proposed package labeling acceptable, as did the Clinical Pharmacology and Pharmacology/Toxicology Reviewers.

The Division of Medication Errors and Technical Support (DMETS) found the proprietary name "more acceptable than the alternatives previously proposed." The Division found the name depo-subQ provera 104 to be acceptable for the drug product for the prevention of pregnancy indication and continues to find it acceptable as it (1) clearly differentiates the subcutaneous formation from the IM formulation and (2) does not imply a clinical benefit (as with the previous ' —— that the Applicant has agreed not to use.

APPEARS THIS WAY
ON ORIGINAL

10 APPENDIX

10.1 EXECUTIVE SUMMARY from clinical review of the original NDA

10.1.1 Recommendation on Regulatory Action

It is recommended that NDA 21-584, Depot Medroxyprogesterone Acetate for subcutaneous injection, be approved for the indication of management of endometriosis-associated pain in women with endometriosis, contingent upon submission of acceptable labeling by the applicant. It is further recommended that the approved indication limit treatment duration to six months, with retreatment acceptable if warranted by recurrent symptoms. Finally, it is recommended that the [redacted] not be approved.

The primary efficacy findings in the NDA electronically submitted on December 17, 2003 to NDA 21-584 (Depot Medroxyprogesterone Acetate for subcutaneous injection) as N-000 are summarized as follows:

- Both Studies 268 and 270 met the efficacy criteria for non-inferiority on at least four of five outcome categories when analyzed using an observed case (OC) population, which is a per protocol analysis.
- Study 270 also met these criteria when analyzed using an intent to treat (ITT) population with last observation carried forward (LOCF) for subjects who withdrew prior to completing treatment. Study 268 did not meet the criteria for non-inferiority on the ITT-LOCF analysis, demonstrating non-inferiority on only one of the five outcome categories.
- Both studies met the criteria for determining clinical meaningfulness of the treatment effect.

Following the review of the NDA, the clinical reviewer has reached the following conclusions:

- Adequate evidence of efficacy relative to Lupron® (leuprolide, an approved therapy for endometriosis, hereinafter called Lupron) has been demonstrated for subcutaneous Depot Medroxyprogesterone Acetate (depo-subQ provera 104) in management of pain associated with endometriosis.
- There is adequate evidence demonstrating superiority of depo-subQ provera 104 over Lupron in minimizing loss of bone mineral density (BMD).
- depo-subQ provera 104 provides a benefit relative to Lupron in minimizing symptoms of hypoestrogenemia resulting from treatment.
- The safety data do not raise safety concerns and the safety profile is expected to be similar to that of the approved contraceptive product, intramuscular Depot Medroxyprogesterone Acetate (DMPA-IM).
- Considering the risk/benefit profiles of depo-subQ provera 104 and the approved comparator Lupron, there is adequate evidence that depo-subQ provera 104 has acceptable efficacy and superior BMD safety to support approval of the indication for management of endometriosis-associated pain.
- The applicant did not submit data to support [redacted]
- The majority of safety data relevant to BMD loss and subsequent recovery is based upon six months duration of treatment. Additional data from the depo-subQ provera 104 contraceptive trials provides information about BMD loss with two years of treatment. These data support the safety of an initial six month treatment duration and up to three additional courses of treatment, as warranted by recurrent symptoms.
- The relatively prolonged interval until return of ovulation after use of depo-subQ provera 104 must be communicated to endometriosis patients, who often desire fertility.

10.1.2 Recommendations on Post-Marketing Actions

10.1.2.1 Risk Management Activity

No post-marketing risk management plan is recommended.

10.1.2.2 Required Phase 4 Commitments

No phase 4 commitments are requested.

10.1.2.3 Other Phase 4 Requests

There are no other phase 4 requests.

10.1.3 Summary of Clinical Findings

10.1.3.1 Brief Overview of Clinical Program

Two pivotal phase 3, randomized, evaluator-blinded, multinational, multicenter, comparator-controlled trials were conducted to evaluate the efficacy and safety of depo-subQ provera 104 for endometriosis. Both studies used Lupron, a currently approved treatment for endometriosis, as the comparator. The studies were 18 months in duration, comprising a six-month treatment phase and a 12-month follow-up period, during which neither drug could be used. The population studied in each trial was premenopausal women with endometriosis diagnosed by laparoscopy within 42 months of enrollment, who had experienced recurrent or persistent pain symptoms.

Study 268 enrolled 274 subjects from the U.S. and Canada; Study 270 enrolled 299 subjects from South American, Europe and Asia. All subjects receiving depo-subQ provera 104 were dosed with 104 mg SC every three months, for two doses. In Study 268, all subjects receiving Lupron were injected with 11.25 mg IM every three months. In Study 270, the majority of subjects on Lupron received 3.75 mg SC monthly, for six doses; however, small subsets of subjects received either 3.75 mg IM monthly or 11.25 mg SC every three months, depending on local clinical practice and approved labeling.

10.1.3.2 Efficacy

The clinical efficacy variables were based on the five symptoms/signs from the Biberoglu and Behrman scale[1] commonly used to assess endometriosis: dysmenorrhea, pelvic pain, dyspareunia, pelvic tenderness and induration. Each category was rated as none, mild, moderate or severe (equivalent to a numeric score of 0, 1, 2 or 3, respectively) at baseline and all scheduled visits.

The primary efficacy endpoint was demonstration of non-inferiority of depo-subQ provera 104 compared to Lupron in the reduction of endometriosis-associated pain, as determined by ratings on the five pain signs/symptoms. A responder analysis was used, comparing the proportion of subjects in each treatment arm who improved at least one point from baseline in each of the five categories. Non-inferiority was defined per protocol where the lower bound of the 96% two-sided confidence interval for the difference between the two drugs' improvement rates was no worse than -20%. In order for depo-subQ provera 104 to be considered clinically non-inferior, statistical non-inferiority was to be demonstrated on at least four of the five signs/symptoms evaluated.

In addition, an overall clinically meaningful improvement over baseline was required, as demonstrated by an improvement of at least 4 points over baseline in the total composite score (3 points when dyspareunia was excluded to allow evaluation of those subjects who were sexually inactive for reasons unrelated to endometriosis).

Efficacy analysis was done using Intent to Treat (ITT) with both last-observation-carried forward (LOCF) and observed case (OC) populations. ITT was defined as all subjects who received at least one dose of study medication; with LOCF analysis, where subjects discontinued treatment prior to a given assessment

point, the baseline or last visit data were imputed for all subsequent time periods; with OC analysis, only the data collected on subjects continuing in treatment at each assessment point were used.

The primary efficacy analysis demonstrated statistically significant non-inferiority on four of five pain categories in Study 268 and on all five categories in Study 270, when analyzed in the ITT-OC population, thus meeting the pre-specified criteria for non-inferiority. In the ITT-LOCF population, Study 270 again demonstrated statistically significant non-inferiority on all five categories. In Study 268, however, this analysis failed to meet criteria for non-inferiority, as only one of five categories was statistically significantly non-inferior. On the composite score, used to assess the clinical meaningfulness of the treatment effect, both studies met the pre-set criteria for magnitude of improvement, and these results were robust over both analysis populations.

The single analysis that failed to meet the pre-specified criteria for non-inferiority, the ITT-LOCF analysis in Study 268, was likely hampered by below-target recruitment, and an elevated drop-out rate, particularly in the depo-subQ provera 104 group. Where subject withdrawal required data imputation in the LOCF analysis, it appears that the Lupron subjects would have more favorable data imputed, as the treatment effect of Lupron appears to have an onset earlier in the course of treatment than does that for depo-subQ provera 104.

Due to concerns about the use of LOCF analyses in a non-inferiority trial, the FDA statistician recommended during the development of the clinical trial protocols that both ITT and per protocol analyses be conducted. The analysis based on the OC population is an accurate assessment of the benefit accrued to subjects who stay on the treatment. Given that the treatment effect of depo-subQ provera 104 continues to increase over the six month course of treatment; the OC analysis is expected to be more representative of the actual clinical experience of patients who receive two doses of depo-subQ provera 104.

To summarize the efficacy data, the OC analysis met the criteria for non-inferiority on at least four of five outcome categories in both trials. In addition, the criterion for judging the clinical meaningfulness of the treatment effect, which was specifically requested by the Division of Reproductive and Urologic Drug Products (DRUDP), was achieved in both trials and results were robust regardless of whether OC or LOCF analysis was done. The remainder of the endpoints, while not expressly used to test non-inferiority of depo-subQ provera 104 compared to Lupron, support the proposition that depo-subQ provera 104 confers a clinically meaningful treatment benefit, provides significant improvement over baseline symptomatology at all months of treatment, is associated with time to recurrence similar to or of longer latency than Lupron, and results in improved quality of life, as measured by pre-specified scales. Finally, comparison of depo-subQ provera 104 treatment effects in these clinical trials with those seen in placebo subjects from a 1990 randomized, double-blind, placebo-controlled Lupron trial, indicates that the depo-subQ provera 104 subjects' change in pain scores, responder rates and downward shifts in severity scores are much higher than what would likely be attributable to a placebo effect.

Overall, this reviewer concludes that adequate evidence of efficacy relative to Lupron has been demonstrated for depo-subQ provera 104 in management of pain associated with endometriosis. While the results of the two pivotal trials are not completely concordant, the preponderance of evidence supports a finding of non-inferiority of depo-subQ provera 104 as compared to Lupron.

[redacted] is not supported by evidence [redacted]

10.1.3.3 Safety

No deaths occurred in any of the trials. Serious adverse events (SAEs) occurred in 2.8% of depo-subQ provera 104 subjects and 2.2% of Lupron subjects. No correctly classified SAEs occurring during

treatment were judged by the applicant to be drug-related. Appendicitis was the only SAE occurring in more than a single subject in the same treatment group.

Adverse events occurred in 77% of depo-subQ provera 104 subjects and 75% of Lupron subjects. Similar proportions of subjects in each group withdrew due to adverse events (10.8% of depo-subQ provera 104 and 9.4% of Lupron subjects). Events that were judged to be treatment-related and differentially distributed across treatment groups are: injection site reactions and uterine bleeding events (more frequent in the depo-subQ provera 104 group) and hot flushes (more frequent in the Lupron group); these are discussed below.

Laboratory and vital signs measures do not demonstrate clinically relevant changes from baseline in either treatment group. In particular, despite increased frequency of bleeding in the depo-subQ provera 104 group, hemoglobin and hematocrit did not decrease over the course of treatment.

Data from the pivotal clinical trials indicates a clear superiority of depo-subQ provera 104 over Lupron in causing less of a BMD decrease over the course of treatment. At the end of the six-month treatment, the depo-subQ provera 104 subjects had lost a median of 0.4% at the femur and 1% at the spine, compared to Lupron subjects' loss of 1.9% at the femur and 4% at the spine. These differences were statistically significant in the individual studies. Recovery of BMD following cessation of treatment was virtually complete after 12 months in the depo-subQ provera 104 group, while the Lupron group BMD values were still 1.2 to 1.4% below baseline values.

Injection site reactions appear to be associated with SC administration of DMPA, as they were seen at higher rates with DEPO-SUBQ PROVERA 104 than with either DMPA-IM or Lupron IM. In a number of cases, they appeared as areas of indentation or induration at the injection site. However, none was rated severe, and only a single subject withdrew due to this reaction. Subjects' willingness to recommend DEPO-SUBQ PROVERA 104 to a friend or to consider using it again did not appear to be decreased by the occurrence of these reactions.

Uterine/vaginal bleeding, whether minor spotting or hemorrhagic events, occurred more frequently in the depo-subQ provera 104 group. In the 90 days following the second injection, depo-subQ provera 104 subjects experienced over 30 days of spotting or bleeding, compared to fewer than 2 days in the Lupron subjects. In contrast, amenorrhea occurred in about 80% of Lupron subjects by months 4-6, but in less than 10% of depo-subQ provera 104 subjects. More significant bleeding, classified as an adverse event, occurred in 4% of depo-subQ provera 104 subjects, but less than 1% of Lupron subjects.

Diary data on hot flush frequency and severity was used to assess the extent of symptoms attributable to hypoestrogenemia. Median number and severity of daily hot flushes was statistically significantly lower in the depo-subQ provera 104 group at each month of treatment in both studies.

Weight gain occurred in both treatment arms during the course of treatment and continued for the first six months of follow-up. By one year after discontinuing treatment, both groups had lost some of the weight gained, but had still not returned to their baseline weight. Mean magnitude of the weight gain was similar in each group, representing about 1-3/4 lb in the depo-subQ provera 104 group and 1-1/3 lb in the Lupron group at the end of treatment.

The rates of depression reported in Studies 268 and 270 were similar between depo-subQ provera 104 and Lupron, and were close to the incidence reported for females in the general population.

Comparative data on return of ovulatory function for depo-subQ provera 104 and Lupron were not presented; however, two studies outside of the endometriosis trials indicate that resumption of ovulation may take about 7-10 months following cessation of treatment with depo-subQ provera 104.

10.1.3.4 Dosing Regimen and Administration

The dose proposed for this indication is 104 mg of MPA administered subcutaneously in the anterior thigh or abdomen every three months. This dose was determined based on dose ranging studies evaluating suppression of ovulation, rather than on suppression of estradiol, which is the relevant mechanism for the endometriosis indication. The efficacy data suggest that a lower dose would likely not attain statistical non-inferiority to Lupron. Safety data from this submission as well as from clinical trials submitted in support of a contraceptive indication, which examined longer duration of treatment, indicate that this dose is not associated with significant safety concerns. A higher dose of depo-subQ provera 104 would likely suppress the secretion of estradiol to a greater degree and might be associated with more rapid and greater improvement in painful symptoms of endometriosis. However, this might also be associated with a greater decrease in BMD and increased symptoms of hypoestrogenism. The net effect on the risk/benefit ratio cannot be ascertained from the existing data.

10.1.3.5 Drug-Drug Interactions

Drug-drug interactions were not assessed in the development program for depo-subQ provera 104 for endometriosis. The applicant submitted literature that was found acceptable by the Clinical Pharmacology reviewer to demonstrate the unlikelihood of a clinically significant interaction with CYP3A4 inducers. No pregnancies were noted in those subjects in NDA 21-583 who concomitantly used CYP3A4 inducers.

10.1.3.6 Special Populations

This product is indicated only for women, so no gender-based analyses were needed. DRUDP waived the requirement for pediatric studies, as this product will only be indicated for postmenarchal females.

Subgroup analyses of racial and weight groups were performed. Pharmacokinetic (PK) and pharmacodynamic (PD) results were obtained in Caucasian, African-American and Asian women, with no significant differences noted. Similarly, no dosage adjustment is needed based upon body weight or BMI. Safety endpoints were also analyzed by race. No effect of race was evident; however, numbers of non-white subjects were low.

No formal studies have evaluated PK/PD in subjects with hepatic or renal dysfunction. Severe hepatic dysfunction is listed as a contraindication in the labeling for DMPA-IM, as the drug is primarily metabolized in the liver.

MPA is contraindicated in pregnancy, although there is no evidence of increased congenital anomalies in infants exposed to DMPA-IM secondary to contraceptive failure. No adverse effects on lactation or on children exposed through breast milk have been detected.

10.2 Line-by-line labeling review

The Division proposed the following label revisions to the Applicant during the present review cycle:

- Reversion to the earlier contraceptive labeling regarding use for longer than 2 years only if other birth control methods are inadequate. The Division added a statement pertaining to endometriosis treatment in the Dosage and Administration section recommending against use beyond two years for this indication, although allowing the option for retreatment if (1) symptoms recur after discontinuation of treatment and (2) bone mineral density is evaluated prior to retreatment.
- Clarification of the likely mechanism of action for the endometriosis indication in the Clinical Pharmacology section.
- Revision of the Indications and Usage – Endometriosis section to describe the individual phase 3 studies that provided efficacy data.

- Presentation of endometriosis efficacy data in graphical format, rather than tabular form, with data presented for each study individually, using only the primary endpoint assessment period of End of Treatment, and based upon the LOCF analysis.
- Statements [redacted] have been eliminated.
- Hot flush frequency data provided for the categories of moderate and severe hot flushes.
- Addition of injection site reactions to the list of adverse events experienced by more than 5% of subjects across indications.

In an email submitted on March 23, 2005, the Applicant responded that they were willing to make all recommended changes. The revised label is acceptable to the reviewer.

[i] Biberoglu KO and Behrman SJ Dosage aspects of Danazol therapy in endometriosis: Short-term and long-term effectiveness. Am J Obstet Gynecol 139: 645-54, 1981

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/s/

Lisa Soule
3/24/05 10:33:30 AM
MEDICAL OFFICER

Scott Monroe
3/24/05 12:00:27 PM
MEDICAL OFFICER
I concur with Dr. Soule's recommendation that depo-subQ provera 104 (1) be approved for "management of endometriosis-associated pain" and (2) not be approved for

Memo: Consultation regarding efficacy approval
NDA: 21-584 (Depo-SubQ-Provera)
Sponsor: Pharmacia & Upjohn (Pfizer)

This consultative review for the efficacy of depot medroxyprogesterone (subcutaneous) for endometriosis consists of summary statements regarding:

- Historical perspective
- Efficacy from the pivotal clinical trials (NDA 21-584)
- Risk/ Benefit Analysis

Historical Perspective

The use of medroxyprogesterone acetate alone for endometriosis has been recommended in the medical literature for over twenty-five years. I could not find any literature that provided significant arguments against its use for this condition, except for the caveat that women using the depot formulation may have a significant delay in their resumption of menses. Vercillini's study of depot intramuscular medroxyprogesterone acetate (150mg every three months) is the study that most closely compares to the studies presented in NDA 21-584. This study* was a one year open label randomized comparative trial of the IM medroxyprogesterone acetate formulation versus a combination of a birth control pill and low dose danazol (40 subjects in each arm). The depot medroxyprogesterone acetate arm showed excellent pain relief at both 6 months and 12 months. Although a double blind, double dummy approach would have been a much better study, it is noteworthy that there was only one drop out for persistent endometriotic pain in the depot medroxyprogesterone acetate arm over the one year study.

* Vercillini P, De Giorgi O, Oldani S, Cortesi I, Panazza S, Crosignani PG. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol. 1996 Aug; 175(2): 396-401.

Efficacy from the pivotal clinical trials

- Both studies 268 and 270 met efficacy criteria compared to Lupron (improvement not less than –20% using the lower bound of the 96% two-sided confidence interval) when utilizing an observed case population.

- The utilization of an observed case population was suggested to the sponsor as one of the analyses that would be evaluated by the agency.

- Study 270 (but not study 268) also met the –20% comparative goal versus Lupron in the ITT-LOCF (Intent to treat, last observation carried forward) analysis. This type of analysis will not be as favorable for a product that shows a delayed efficacy response. The study data indicates that there is a delayed symptom response for depot subcutaneous medroxyprogesterone acetate. However there appears to be a better comparability of symptom relief compared to Lupron when looking at the post treatment symptom effects at 6 and 12 months following the end of treatment.

- Depot subcutaneous medroxyprogesterone acetate met the clinical efficacy goals by demonstrating an improvement of at least 4 points in the composite score compared to baseline.

- The scoring analysis, when compared to historic levels for placebo response (in an early Lupron trial) is also supportive for approval.

Risk / Benefit Analysis

There is no approved medical therapy that is curative for endometriosis. The approved medical therapies will ameliorate the pain symptoms, but both classes of medical agents (GnRH agonists and danazol) also have significant side effects. Endometriosis symptoms vary in intensity from individual to individual. Standard medical therapy for less symptomatic endometriosis employs initial off-label use of oral contraceptives and NSAIDs *

Olive DL, Pritts EA. Treatment of endometriosis. N Engl J Med. 2001 Jul 26;345(4):266-75. Review.

Depot subcutaneous medroxyprogesterone acetate showed less bone loss and less vasomotor symptoms in the clinical trials in NDA 21-584 compared to Lupron. The lesser risk clearly provides added support for approvability for this product.

Summary

The follow table summarizes the supportive evidence for approvability:

Evidence	Supports approval	Does not support approval
Compares to Lupron on observed case analysis (Studies 268 and 270)	X	
Compares to Lupron on ITT-LOCF (study 270)	X	
Compares to Lupron on ITT-LOCF (study 268)		X
Meets clinical efficacy of 4-point composite score improvement	X	
Performs better than placebo (based on comparison scoring to historical data in Lupron trial)	X	
Risk/Benefit Analysis (less bone loss and vasomotor symptoms)	X	
Historical literature support	X	

Recommendation

Based on the six categories of supportive evidence presented in the previous table, I would recommend approval of the 104 mg depot subcutaneous medroxyprogesterone acetate formulation for treatment of endometriosis symptoms. This is contingent on appropriate labeling that specifies the efficacy and risks demonstrated for the depot subcutaneous medroxyprogesterone acetate and its leuprolide acetate comparator in the clinical trials.

Gerald Willett MD (Medical Officer, HFD-580)

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/s/

Gerald Willett
10/6/04 09:13:28 AM
MEDICAL OFFICER

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Application Type	NDA
Submission Number	21-584
Submission Code	N-000
Letter Date	December 17, 2003
Stamp Date	December 18, 2003
PDUFA Goal Date	October 18, 2004
Reviewer Name	Lisa M. Soule, M.D.
Review Completion Date	October 12, 2004
Established Name	Medroxyprogesterone Acetate Injectable Suspension
(Proposed) Trade Name	Pending
Therapeutic Class	17-α hydroxyprogesterone analogue
Applicant	Pfizer, Inc.
Priority Designation	S
Formulation	Subcutaneous injection
Dosing Regimen	104 mg every three months
Indication	Management of endometriosis-associated pain
Intended Population	Females with endometriosis-associate pain

Clinical Review
Lisa M. Soule, M.D.
NDA 21-584, N-000
{Depo-SubQ-Provera}

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that NDA 21-584, Depot Medroxyprogesterone Acetate for subcutaneous injection, be approved for the indication of management of endometriosis-associated pain in women with endometriosis, contingent upon submission of acceptable labeling by the applicant. It is further recommended that the approved indication limit treatment duration to six months, with retreatment acceptable if warranted by recurrent symptoms. Finally, it is recommended that the additional — not be approved.

The primary efficacy findings in the NDA electronically submitted on December 17, 2003 to NDA 21-584 (Depot Medroxyprogesterone Acetate for subcutaneous injection) as N-000 are summarized as follows:

- Both Studies 268 and 270 met the efficacy criteria for non-inferiority on at least four of five outcome categories when analyzed using an observed case (OC) population, which is a per protocol analysis.
- Study 270 also met these criteria when analyzed using an intent to treat (ITT) population with last observation carried forward (LOCF) for subjects who withdrew prior to completing treatment. Study 268 did not meet the criteria for non-inferiority on the ITT-LOCF analysis, demonstrating non-inferiority on only one of the five outcome categories.
- Both studies met the criteria for determining clinical meaningfulness of the treatment effect.

Following the review of the NDA, the clinical reviewer has reached the following conclusions:

- Adequate evidence of efficacy relative to Lupron® (leuprolide, an approved therapy for endometriosis, hereinafter called Lupron) has been demonstrated for subcutaneous Depot Medroxyprogesterone Acetate (DMPA-SC) in management of pain associated with endometriosis.
- There is adequate evidence demonstrating superiority of DMPA-SC over Lupron in minimizing loss of bone mineral density (BMD).
- DMPA-SC provides a benefit relative to Lupron in minimizing symptoms of hypoestrogenemia resulting from treatment.
- The safety data do not raise safety concerns and the safety profile is expected to be similar to that of the approved contraceptive product, intramuscular Depot Medroxyprogesterone Acetate (DMPA-IM).
- Considering the risk/benefit profiles of DMPA-SC and the approved comparator Lupron, there is adequate evidence that DMPA-SC has acceptable efficacy and superior BMD safety to support approval of the indication for management of endometriosis-associated pain.
- The applicant did not submit data to support the
- The majority of safety data relevant to BMD loss and subsequent recovery is based upon six months duration of treatment. Additional data from the DMPA-SC contraceptive trials provides information about BMD loss with two years of treatment. These data support the safety of an initial six month treatment duration and up to three additional courses of treatment, as warranted by recurrent symptoms.
- The relatively prolonged interval until return of ovulation after use of DMPA-SC must be communicated to endometriosis patients, who often desire fertility.

1.2 Recommendations on Post-Marketing Actions

1.2.1 Risk Management Activity

No post-marketing risk management plan is recommended.

1.2.2 Required Phase 4 Commitments

No phase 4 commitments are requested.

1.2.3 Other Phase 4 Requests

There are no other phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Two pivotal phase 3, randomized, evaluator-blinded, multinational, multicenter, comparator-controlled trials were conducted to evaluate the efficacy and safety of DMPA-SC for endometriosis. Both studies used Lupron, a currently approved treatment for endometriosis, as the comparator. The studies were 18 months in duration, comprising a six-month treatment phase and a 12-month follow-up period, during which neither drug could be used. The population studied in each trial was premenopausal women with endometriosis diagnosed by laparoscopy within 42 months of enrollment, who had experienced recurrent or persistent pain symptoms.

Study 268 enrolled 274 subjects from the U.S. and Canada; Study 270 enrolled 299 subjects from South American, Europe and Asia. All subjects receiving DMPA-SC were dosed with 104 mg SC every three months, for two doses. In Study 268, all subjects receiving Lupron were injected with 11.25 mg IM every three months. In Study 270, the majority of subjects on Lupron received 3.75 mg SC monthly, for six doses; however, small subsets of subjects received either 3.75 mg IM monthly or 11.25 mg SC every three months, depending on local clinical practice and approved labeling.

1.3.2 Efficacy

The clinical efficacy variables were based on the five symptoms/signs from the Biberoglu and Behrman scale[1] commonly used to assess endometriosis: dysmenorrhea, pelvic pain, dyspareunia, pelvic tenderness and induration. Each category was rated as none, mild, moderate or severe (equivalent to a numeric score of 0, 1, 2 or 3, respectively) at baseline and all scheduled visits.

The primary efficacy endpoint was demonstration of non-inferiority of DMPA-SC compared to Lupron in the reduction of endometriosis-associated pain, as determined by ratings on the five pain signs/symptoms. A responder analysis was used, comparing the proportion of subjects in each treatment arm who improved at least one point from baseline in each of the five categories. Non-inferiority was defined per protocol where the lower bound of the 96% two-sided confidence interval for the difference between the two drugs' improvement rates was no worse than -20%. In order for DMPA-SC to be considered clinically non-inferior, statistical non-inferiority was to be demonstrated on at least four of the five signs/symptoms evaluated.

In addition, an overall clinically meaningful improvement over baseline was required, as demonstrated by an improvement of at least 4 points over baseline in the total composite score (3 points when dyspareunia was excluded to allow evaluation of those subjects who were sexually inactive for reasons unrelated to endometriosis).

Efficacy analysis was done using Intent to Treat (ITT) with both last-observation-carried forward (LOCF) and observed case (OC) populations. ITT was defined as all subjects who received at least one dose of study medication; with LOCF analysis, where subjects discontinued treatment prior to a

given assessment point, the baseline or last visit data were imputed for all subsequent time periods; with OC analysis, only the data collected on subjects continuing in treatment at each assessment point were used.

The primary efficacy analysis demonstrated statistically significant non-inferiority on four of five pain categories in Study 268 and on all five categories in Study 270, when analyzed in the ITT-OC population, thus meeting the pre-specified criteria for non-inferiority. In the ITT-LOCF population, Study 270 again demonstrated statistically significant non-inferiority on all five categories. In Study 268, however, this analysis failed to meet criteria for non-inferiority, as only one of five categories was statistically significantly non-inferior. On the composite score, used to assess the clinical meaningfulness of the treatment effect, both studies met the pre-set criteria for magnitude of improvement, and these results were robust over both analysis populations.

The single analysis that failed to meet the pre-specified criteria for non-inferiority, the ITT-LOCF analysis in Study 268, was likely hampered by below-target recruitment, and an elevated drop-out rate, particularly in the DMPA-SC group. Where subject withdrawal required data imputation in the LOCF analysis, it appears that the Lupron subjects would have more favorable data imputed, as the treatment effect of Lupron appears to have an onset earlier in the course of treatment than does that for DMPA-SC.

Due to concerns about the use of LOCF analyses in a non-inferiority trial, the FDA statistician recommended during the development of the clinical trial protocols that both ITT and per protocol analyses be conducted. The analysis based on the OC population is an accurate assessment of the benefit accrued to subjects who stay on the treatment. Given that the treatment effect of DMPA-SC continues to increase over the six month course of treatment; the OC analysis is expected to be more representative of the actual clinical experience of patients who receive two doses of DMPA-SC.

To summarize the efficacy data, the OC analysis met the criteria for non-inferiority on at least four of five outcome categories in both trials. In addition, the criterion for judging the clinical meaningfulness of the treatment effect, which was specifically requested by the Division of Reproductive and Urologic Drug Products (DRUDP), was achieved in both trials and results were robust regardless of whether OC or LOCF analysis was done. The remainder of the endpoints, while not expressly used to test non-inferiority of DMPA-SC compared to Lupron, support the proposition that DMPA-SC confers a clinically meaningful treatment benefit, provides significant improvement over baseline symptomatology at all months of treatment, is associated with time to recurrence similar to or of longer latency than Lupron, and results in improved quality of life, as measured by pre-specified scales. Finally, comparison of DMPA-SC treatment effects in these clinical trials with those seen in placebo subjects from a 1990 randomized, double-blind, placebo-controlled Lupron trial, indicates that the DMPA-SC subjects' change in pain scores, responder rates and downward shifts in severity scores are much higher than what would likely be attributable to a placebo effect.

Overall, this reviewer concludes that adequate evidence of efficacy relative to Lupron has been demonstrated for DMPA-SC in management of pain associated with endometriosis. While the results of the two pivotal trials are not completely concordant, the preponderance of evidence supports a finding of non-inferiority of DMPA-SC as compared to Lupron.

is not supported by evidence.

1.3.3 Safety

No deaths occurred in any of the trials. Serious adverse events (SAEs) occurred in 2.8% of DMPA-SC subjects and 2.2% of Lupron subjects. No correctly classified SAEs occurring during treatment were judged by the applicant to be drug-related. Appendicitis was the only SAE occurring in more than a single subject in the same treatment group.

Adverse events occurred in 77% of DMPA-SC subjects and 75% of Lupron subjects. Similar proportions of subjects in each group withdrew due to adverse events (10.8% of DMPA-SC and 9.4% of Lupron subjects). Events that were judged to be treatment-related and differentially distributed across treatment groups are: injection site reactions and uterine bleeding events (more frequent in the DMPA-SC group) and hot flushes (more frequent in the Lupron group); these are discussed below.

Laboratory and vital signs measures do not demonstrate clinically relevant changes from baseline in either treatment group. In particular, despite increased frequency of bleeding in the DMPA-SC group, hemoglobin and hematocrit did not decrease over the course of treatment.

Data from the pivotal clinical trials indicates a clear superiority of DMPA-SC over Lupron in causing less of a BMD decrease over the course of treatment. At the end of the six-month treatment, the DMPA-SC subjects had lost a median of 0.4% at the femur and 1% at the spine, compared to Lupron subjects' loss of 1.9% at the femur and 4% at the spine. These differences were statistically significant in the individual studies. Recovery of BMD following cessation of treatment was virtually complete after 12 months in the DMPA-SC group, while the Lupron group BMD values were still 1.2 to 1.4% below baseline values.

Injection site reactions appear to be associated with SC administration of DMPA, as they were seen at higher rates with DMPA-SC than with either DMPA-IM or Lupron IM. In a number of cases, they appeared as areas of indentation or induration at the injection site. However, none was rated severe, and only a single subject withdrew due to this reaction. Subjects' willingness to recommend DMPA-SC to a friend or to consider using it again did not appear to be decreased by the occurrence of these reactions.

Uterine/vaginal bleeding, whether minor spotting or hemorrhagic events, occurred more frequently in the DMPA-SC group. In the 90 days following the second injection, DMPA-SC subjects experienced over 30 days of spotting or bleeding, compared to fewer than 2 days in the Lupron subjects. In contrast, amenorrhea occurred in about 80% of Lupron subjects by months 4-6, but in less than 10% of DMPA-SC subjects. More significant bleeding, classified as an adverse event, occurred in 4% of DMPA-SC subjects, but less than 1% of Lupron subjects.

Diary data on hot flush frequency and severity was used to assess the extent of symptoms attributable to hypoestrogenemia. Median number and severity of daily hot flushes was statistically significantly lower in the DMPA-SC group at each month of treatment in both studies.

Weight gain occurred in both treatment arms during the course of treatment and continued for the first six months of follow-up. By one year after discontinuing treatment, both groups had lost some of the weight gained, but had still not returned to their baseline weight. Mean magnitude of the weight gain was similar in each group, representing about 1-3/4 lb in the DMPA-SC group and 1-1/3 lb in the Lupron group at the end of treatment.

The rates of depression reported in Studies 268 and 270 were similar between DMPA-SC and Lupron, and were close to the incidence reported for females in the general population.

Comparative data on return of ovulatory function for DMPA-SC and Lupron were not presented; however, two studies outside of the endometriosis trials indicate that resumption of ovulation may take about 7-10 months following cessation of treatment with DMPA-SC.

1.3.4 Dosing Regimen and Administration

The dose proposed for this indication is 104 mg of MPA administered subcutaneously in the anterior thigh or abdomen every three months. This dose was determined based on dose ranging studies evaluating suppression of ovulation, rather than on suppression of estradiol, which is the relevant mechanism for the endometriosis indication. The efficacy data suggest that a lower dose would likely not attain statistical non-inferiority to Lupron. Safety data from this submission as well as from clinical trials submitted in support of a contraceptive indication, which examined longer duration of treatment, indicate that this dose is not associated with significant safety concerns. A higher dose of DMPA-SC would likely suppress the secretion of estradiol to a greater degree and might be associated with more rapid and greater improvement in painful symptoms of endometriosis. However, this might also be associated with a greater decrease in BMD and increased symptoms of hypoestrogenism. The net effect on the risk/benefit ratio cannot be ascertained from the existing data.

1.3.5 Drug-Drug Interactions

Drug-drug interactions were not assessed in the development program for DMPA-SC for endometriosis. The applicant submitted literature that was found acceptable by the Clinical Pharmacology reviewer to demonstrate the unlikelihood of a clinically significant interaction with CYP3A4 inducers. No pregnancies were noted in those subjects in NDA 21-583 who concomitantly used CYP3A4 inducers.

1.3.6 Special Populations

This product is indicated only for women, so no gender-based analyses were needed. DRUDP waived the requirement for pediatric studies, as this product will only be indicated for postmenarchal females.

Subgroup analyses of racial and weight groups were performed. Pharmacokinetic (PK) and pharmacodynamic (PD) results were obtained in Caucasian, African-American and Asian women, with no significant differences noted. Similarly, no dosage adjustment is needed based upon body weight or BMI. Safety endpoints were also analyzed by race. No effect of race was evident; however, numbers of non-white subjects were low.

No formal studies have evaluated PK/PD in subjects with hepatic or renal dysfunction. Severe hepatic dysfunction is listed as a contraindication in the labeling for DMPA-IM, as the drug is primarily metabolized in the liver.

MPA is contraindicated in pregnancy, although there is no evidence of increased congenital anomalies in infants exposed to DMPA-IM secondary to contraceptive failure. No adverse effects on lactation or on children exposed through breast milk have been detected.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Depot medroxyprogesterone acetate administered subcutaneously (DMPA-SC) contains medroxyprogesterone acetate (MPA), a derivative of progesterone, which inhibits gonadotropin secretion, thus preventing follicle maturation and ovulation, suppressing estrogen secretion, and resulting in endometrial atrophy. Depo-Provera is currently available as an intramuscular formulation for the indications of contraception, and palliation of renal and endometrial cancer. DMPA-SC is a new formulation, combining a lower dose and a new route of administration, for a new indication - management of endometriosis-associated pain. The dosing regimen remains injection once every three months.

2.2 Currently Available Treatment for Endometriosis

Endometriosis is treated both medically and surgically. Medical treatments focus upon the suppression of estrogen, either by suppressing gonadotropin secretion or by altering the local hormonal milieu towards an androgen or progesterone-dominated environment. Currently approved drugs for endometriosis are Danazol, an orally active attenuated androgen that produces a hypoestrogenic and hyperandrogenic effect, and by use of gonadotropin release hormone agonists (GnRHa), such as leuprolide (Lupron), nafarelin (Synarel) and goserelin (Zoladex)[2]. Side effects that limit the use of these agents include androgenic effects for Danazol, decrease in bone mineral density (BMD) for GnRHa's, and symptoms of hypoestrogenism for all products. Additional marketed products that are not approved for endometriosis but are commonly used include DMPA-IM and oral contraceptives.

2.3 Availability of Proposed Active Ingredient in the United States

Medroxyprogesterone acetate (MPA) is currently available as depot medroxyprogesterone acetate intramuscular injection and as Provera tablets. Currently approved indications for MPA include:

- Depo Provera contraceptive injection – 150 mg IM – for prevention of pregnancy
- Depo Provera sterile aqueous suspension – 100 and 400 mg/ml IM – for adjunctive therapy and palliative treatment of inoperable recurrent and metastatic endometrial or renal carcinoma
- Provera tablets – 2.5, 5 and 10 mg po – for secondary amenorrhea and for abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology such as fibroids or uterine cancer; to reduce the incidence of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving 0.625 mg of conjugated estrogen

2.4 Important Issues with Pharmacologically Related Products

An extensive safety database is available for DMPA-IM, which has been marketed in the U.S. since 1960 for cancer palliation and since 1992 for contraception. The major safety issue noted for this product is loss of BMD, which increases with duration of use and appears to be at least partly reversible with cessation of treatment. Additional issues of concern include weight gain of about 5 lb with one year of use and which increases with continued administration. Irregular vaginal bleeding is noted in "most" users, according to the DMPA-IM label. Return to fertility is delayed beyond the time seen with other reversible contraceptive methods. Evidence concerning possible small increases in breast cancer risk and risk of venous thromboembolism is currently debated.

2.5 Pre-submission Regulatory Activity

Several related INDs and NDAs have been filed, beginning with NDA 12-541, which was approved September 23, 1960 for the indication of palliation of renal and endometrial cancer, at a dose of 400 - 1000 mg/week administered intramuscularly (IM). On October, 29, 1992, NDA 20-246 was

approved for a contraception indication at a dose of 150 mg IM every three months. IND 61,389 was filed on December 8, 2000 for development of a subcutaneous injection for endometriosis, and NDA 21-583 was filed June 30, 2003 for the subcutaneous formulation for a contraception indication.

Major milestones in the development plan for the current application included:

- A clinical guidance meeting was held with then-sponsor Pharmacia & Upjohn on October 2, 2000 to discuss clinical trials to support an endometriosis indication. FDA advised the sponsor that superiority claims for BMD would require two trials appropriately powered for superiority. It was recommended that the primary efficacy endpoint should include both individual symptom scores and summary score, looking at pre and post-treatment differences and that the magnitude of reduction in summary pain scores that would be clinically significant should be proposed *a priori.* The study population proposed by the agency was women with a pain score of at least 2 or greater (out of a maximum possible score of 3) on each of the three symptoms of dysmenorrhea, dyspareunia and pelvic pain (summary score >=6).
- Statistical review of an SPA for studies 268 and 270 was conducted in January 2001. The sponsor proposed the following major points:
    - Primary endpoint: response in each of five individual endometriosis pain categories on a slightly modified Biberoglu and Behrman (B&B) scale; response defined as >=1 point improvement from baseline in the respective category
    - Primary comparison is proportion of responders in each treatment group for each category
    - Non-inferiority would be demonstrated if the confidence interval around the difference between DMPA-SC response and comparator response is no worse than -20% for each category, with 80% power
    - Intent to treat (ITT) with last observation carried forward (LOCF) will be the primary analysis population
    - Power of 80% to detect 2% BMD difference; power of 90% of detect >=6 pt difference on Kupperman Index
    - Enrollment of 160 subjects/arm planned

    The FDA statistical reviewer advised the sponsor that clinical confirmation of the validity of the 20% non-inferiority margin chosen by sponsor was recommended, since this margin was not based on effect size of comparator against placebo. Additionally, it was noted that the ICH E9 has reservations that ITT analysis in equivalence or non-inferiority trials may not be conservative; therefore, sponsor should demonstrate consistency of these results with a per-protocol (PP) analysis.
- Protocols 268 and 270 were reviewed by the DRUDP Medical Officer in January 2001, with the recommendation made that the primary endpoint should combine non-inferiority analysis and quantitative improvement: non-inferiority on at least 4 of 5 symptoms/signs at the end of 6 months of treatment, along with mean improvement of at least 4 points from baseline on the summary (total) B&B score in each treatment group. Diary entries for painful symptoms of endometriosis should support these results. The sponsor was also advised that quality of life measures were to be secondary endpoints, but should be assessed carefully to ensure they support the primary findings. Secondary efficacy endpoints are considered by DRUDP to be supportive, not sufficient for labeling claims

- A teleconference with the sponsor was held on March 7, 2001. In response to questions from the sponsor, DRUDP noted that the recommended primary analysis was not an absolute requirement, but that failure to show equivalency in 4 of 5 symptoms/signs would be a review issue. Additionally, the sponsor was advised that, since it seeks superiority claims for BMD and hypoestrogenic symptoms, these will need to be co-primary endpoints, powered for superiority. Frequency/severity of hot flushes was recommended for evaluation of hypoestrogenic symptoms; quality of life endpoints are generally not accepted for labeling claims. The sponsor should demonstrate adequate validation for any quality of life tools used. The Kupperman Index has been criticized for unjustified weighting, overlapping criteria, and suboptimal patient understanding. Finally, it was again noted that DRUDP does not agree to ITT analysis alone. Discrepancy between ITT and PP will be a review issue.
- Amended protocol 268 was reviewed by the DRUDP Medical Officer in May 2001, with recommendations that no more than 20% of subjects should be sexually inactive at entry and that monthly and end-of-study pain assessments should reflect the diary information provided by the subjects.

Medical Reviewer's Comments:

1) ***The applicant followed DRUDP's recommendations in regard to subject selection and primary efficacy and BMD safety endpoints.***
2) ***In response to the request for clinical validation of the use of a -20% margin for evidence of non-inferiority, the applicant noted that Synarel (NDA 19-886) was approved based upon this same margin.***
3) ***The statistical analyses presented by the sponsor include both the ITT last observation carried forward (LOCF) analysis and an ITT observed case (OC) analysis, the latter being equivalent to a per protocol analysis, in that only subjects continuing treatment at each assessment point are included in the analysis.***
4) ***The sponsor was clearly informed that quality of life measures and outcomes based on the Kupperman Index were unlikely to be acceptable for labeling claims.***

2.6 Other Relevant Background Information

Depo-Provera, the IM formulation, is approved in a number of foreign countries for the endometriosis indication. Information provided by the applicant indicates that approval for marketing for this indication has been given in 21 countries, with the most common dosing regimen being 50 mg IM weekly, or 100 mg IM every two weeks. DMPA-SC has not been approved for marketing in any foreign country. An application (NDA 21-583) for the indication of contraception received an approvable action on August 2, 2004, pending submission of acceptable labeling by the applicant.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC and Product Microbiology

DMPA-SC is supplied in a pre-filled syringe and co-packaged with a 26-guage, 3/8 inch needle appropriate only for SC injection. The drug substance is the same as that used in Depo-Provera, and the drug product contains the same active ingredient and excipients as Depo-Provera, with the addition of three new excipients (povidine USP, methionine USP and phosphate buffer USP). The drug product complies with the current USP monograph for medroxyprogesterone acetate injectable suspension. The chemistry reviewer recommended approval of this NDA, with no recommendations for phase 4 post-marketing commitments or risk management plans.

The microbiology reviewer recommended approval on the basis of product quality microbiology.

3.2 Animal Pharmacology/Toxicology

The pharmacology/toxicology reviewer recommended approval based on the lower dosage of the SC formulation as compared to the currently approved IM formulation and the similar systemic exposure of the two formulations. A single-dose preclinical toxicity study evaluating dose tolerance and potential injection site effects of the SC formulation in the female rabbit found no treatment-related mortality and good tolerability, with less tolerability if inadvertently injected into the dermis.

4 DATA SOURCES, REVIEW STRATEGY AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary data sources for this NDA are the two phase 3 trials evaluating the efficacy and safety of DMPA-SC for endometriosis-associated pain as compared to Lupron. Additional BMD safety data were provided by Study 267BMD, conducted for the contraceptive indication, which is ongoing and currently has data on BMD loss after 24 months of use. Three PK or PK/PD studies and a PK substudy of 267BMD were also conducted.

4.2 Tables of Clinical Studies

Table 1 provides a more detailed overview of each clinical trial in the clinical development plan for endometriosis, including information regarding the study design, the drug formulation and comparator evaluated, number of patients enrolled and study treatments.

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Table 1 Tabular Listing of Submitted Clinical Investigations*

Type of Study	Study ID	Location of Study Report	Objective(s) of Study	Study Design & Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK/PD	265	See NDA 21-583 , Section 5.3.3.1.1	Determine PK and PD (suppression of ovulation) of MPA after a single SC injection	Open-label, randomized, single-dose (4 levels) outpatient, parallel-group study	Single SC injection of either a 50-, 75-, 100-, or 150-mg dose of MPA	47	Healthy subjects	Single dose	Complete; Full
PK	271	See NDA 21-583 , Section 5.3.3.1.2	Determine duration of ovulation suppression in Asian women after SC administration of MPA	Single center, open-label, single-dose, outpatient, parallel-group study	Single SC injection of 104 mg DMPA in either the leg or the abdomen	24	Healthy subjects	Single dose	Complete, Full
PK	267BMD Amend G	5.3.3.1.1	Collect MPA samples for a steady-state PK analysis after multiple doses of DMPA-SC	Open-label multicenter study	DMPA-SC 104 mg q 3 mo	8	Healthy subjects	One dosing interval in 2nd year of study	Completed Full
PK/PD	272	See NDA 21-583 , Section 5.3.4.1.1	Compare cumulative rate of ovulation at 12 mo following a single injection of either DMPA SC or DMPA-IM	Single-center, evaluator-blinded, single-dose, outpatient study	Single injection of either DMPA-SC 104 mg or DMPA-IM 150 mg	68	Healthy subjects	Single dose	Complete, Full
Efficacy/ Safety	268	5.3.5.1.1	Compare efficacy and safety of DMPA-SC with those of leuprolide	Randomized, evaluator-blind, multinational (United States and Canada), multicenter study	DMPA-SC 104 mg q 3 mo or leuprolide 11.25 mg IM q 3 mo	274: 136 received DMPA-SC, 138 received leuprolide	Women with endometriosis	18 mo	Ongoing, Full (interim analysis)
Efficacy/ Safety	270	5.3.5.1.2	Compare efficacy and safety of DMPA-SC with those of leuprolide	Randomized, evaluator-blind, multinational (Europe, Latin America, Asia) multicenter study	DMPA-SC 104 mg q 3 mo or leuprolide 11.25 mg IM q 3 mo or 3.75 mg monthly for 6 mo	300: 153 received DMPA-SC 146 received leuprolide	Women with endometriosis	18 mo	Ongoing Full (interim analysis)
Efficacy/ Safety	267BMD	5.3.5.1.3	Assess treatment failure, cumulative pregnancy rate, and safety of DMPA-SC or DMPA-IM and BMD changes	Randomized, evaluator-blinded study	DMPA-SC 104 mg q 3 mo or DMPA-IM 150 mg q 3 mo	534: 266 received DMPA-SC, 268 received DMPA-IM	Subjects requiring long-term contraception	2 y	Ongoing Full (interim analysis)

- NDA 21-583 was submitted on 30 June 2003

Abbreviations: BMD = bone mineral density, DMPA = depot medroxyprogesterone acetate, DMPA-IM = depot medroxyprogesterone acetate-intramuscular, DMPA-SC = depot medroxyprogesterone acetate-subcutaneous, IM = intramuscular, MPA = medroxyprogesterone acetate, PD = pharmacodynamics, PK = pharmacokinetics, SC = subcutaneous

*There is an error in "Duration of Treatment" listed for Studies 268 and 270; the active treatment was 6 months, with an additional 12 months of follow-up, resulting in an overall study duration of 18 months

Source: Table 5.1, Module 5.2, pp 2-3

4.3 Review Strategy

4.3.1 Materials Consulted during Medical Review

The following materials were consulted during the conduct of this review:

- NDA 21-584; Submission Date of December 17, 2003
- NDA 21-228 4-Month Safety Update; Submission Date of April 14, 2004
- Minutes of all regulatory meetings and telephone conferences with the Applicant that were contained in Division files
- Applicant responses to FDA queries, submitted March 26, August 31, September 22, 2004 and October 7, 2004
- BMD, general safety and PK/PD data from NDA-21-583 (DMPA-SC for contraception)

4.3.2 Review Processes and Procedures

The clinical review was based on the medical officer's review of the material delineated above and supplemented by the reviews conducted by Clinical Pharmacology and Statistics. A consult was obtained from the Division of Scientific Investigations (DSI). The Division of Metabolic and Endocrine Drug Products (DMEDP) was consulted during review of NDA 21-583 (DMPA-SC for contraception) for input into review of the BMD data. The Division of Drug Marketing, Advertising and Communication (DDMAC), Division of Medication Errors and Technical Support (DMETS), and the Division of Surveillance, Research and Communication Support (DSRCS) will be consulted when the applicant submits the proposed trade name and labeling.

4.3.3 Materials Reviewed

The review conducted by this medical officer focused on the two pivotal randomized clinical trials comparing DMPA-SC and Lupron for efficacy in managing symptoms and signs associated with endometriosis, and safety, particularly with regard to changes in bone mineral density and other signs of hypoestrogenemia. Two-year BMD safety data from the contraception study 267BMD were also reviewed. All materials submitted on December 17, 2003, in electronic format for these studies were considered during the conduct of this review. Additionally, safety update material submitted on April 14, 2004, which provided the final six months of follow-up data on the two pivotal studies, as well as two-year BMD data on over 200 subjects from Study 267BMD, was reviewed. Post-marketing surveillance data from September 20, 1999 to January 31, 2004, and SAE data from three phase 4 trials of the IM formulation for contraception were also reviewed.

4.4 Data Quality and Integrity

Audits were requested on four study sites, two in the US, based on the sites' contributions to the overall subject pool, and two in Brazil, where results were noted to be discrepant from overall results in terms of higher efficacy and lower rates of adverse events. Two investigators from Study 268, Drs. Gordon and Sundwall were audited. Dr. Gordon had enrolled 13 subjects, two of whom completed the trial. The audit concluded that this site had adhered to applicable statutory requirements and FDA regulations. Dr. Sundwall had enrolled 18 subjects, five of whom completed the trial. A form 483 notice of violation was issued, but only a "voluntary action indicated" notice was issued. However, an extensive list of deficiencies was generated for this site, prompting the FDA to request that the sponsor provide a reanalysis of the efficacy data with the omission of this site.

Two investigators for Study 270 were audited, Drs. Filho and Tadini, both from Brazil. Dr. Filho randomized 23 subjects; no violations were identified and therefore, a form 483 was not issued. The audit concluded that this site had adhered to applicable statutory requirements and FDA regulations. Dr. Tadini randomized 23 subjects to the study; a form 483 and a "voluntary action indicated" notice were issued.

Medical Reviewer's Comment:

1) ***The overall assessment of the four audits concluded that the data submitted by the four investigators was adequate in support of the submission.***

2) ***No significant changes in the efficacy results occurred upon reanalysis of the data omitting Dr. Sundwall's site.***

4.5 Compliance with Good Clinical Practices

Pharmacia was responsible for quality assurance audits at clinical study sites worldwide to ensure compliance with Good Clinical Practice (GCP). [redacted] provided quality assurance regarding the

BMD assessments. [redacted] provided study monitoring in Study 268; Pfizer (Pharmacia) in Study 270. Laboratory analysis was performed by [redacted] (in both studies) and [redacted] (in Study 270).

Data from one site in Study 270 (Investigator 50623, Indonesia, N=19) were eliminated from analysis due to data quality issues. Specifically, information from the daily diary could not be verified, as the source material had been discarded and the existing data was unreliable due to transcription errors and multiple transcriptions, sometimes by non-study personnel; the integrity of the evaluator-blinding was compromised, as the unblinded injectionist was also the study nurse who transcribed the diary records; and the treatment blind was broken early in the study and review of efficacy results from this site revealed them to be discrepant with other sites' results.

4.6 Financial Disclosure

The applicant submitted financial disclosure statements for investigators who participated in the two pivotal phase 3 trials (Studies 268 and 270). This information was reviewed as part of the clinical review, and it was concluded that for all 54 investigators in Study 268 and all 38 investigators in Study 270:

- the information was complete
- appropriate documentation was received
- the information complied with 21 CFR 54
- no disclosable information was reported
- no conflicts of interests were noted
- there was no disclosure of financial interests that could bias the outcome of the trials

Financial disclosure information was unobtainable after due diligence attempts by the applicant from six sub-investigators in Study 268.

One sub-investigator, [redacted] who participated in [redacted] disclosed significant payments from the applicant as a paid consultant to Pfizer. It is documented that his site enrolled only two subjects, was monitored with source document verification every 10-12 weeks, and had the average number of edits.

Medical Reviewer's Comment:

1) ***From the information provided by the applicant, it is not possible to identify the specific US or Canadian sites employing the six sub-investigators who did not provide financial disclosure information. However, it is unlikely that this information would have significant impact on the findings of or conclusions made from the studies.***

5 CLINICAL PHARMACOLOGY

Three phase 1/2 single-dose pharmacokinetic/pharmacodynamic (PK/PD) studies were submitted with NDA 21-583. Study 265 was a dose-ranging study evaluating four doses on the endpoint of ovulation suppression. Study 271 assessed PK/PD in Asian women, and Study 272 investigated the return of ovulation following a single dose. Potential effects of BMI, race/ethnicity and site of SC injection (anterior thigh, abdomen) on the PK/PD profile were evaluated. An additional study, 267BMD, assessed PK/PD parameters following administration of multiple doses. The Clinical Pharmacology reviewer concluded that the Human PK Section is acceptable.

5.1 Pharmacokinetics

Four studies provided PK data for this NDA. Study 265 characterized the PK of DMPA-SC at four dose levels, assessed dose proportionality and evaluated the influence of injection site. Study 271, in

Asian women using the 104 mg dose, evaluated the effect of Asian ethnicity on the parameters evaluated above. In Study 272, PK was determined and subgroup analyses by race and BMI were conducted. A substudy of Study 267BMD evaluated drug concentrations after 6, 12 and 24 months of use as well as bi-weekly concentrations within a single dosing interval in the second year of use.

Study 265 demonstrated immediate and prolonged absorption of MPA from the SC injection site, with serum concentrations, while highly variable, exceeding the threshold of 0.2 ng/ml for consistent contraceptive effect for 91 days in both the 100 and 150 mg dose groups. In the subjects receiving a dose of 75 mg, 42% failed to achieve C_{91} above the threshold level. No difference in PK profiles was seen when injection was given in the anterior thigh vs. the abdomen. Similarly, Study 271 found no significant difference in PK parameters for the two injection sites, except that C_{max} was lower for abdominal injectors and t_{max} was non-significantly longer.

Study 272 demonstrated achievement of sufficient MPA concentrations after a single 104 mg dose of DMPA-SC to provide consistent contraceptive efficacy by 24 hours post-injection. Serum levels were maintained above the 0.2 ng/ml threshold for the planned dosing interval of 13 +/-1 weeks. Subgroup analysis from Studies 271 and 272 found that small differences in PK parameters by racial (white, black and five Asian ethnic groups) and BMI groups (classified as healthy, overweight and obese) did not result in different PD responses (ovulation suppression). Obese women (>38 kg/m^2) did tend to have lower MPA concentrations, but the trough values remained above the efficacy threshold.

Comparative PK parameters from the three studies are displayed in Table 2.

Table 2 Mean (SD) PK Parameters for MPA after DMPA-SC Administration

Study [Ref]	Cmax (pg/mL)	tmax (day)	AUC0-91 (ng day/mL)	AUC0-∞ (ng•day/mL)	C91 (ng/mL)	t1/2,z (day)
265* [10]	0.90 (0.35)	21 (21)	41.5 (13.4)	54.0 (15.9)	0.332 (0.137)	27 (12)
271 [11]	1.29 (0.6)	13 (23)	63.9 (16.2)	118.1 (16.4)	0.441 (0.177)	91 (59)
272 [12]	1.56 (0.67)	9 (13)	66.9 (24.9)	92.8 (23.5)	0.402 (0.147)	43 (21)

* Dose was 100 mg per 0.5 mL

Source: Table 11, Module 2.7.2, p 28

Study 267BMD showed that no unexpected accumulation occurred following multiple SC injections over a six to 24-month sampling period.

Medical Reviewer's Comment:

1) ***The MPA concentrations targeted in these studies were based upon levels anticipated to provide contraceptive efficacy. Few data are provided regarding MPA levels required to suppress estradiol, which is the relevant pharmacodynamic endpoint for management of endometriosis.***

5.2 Pharmacodynamics

Three of the studies noted above contributed PD information, although the majority of the data relate to ovulation suppression, relevant for the contraceptive indication, but less so for the endometriosis indication. Study 265 did evaluate estradiol levels following administration of one of four doses of

DMPA-SC ranging from 50-150 mg. Reduction in estradiol levels showed a dose-response, with mean concentrations of 100-150 pg/ml, 50-100 pg/ml and 50 pg/ml following the 50 mg, 75-100 mg and 150 mg dose, respectively.

Study 265 determined dose-response as measured by suppression of ovulation, evaluated ovarian function over time and identified the lowest effective dose of DMPA-SC administered every three months for ovulation suppression. In Study 271, the duration of ovulation suppression resulting from the 104 mg dose was determined. Return to ovulation and cumulative rate of ovulation at one year following a single dose of DMPA-SC was assessed in Study 272.

Study 265 evaluated ovulation suppression by measurement of serum progesterone, supplemented by E2, LH and FSH levels. Subjects receiving the 100 mg dose also underwent ultrasonography to detect follicular growth and maturation. Resumption of ovulation was inferred by serum progesterone levels >= 4.7 ng/ml. This study identified both 100 mg and 150 mg of MPA as effective doses. The lower dose was chosen for phase 3 testing; using the most stable formulation resulted in a study drug dosed at 104 mg/0.65 ml. Study 271, using the 104 mg dose in Asian women, confirmed the efficacy of this dose in suppressing ovulation for the 112 day study period.

Study 272 compared return of ovulatory function between subjects randomized to a single-dose of DMPA-SC or DMPA-IM in a 2:1 ratio. Whether assessed by serum progesterone level or urinary pregnanediol-3-glucuronide (Pd-3-G), the cumulative rate of ovulation at 12-months post-injection and the median time to return of ovulation did not differ significantly between the two groups. Based on the progesterone level, the earliest return to ovulation in the DMPA-SC group was 15 weeks post-dose, and the median was 30 weeks. Subgroup analyses found no effects of race or BMI on either suppression of ovulation or on cumulative rate of return of ovulation post-treatment. However, the median time to resumption of ovulation was greater in white women and women of BMI <=25, which was associated with the higher MPA concentration in these thinner women. A substudy of Study 267 evaluated return to ovulation following one year of treatment with DMPA-SC (four doses) and found that 80% of subjects ovulated within a year after the last dose, with the median occurrence of first post-treatment ovulation at 291 days.

5.3 Exposure-Response Relationships

According to the applicant, an efficacy threshold for serum MPA concentration has been established for the contraceptive action, with range of 0.1 to 0.2 ng/ml. Above 0.2 ng/ml, suppression of ovulation occurs in virtually all women administered DMPA-SC; below 0.1 ng/ml, ovulation is no longer suppressed in the majority of women. In selecting the dose, maintaining the trough concentration (C_{91}) above 0.2 ng/ml was the goal. In fact, no pregnancies occurred in the DMPA-SC group in the phase 3 contraceptive trials.

Medical Reviewer's Comment:

1) ***No threshold MPA concentration has been established for estradiol suppression, which is the likely mechanism of mitigating symptoms of endometriosis. The poor sensitivity of the estradiol assay used in the two pivotal trials for the endometriosis indication precludes any assessment of exposure-response. A search of PubMed was unable to identify any publications relevant to a threshold level of MPA necessary for the mitigation of symptoms of endometriosis.***
2) ***A dose of less than 104 mg MPA every three months is not likely to provide an acceptable level of effectiveness for the treatment of painful symptoms of endometriosis (see Section 1.3.4).***

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication evaluated in this NDA is management of endometriosis-associated pain.

6.1.1 Methods

Data from the two pivotal phase 3 randomized, comparator-controlled trials, Studies 268 and 270, were submitted and reviewed in support of the proposed indications.

6.1.2 General Discussion of Endpoints

The clinical efficacy variables were based on the five symptoms/signs from the Biberoglu and Behrman scale (Table 3):

Table 3 Biberoglu and Behrman Scale

Category	Score		Description
Dysmenorrhea	0	Absent	No discomfort
	1	Mild	Some loss of work efficiency. Use of mild analgesics
	2	Moderate	Occasional loss of work efficiency. Use of moderate analgesics
	3	Severe	Incapacitation. Use of strong analgesics
Dyspareunia	0	Absent	No discomfort
	1	Mild	Tolerated discomfort
	2	Moderate	Intercourse painful to the point of interruption of intercourse
	3	Severe	Avoids intercourse because of pain
	NA		No intercourse for reasons other than pain or patient prefers not to answer
Pelvic pain	0	Absent	No discomfort
	1	Mild	Occasional pelvic discomfort or pain
	2	Moderate	Noticeable discomfort during most of the cycle
	3	Severe	Persistent pain other than during menses. Use of strong analgesics
Pelvic tenderness	0	None	No tenderness on palpation
	1	Mild	Minimal tenderness on palpation
	2	Moderate	Excessive tenderness on palpation
	3	Severe	Unable to palpate due to tenderness
Induration	0	None	None
	1	Mild	Uterus freely mobile, induration in cul-de-sac
	2	Moderate	Thickening and indurated adnexa and cul-de-sac
	3	Severe	Nodular adnexa and cul-de-sac, uterus frequently frozen

Abbreviations: NA = not applicable
Source: Table 1, *5.3.5.1.1, p26*

These categories were evaluated at baseline and at all scheduled visits. A positive response was defined as an improvement of at least one point in the score for each category after six months of treatment as compared to baseline.

The primary efficacy analysis was based on demonstration of non-inferiority of DMPA-SC compared to Lupron in the reduction of endometriosis-associated pain, as determined by ratings on the five pain signs/symptoms. A responder analysis was used, comparing the proportion of subjects in each treatment arm who improved at least one point from baseline in each of the five categories. Non-inferiority for each category was defined when the lower bound of the 96% two-sided confidence

interval for the difference between the two drugs' improvement rates for the respective category was no worse than -20%. In order for DMPA-SC to be considered clinically non-inferior, statistical non-inferiority was required on at least four of the five signs/symptoms evaluated.

In addition, to demonstrate clinical non-inferiority, an overall clinically meaningful improvement over baseline was required, as demonstrated by a reduction (i.e., an improvement) of at least 4 points over baseline in the total composite score. In order to allow use of data from those subjects who were sexually inactive for reasons unrelated to endometriosis, an additional analysis of the composite score excluding dyspareunia was conducted, and the clinically meaningful criterion was modified to a reduction of at least 3 points in the remaining four categories.

Efficacy analysis was done on both the Intent to Treat (ITT) and the Evaluable Patient (EP) populations. The former was defined as all subjects who received at least one dose of study medication; the latter as all subjects who received their three and six-month injection/visits within +/- 7 days of the expected date and who did not use any excluded concomitant medications. In the ITT population, both last-observation-carried forward (LOCF) and observed case (OC) analyses were done; in the EP population, only the OC analyses was conducted. With the LOCF analysis, where there was no data after the baseline visit, the baseline data were imputed for all subsequent time periods; with the OC analysis, only the collected data were used.

Medical Reviewer's Comments:

1) ***The only excluded concomitant medication was aminoglutethimide, which may decrease serum levels of MPA. No subjects were withdrawn based on use of this drug.***
2) ***In study 268, 11 DMPA-SC and 5 Lupron subjects withdrew between baseline and month 1 and are therefore likely to have had baseline data imputed in place of actual 6 month data. In comparison, in Study 270, four subjects in each group withdrew during this interval.***

6.1.3 Study Design

Two pivotal phase 3, randomized, evaluator-blinded, multinational, multicenter comparator-controlled trials were conducted to evaluate the efficacy and safety of DMPA-SC for endometriosis. Both studies used Lupron, a current approved treatment for endometriosis, as the comparator. All subjects receiving DMPA-SC were dosed with 104 mg SC every three months, for two doses. In Study 268, all subjects receiving Lupron were injected with 11.25 mg IM every three months. In Study 270, the majority of subjects on Lupron received 3.75 mg SC monthly, for six doses; however, small subsets of subjects received either 3.75 mg IM monthly or 11.25 mg SC every three months, depending on local clinical practice and local approved labeling.

The studies were 18 months in duration, comprising a six-month treatment phase and a 12-month follow-up period during which neither drug could be used. The population studied in each trial was premenopausal women with endometriosis diagnosed by laparoscopy within 42 months of enrollment, who had experienced recurrent or persistent pain symptoms. Inclusion and exclusion criteria were:

Inclusion Criteria

- Premenopausal women between 18-49 years
- Willing to use nonhormonal barrier contraception for 18 months
- Persistent symptoms associated with laparoscopically diagnosed endometriosis (preferably confirmed by biopsy pathology)
    - Patient experienced return of pain to its previous level within 30 days of surgery where only a diagnostic laparoscopy was performed, and within 3 months of surgery if surgical treatment was performed during the laparoscopy

  - Recurrent pain following diagnostic laparoscopy must have persisted for at least 3 months
  - Subjects with more remote laparoscopy must have had vaginal sonography and vaginal cultures to rule out other possible etiologies of chronic pelvic pain
- Total score of 6 or greater in the following 5 categories: dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness and induration. The total score must include a total of at least 2 in each of the categories of dysmenorrhea, dyspareunia, and pelvic pain. If a patient is sexually inactive for reasons other than endometriosis, the total score must be 4 or greater, with at least 2 in the categories of dysmenorrhea and pelvic pain.
- Normal results on a Pap test within the last 6 months
- Normal results on a mammogram within the last 12 months (for subjects 35 or older)
- Provide informed consent
- Willing and able to comply with study-specific procedures

Exclusion Criteria

- Pregnant or breastfeeding
- Known breast cancer or mammographic results suspicious of breast cancer or requiring 6-month follow-up
- Hysterectomy and/or bilateral oophorectomy (Study 268 only)
- Current or recent use of hormonal agents (Wash out periods: 2 months for oral contraceptives, 6 months for Danazol, 12 months for GnRHa or DMPA-IM)
- BMD with both lumbar spine and femur T-scores below -1.0, or history of pathologic or compression fractures
- Abnormal cervical cytology within 6 months; ASCUS and ASCUS favoring reactive changes allowed
- Presence of disease state that could cause chronic abdominal/pelvic pain, including inflammatory bowel disease, fibromyalgia and interstitial cystitis. Large uterine fibroids palpated on bimanual examination were required to be ruled out as the source of the pain.
- Active or history of hepatic or renal disease (AST, ALT or total bilirubin >= 2.5x the upper limit of normal; creatinine > 1.8 mg/dl)
- History of severe hypersensitivity or virilization due to an endocrine disorder, hormone or Danazol therapy
- Well-documented history of thrombotic event (stroke, DVT or pulmonary embolus)
- Anticoagulant therapy or any drug therapy within the past 6 months that could suppress the hypothalamic-pituitary axis
- Uncontrolled hypertension (>180/110)
- Insulin-dependent or poorly controlled non-insulin-dependent diabetes
- Undiagnosed abnormal vaginal bleeding
- Concurrent use of other investigational medications
- Any condition that might cause the subject to be unable to comply with study instructions
- Use of aminoglutethimide

Medical Reviewer's Comments:

1) ***The only difference of potential significance between Studies 268 and 270 was that 270 did not exclude subjects who had had a hysterectomy and/or bilateral oophorectomy. It is unclear if any such subjects actually enrolled in Study 270, although it is unlikely that such women would meet the severity criteria for enrollment.***
2) ***There were other, very minor, differences in inclusion/exclusion criteria between the two studies that are not believed to impact upon the conduct or results of the studies.***

Table 4 shows the Schedule of Assessments for Study 268. Study 270 was very similar, with deviations including:

- Omission of the pelvic exams at months 2 and 5
- Use of sonography only in subjects whose diagnosis was made more than 42 months prior to enrollment
- Assessment of coagulation and fasting lipid panels at the time of the other laboratory assays in a subset of subjects
- Administration of Lupron 3.75 mg on a monthly basis, except as noted in the Netherlands, where 11.25 mg was administered every three months

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Table 4 Schedule of Study Assessments

Study Activity	Visit X-Month									
	0*	1†	2 1-m	3 2-m	4 3-m	5 4-m	6 5-m	7 6-m	T‡	F§
Laparoscopy¶	X									
Informed consent	X									
Medical history	X									
Physical examination	X							X		
Pelvic examination	X	X	X	X	X	X	X	X		X
Sonogram & STD testing	X							X#		
Laboratory assays (hematology, chemistry, and urine analysis)	X				X			X		
Weight & sitting blood pressure	X	X	X	X	X	X	X	X		X
Urine pregnancy test**	X		X	X	X	X	X	X		X
Collection of patient diaries††		X	X	X	X	X	X	X		X
Pain assessment	X	X	X	X	X	X	X	X	X	X
Kupperman Index & uterine bleeding	X	X	X	X	X	X	X	X		
BMD§§	X							X		X
SHBG, serum estradiol, & progesterone		X			X			X		
EHP-30 & SF-36		X			X			X		X
PSQ		X			X			X		
Study medication injection		X			X					
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X

* Baseline visit
† Randomization and injection visit
‡ Telephone interview conducted at 7, 8, 10, 11, 13, 14, 16, and 17 months after injection
§ Follow-up visit at 9, 12, 15, and 18 months after injection
¶ First-time diagnostic laparoscopy must be performed before this visit.
# Vaginal sonogram performed at visit 7 if clinically indicated.
** Urine pregnancy test required 104 days after the last dose, regardless of time of study discontinuation.
†† Patient diary (endometriosis-impact diary including bleeding pattern information) was distributed monthly during the treatment period and every 3 months during the follow-up period (no bleeding pattern information was collected during follow-up).
§§ BMD evaluated using dual energy x-ray absorptiometry (DXA) at visits 0, 7, and at the follow-up visits at 12 and 18 months.
Abbreviations: BMD = bone mineral density, EHP-30 = Endometriosis Health Profile Questionnaire, F = follow-up visit, m = month; PSQ = Patient Satisfaction Questionnaire, SF-36 = Short Form-36 (quality of life questionnaire), SHBG = sex hormone binding globulin, STD = sexually transmitted disease, T = telephone follow-up

Source: Table 2, *5.3.5.1.1, p 31*

6.1.4 Efficacy Findings

In the two pivotal studies, the primary efficacy results support statistical non-inferiority of DMPA-SC to Lupron on four of five pain categories when analyzed at the end of 6 months of treatment using the ITT-OC population, where only those subjects with data at six months were included (Table 5 and Table 6). Analyzed by this ITT-OC method, both studies demonstrated non-inferiority as defined by the respective study protocols; Study 268 on all outcome measures except induration and Study 270 on all five measures.

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Table 5 Comparative Response to Treatment by Treatment Group (Study 268, ITT-OC Population)

Component Visit	DMPA-SC		Leuprolide		P-Value‡	96% CI
	Total Reported	n (%)†	Total Reported	n (%)†		
Dysmenorrhea						
Month 1	125	94 (75.2)	132	96 (72.7)	<0.001§	-8.77, 13.72
Month 2	120	93 (77.5)	125	118 (94.4)	0.237	-25.80, -8.00
Month 3	105	90 (85.7)	117	113 (96.6)	0.008§	-18.69, -3.05
Month 4	94	86 (91.5)	109	105 (96.3)	<0.001§	-11.82, 2.14
Month 5	87	78 (89.7)	104	102 (98.1)	<0.001§	-15.68, -1.16
Month 6 (EOT)	88	80 (90.9)	100	97 (97.0)	<0.001§	-13.30, 1.12
Month 12	51	37 (72.5)	64	42 (65.6)	<0.001§	-10.79, 24.64
Month 18	36	24 (66.7)	44	27 (61.4)	0.009§	-16.79, 27.40
Dyspareunia						
Month 1	90	59 (65.6)	103	68 (66.0)	0.002§	-14.53, 13.60
Month 2	84	68 (81.0)	95	78 (82.1)	<0.001§	-13.10, 10.80
Month 3	78	60 (76.9)	94	78 (83.0)	0.012§	-18.69, 6.58
Month 4	73	56 (76.7)	84	72 (85.7)	0.039	-21.84, 3.84
Month 5	64	49 (76.6)	76	64 (84.2)	0.034	-21.52, 6.22
Month 6 (EOT)	65	51 (78.5)	79	67 (84.8)	0.018§	-19.72, 7.02
Month 12	35	28 (80.0)	45	38 (84.4)	0.036	-22.23, 13.34
Month 18	29	27 (93.1)	29	22 (75.9)	<0.001§	-1.74, 36.22
Pelvic Pain						
Month 1	126	82 (65.1)	132	85 (64.4)	<0.001§	-11.54, 12.91
Month 2	119	90 (75.6)	127	106 (83.5)	0.009§	-18.38, 2.72
Month 3	106	79 (74.5)	120	101 (84.2)	0.027	-20.71, 1.43
Month 4	95	73 (76.8)	110	91 (82.7)	0.006§	-17.46, 5.69
Month 5	86	66 (76.7)	106	88 (83.0)	0.009§	-18.27, 5.72
Month 6 (EOT)	86	71 (82.6)	101	88 (87.1)	0.002§	-15.42, 6.27
Month 12	51	37 (72.5)	64	44 (68.8)	0.003§	-13.71, 21.31
Month 18	37	29 (78.4)	44	35 (79.5)	0.019§	-19.86, 17.53
Pelvic Tenderness						
Month 1	125	72 (57.6)	130	78 (60.0)	0.002§	-15.07, 10.27
Month 2	118	77 (65.3)	121	87 (71.9)	0.013§	-18.96, 5.67
Month 3	104	74 (71.2)	116	86 (74.1)	0.002§	-15.36, 9.39
Month 4	95	71 (74.7)	106	84 (79.2)	0.005§	-16.73, 7.72
Month 5	83	58 (69.9)	103	79 (76.7)	0.022	-20.25, 6.61
Month 6 (EOT)	85	65 (76.5)	98	79 (80.6)	0.005§	-16.66, 8.38
Month 12	49	36 (73.5)	62	45 (72.6)	0.007§	-16.53, 18.31
Month 18	35	25 (71.4)	44	29 (65.9)	0.007§	-15.97, 27.01
Induration						
Month 1	96	51 (53.1)	99	62 (62.6)	0.068	-23.97, 4.97
Month 2	86	49 (57.0)	92	71 (77.2)	0.511	-34.38, -6.01
Month 3	79	56 (70.9)	89	71 (79.8)	0.047	-22.56, 4.78
Month 4	69	46 (66.7)	80	67 (83.8)	0.339	-31.5, -2.67
Month 5	61	44 (72.1)	77	65 (84.4)	0.138	-26.82, 2.25
Month 6 (EOT)	66	49 (74.2)	75	65 (86.7)	0.128	-26.12, 1.27
Month 12	37	30 (81.1)	50	40 (80.0)	0.007§	-16.53, 18.69
Month 18	27	24 (88.9)	35	31 (88.6)	0.006§	-16.31, 16.95

* Response (ie, improvement) defined as a decrease of at least 1 point in the score relative to pretreatment (primary endpoint was the response at month 6)

† % = (n/total reported within period) x 100

‡ The p-value tests the null hypothesis DMPA-SC % improved - leuprolide % improved ≤-20%. Treatment equivalence was concluded when p<0.02

Note: Enrollment was 136 in the DMPA-SC group, 138 in the Lupron group.

Source: Table 10, *5.3.5.1.1, p 73*

Table 6 Comparative Response to Treatment by Treatment Group (Study 270, ITT-OC Population)

Component Visit	DMPA-SC		Leuprolide		P-Value‡	96% CI
	Total Reported	n (%)†	Total Reported	n (%)†		
Dysmenorrhea						
Month 1	149	109 (73.2)	142	107 (75.4)	<0.001§	-12.73, 8.33
Month 2	147	124 (84.4)	139	136 (97.8)	0.022	-20.15, -6.83
Month 3	143	123 (86.0)	139	135 (97.1)	0.003§	-17.74, -4.47
Month 4	140	127 (90.7)	137	134 (97.8)	<0.001§	-12.75, -1.44
Month 5	138	127 (92.0)	136	133 (97.8)	<0.001§	-11.16, -0.37
Month 6 (EOT)	135	123 (91.1)	135	131 (97.0)	<0.001§	-11.79, -0.07
Month 12	118	101 (85.6)	118	89 (75.4)	<0.001§	-0.34, 20.68
Month 18	95	77 (81.1)	99	75 (75.8)	<0.001§	-6.81, 17.40
Dyspareunia						
Month 1	104	63 (60.6)	101	55 (54.5)	<0.001§	-8.04, 20.29
Month 2	103	79 (76.7)	101	82 (81.2)	0.003§	-16.20, 7.22
Month 3	101	78 (77.2)	101	81 (80.2)	0.002§	-14.80, 8.86
Month 4	99	71 (71.7)	95	79 (83.2)	0.075	-23.64, 0.76
Month 5	98	77 (78.6)	90	79 (87.8)	0.023	-20.29, 1.88
Month 6 (EOT)	88	73 (83.0)	88	78 (88.6)	0.003§	-16.46, 5.10
Month 12	81	64 (79.0)	79	66 (83.5)	0.006§	-17.18, 8.12
Month 18	63	51 (81.0)	66	60 (90.9)	0.049	-22.46, 2.54
Pelvic Pain						
Month 1	150	85 (56.7)	143	86 (60.1)	0.002§	-15.30, 8.36
Month 2	150	101 (67.3)	140	116 (82.9)	0.184	-25.76, -5.29
Month 3	146	115 (78.8)	140	121 (86.4)	0.003§	-16.81, 1.49
Month 4	141	111 (78.7)	138	118 (85.5)	0.002§	-16.17, 2.60
Month 5	141	112 (79.4)	137	121 (88.3)	0.006§	-17.87, 0.10
Month 6 (EOT)	136	111 (81.6)	136	124 (91.2)	0.006§	-18.02, -1.10
Month 12	120	102 (85.0)	117	93 (79.5)	<0.001§	-4.67, 15.70
Month 18	98	80 (81.6)	100	80 (80.0)	<0.001§	-9.86, 13.13
Pelvic Tenderness						
Month 1	145	61 (42.1)	137	53 (38.7)	<0.001§	-8.62, 15.39
Month 2						
Month 3	141	94 (66.7)	132	101 (76.5)	0.031	-20.99, 1.29
Month 4	138	104 (75.4)	131	107 (81.7)	0.003§	-16.57, 3.93
Month 5						
Month 6 (EOT)	133	108 (81.2)	128	109 (85.2)	<0.001§	-13.45, 5.54
Month 12	116	91 (78.4)	110	86 (78.2)	<0.001§	-11.01, 11.54
Month 18	93	74 (79.6)	94	76 (80.9)	<0.001§	-13.26, 10.69

Table continued on next page

Component Visit	DMPA-SC		Leuprolide		P-Value‡	96% CI
	Total Reported	n (%)†	Total Reported	n (%)†		
Induration						
Month 1	126	37 (29.4)	124	47 (37.9)	0.027	-20.77, 3.70
Month 2						
Month 3	122	71 (58.2)	123	82 (66.7)	0.031	-21.14, 4.20
Month 4	120	80 (66.7)	122	90 (73.8)	0.014§	-19.15, 4.95
Month 5						
Month 6 (EOT)	117	84 (71.8)	119	95 (79.8)	0.016§	-19.45, 3.38
Month 12	100	80 (80.0)	104	82 (78.8)	<0.001§	-10.48, 12.79
Month 18	82	64 (78.0)	87	69 (79.3)	0.001§	-14.22, 11.70

* Response (ie, improvement) defined as a decrease of at least 1 point in the score relative to pretreatment (primary endpoint was the response at month 6).
† % = (n/total reported within period) x 100
‡ The p-value tests the null hypothesis DMPA-SC % improved - leuprolide % improved ≤-20%. Treatment equivalence was concluded when p<0.02.
§ Statistically equivalent between treatment groups (p<0.02).
Note: Enrollment was 153 in the DMPA-SC group, 146 in the Lupron group.
Source: Table 11, *5.3.5.1.2, pp 76-7*

However, in one of the studies, results were discrepant when the analysis was based on the ITT-LOCF population. By this analysis, Study 268, based in the U.S. and Canada, demonstrated non-inferiority of DMPA-SC to Lupron on only one of the five B&B outcomes, pelvic tenderness. Study 270, a multinational study including South American and Asia, met the criteria for non-inferiority on all five of the outcome measures. Table 7 and Table 8 provide comparative results for these two analyses for each study.

Table 7 Study 268: Response at 6 Months: Comparison of OC and LOCF Analyses

Component	Analysis	DMPA-SC		Lupron			
		N	%	N	%	p-value*	96% CI
Dysmenorrhea	ITT-OC	88	90.9	100	97.0	<0.001	-13.3, 1.12
	ITT-LOCF	135	75.6	137	92.0	0.206	-25.39, -7.44
Dyspareunia	ITT-OC	65	78.5	79	84.8	0.018	-19.72, 7.02
	ITT-LOCF	100	66.0	108	80.6	0.185	-27.05, -2.06
Pelvic Pain	ITT-OC	86	82.6	101	87.1	0.002	-15.42, 6.27
	ITT-LOCF	134	67.2	136	80.1	0.093	-23.89, -2.08
Pelvic Tenderness	ITT-OC	85	76.5	98	80.6	0.005	-16.66, 8.38
	ITT-LOCF	134	67.2	133	72.9	0.005	-17.26, 5.73
Induration	ITT-OC	66	74.2	75	86.7	0.128	-26.12, 1.27
	ITT-LOCF	105	63.8	101	82.2	0.394	-30.78, -5.95

N = Total reported; % = % improved (i.e., with >=1 point decrease in score relative to baseline)
*p-value tests the H_0 that DMPA-SC % improved – Lupron % improved <= -20%. Statistical non-inferiority concluded if p <0.02.
CI = 96% confidence intervals around point estimate of difference in improvement rate between DMPA-SC and Lupron
Source: Based on Tables 10-12, *5.3.5.1.1, pp 73-75*

Table 8 Study 270: Response at 6 Months: Comparison of OC and LOCF Analyses

Component	Analysis	DMPA-SC		Lupron			
		N	%	N	%	p-value*	96% CI
Dysmenorrhea	ITT-OC	135	91.1	135	97.0	<0.001	-11.79, -0.07
	ITT-LOCF	151	88.7	145	95.2	<0.001	-12.86, 0.00
Dyspareunia	ITT-OC	88	83.0	88	88.6	0.003	-16.46, 5.10
	ITT-LOCF	101	81.2	95	83.2	<0.001	-13.20, 9.26
Pelvic Pain	ITT-OC	136	81.6	136	91.2	0.006	-18.02, -1.10
	ITT-LOCF	152	80.3	146	88.4	0.002	-16.68, 0.50
Pelvic Tenderness	ITT-OC	133	81.2	128	85.2	<0.001	-13.45, 5.54
	ITT-LOCF	148	78.4	140	80.7	<0.001	-12.10, 7.43
Induration	ITT-OC	117	71.8	119	79.8	0.016	-19.45, 3.38
	ITT-LOCF	128	70.3	127	77.2	0.008	-18.14, 4.44

N = Total reported; % = % improved (i.e., with >=1 point decrease in score relative to baseline)
*p-value tests the H_0 that DMPA-SC % improved – Lupron % improved <= -20%. Statistical non-inferiority concluded if p <0.02.
CI = 96% confidence intervals around point estimate of difference in improvement rate between DMPA-SC and Lupron
Source: Based on Tables 10-12, *5.3.5.1.2, pp 76-79*

Medical Review's Comments:

1) ***A third analysis, EP, was also conducted for both the individual and composite endpoints. As it was a per protocol analysis, similar to the ITT-OC analysis, with the additional restriction that subjects had to receive injections within a certain timeframe, it does not contribute any additional clarification of the efficacy results and is therefore not discussed here.***
2) ***In Study 268, all outcome categories that met the criteria for non-inferiority had confidence intervals that included 0. In Study 270, while meeting the lower bound of the confidence interval criteria for non-inferiority, the ITT-OC results for dysmenorrhea and pelvic pain have confidence intervals that remain below 0, indicating that the DMPA-SC response rate may be statistically significantly less than that of Lupron.***

On the second measure, the change in the composite score, which was used to evaluate the overall clinical meaningfulness of treatment results, both studies met the criterion of a mean decrease from baseline to month 6 of at least four points, regardless of which analysis population was used. Similar consistent results were demonstrated for both studies when the composite score excluding the dyspareunia measure (with a threshold of at least -3 for clinical meaningfulness) was used (see Table 9 and Table 10).

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Table 9 Study 268: Mean Change in Composite Score: OC and LOCF Analyses

Time Period	Analysis Population	DMPA-SC		Lupron		Threshold for Clinical Meaningfulness
		N	Change	N	Change	
Month 6 (End of Treatment)	ITT-OC	64	-6.2	76	-7.7	-4
	ITT-LOCF	100	-4.9	109	-6.9	-4
Month 12 (6 mo F/U)	ITT-OC	35	-4.9	44	-5.7	-4
Month 18 (12 mo F/U)	ITT-OC	27	-5.3	30	-5.1	-4
Composite Score Excluding Dyspareunia						
Month 6 (End of Treatment	ITT-OC	85	-4.8	97	-6.0	-3
	ITT-LOCF	134	-3.9	136	-5.3	-3
Month 12 (6 mo F/U)	ITT-OC	50	-3.8	61	-4.0	-3
Month 18 (12 mo F/U)	ITT-OC	35	-3.7	44	-3.9	-3

Source: Based on Tables 13-18, *5.3.5.1.1, pp 77-82*

Table 10 Study 270: Mean Change in Composite Score: OC and LOCF Analyses

Time Period	Analysis Population	DMPA-SC		Lupron		Threshold for Clinical Meaningfulness
		N	Change	N	Change	
Month 6 (End of Treatment)	ITT-OC	94	-6.3	91	-7.3	-4
	ITT-LOCF	108	-6.0	99	-6.9	-4
Month 12 (6 mo F/U)	ITT-OC	85	-6.5	84	-5.8	-4
Month 18 (12 mo F/U)	ITT-OC	66	-6.6	72	-6.1	-4
Composite Score Excluding Dyspareunia						
Month 6 (End of Treatment	ITT-OC	135	-5.0	132	-6.0	-3
	ITT-LOCF	151	-4.8	143	-5.8	-3
Month 12 (6 mo F/U)	ITT-OC	119	-5.1	113	-4.6	-3
Month 18 (12 mo F/U)	ITT-OC	95	-5.0	96	-4.8	-3

Source: Based on Tables 14-19, *5.3.5.1.2, pp 80-85*

Medical Reviewer's Comment:

1) ***The ITT-LOCF analysis was conducted only at the month 6 assessment period. The EP analysis, which was similar to, but slightly more restrictive than the ITT-OC analysis, had results very similar to the ITT-OC results.***

In the face of results that do not unequivocally support non-inferiority of DMPA-SC to Lupron, trends in the secondary efficacy endpoints were evaluated. No formal testing of non-inferiority was done for these outcome measures. Changes from baseline in each of the five individual parameters on

the B&B scale were evaluated. Both treatment arms in both studies displayed highly significant ($p<0.001$) decreases from baseline in each individual score (see Table 11 and Table 12). The mean change in the DMPA-SC group never exceeded the corresponding change in the Lupron group. The magnitude of the change seen in the Lupron group at the second assessment in the treatment period was often not achieved in the DMPA-SC group until several months later, if ever.

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Table 11 Study 268: Mean Change from Baseline in Symptoms and Signs

	Dysmenorrhea		Dyspareunia		Pelvic Pain		Pelvic Tenderness		Induration	
Visit	DMPA-SC	Lupron	DMPA-SC	Lupron	DMPA-SC	Lupron	DMPA-SC	Lupron	DMPA-SC	Lupron
Pre-tx N, Mean (SD)	**136** 2.4 (0.6)	**137** 2.4 (0.6)	**119** 2.3 (0.6)	**120** 2.4 (0.6)	**136** 2.2 (0.5)	**137** 2.3 (0.5)	**136** 1.9 (0.7)	**137** 1.9 (0.7)	**136** 1.2 (0.9)	**137** 1.3 (1.0)
Month 1 (N, Mean change (SD); p value)	**125** -1.3 (1.0) <0.001	**132** -1.1 (1.0) <0.001	**91** -0.9 (1.0) <0.001	**105** -1.1 (1.0) <0.001	**126** -0.8 (0.9) <0.001	**132** -0.9 (0.9) <0.001	**126** -0.6 (0.7) <0.001	**131** -0.7 (0.9) <0.001	**126** -0.3 (0.9) <0.001	**131** -0.5 ((0.8) <0.001
Month 2 (N, Mean change (SD); p value)	**120** -1.3 (1.0) <0.001	**125** -2.0 (0.9) <0.001	**84** -1.2 (1.0) <0.001	**97** -1.4 (1.0) <0.001	**119** -1.0 (0.8) <0.001	**127** -1.3 (0.9) <0.001	**120** -0.8 (0.9) <0.001	**125** -0.9 (0.8) <0.001	**120** -0.5 (0.9) <0.001	**125** -0.8 (0.9) <0.001
Month 3 (N, Mean change (SD); p value)	**105** -1.5 (0.9) <0.001	**117** -2.1 (0.8) <0.001	**79** -1.3 (1.2) <0.001	**96** -1.5 (1.0) <0.001	**106** -1.1 (0.8) <0.001	**120** -1.3 (0.9) <0.001	**106** -0.9 (0.9) <0.001	**119** -1.1 (0.9) <0.001	**106** -0.6 (0.9) <0.001	**119** -0.8 (1.0) <0.001
Month 4 (N, Mean change (SD); p value)	**94** -1.7 (0.9) <0.001	**109** -2-2 (0.7) <0.001	**73** -1.3 (1.1) <0.001	**86** -1.6 (1.0) <0.001	**95** -1.1 (0.9) <0.001	**110** -1.4 (1.0) <0.001	**96** -1.0 (0.9) <0.001	**109** -1.2 (1.0) <0.001	**96** -0.6 (0.9) <0.001	**109** -0.9 (0.9) <0.001
Month 5 (N, Mean change (SD); p value)	**87** -1.7 (0.9) <0.001	**104** -2-2 (0.7) <0.001	**64** -1.3 (1.1) <0.001	**78** -1.6 (1.0) <0.001	**86** -1.2 (0.9) <0.001	**106** -1.4 (1.0) <0.001	**86** -0.9 (1.1) <0.001	**105** -1.2 (1.0) <0.001	**85** -0.7 (0.9) <0.001	**105** -0.9 (0.9) <0.001
Month 6 (N, Mean change (SD); p value)	**88** -1.8 (0.9) <0.001	**100** -2.2 (0.8) <0.001	**65** -1.4 (1.2) <0.001	**81** -1.6 (1.0) <0.001	**86** -1.2 (0.9) <0.001	**101** -1.4 (0.9) <0.001	**87** -1.0 (0.9) <0.001	**100** -1.3 (0.9) <0.001	**87** -0.7 (1.0) <0.001	**100** -1.0 (1.0) <0.001
Early W/D (N, Mean change (SD); p value)	**17** -1.1 (1.1) 0.002	**10** -1.4 (0.8) 0.008	**11** -0.5 (1.3) NS	**9** -1.2 (1.0) 0.016	**8** -0.6 (0.7) NS	**12** -0.7 (0.9) NS	**17** -0.6 (0 9) 0.031	**11** -0.8 (1.1) NS	**17** -0.4 (0.9) NS	**11** -0.8 (0.6) 0.008
Month 9 (N, Mean change (SD); p value)	**61** -1.4 (1.0) <0.001	**76** -1.4 (1.0) <0.001	**44** -1.2 (1.0) <0.001	**55** -1.8 (1.1) <0.001	**61** -1.0 (0.9) <0.001	**77** -1.2 (0.9) <0.001	**62** -0.8 (1.0) <0.001	**75** -1.2 (0.9) <0.001	**62** -0.7 (0.9) <0.001	**75** -1.0 (0.9) <0.001
Month 12 (N, Mean change (SD); p value)	**51** -1.1 (1.0) <0.001	**64** -0.9 (1.0) <0.001	**35** -1.2 (1.0) <0.001	**46** -1.5 (1.1) <0.001	**51** -1.1 (1.0) <0.001	**64** -1.1 (0.9) <0.001	**50** -1.0 (1.1) <0.001	**62** -1.0 (0.9) <0.001	**50** -0.7 (0.9) <0.001	**61** -1.0 (1.0) <0.001
Month 15 (N, Mean change (SD); p value)	**38** -1.0 (0.9) <0.001	**46** -0.8 (0.9) <0.001	**30** -1.4 (0.9) <0.001	**32** -1.5 (1.1) <0.001	**38** -0.9 (0.7) <0.001	**46** -1.2 (0.8) <0.001	**37** -1.0 (1.0) <0.001	**45** -1.1 (0.9) <0.001	**37** -0.9 (0.9) <0.001	**45** -1.1 (1.0) <0.001
Month 18 (N, Mean change (SD); p value)	**36** -0.8 (0.8) <0.001	**44** -0.8 (0.9) <0.001	**29** -1.5 (0.9) <0.001	**30** -1.3 (1.0) <0.001	**37** -1.0 (0.8) <0.001	**44** -1.1 (0.8) <0.001	**36** -0.8 (1.1) <0.001	**44** -1.0 (0.9) <0.001	**35** -1.0 (0.9) <0.001	**44** -1.0 (0.9) <0.001

The p-value is based on the Kruskal-Wallis evaluation of **median change** from baseline within each treatment group

The highlighted cells indicate the earliest assessment period at which the maximal mean change was attained.

Note: Only data from those follow-up assessments at which all five signs/symptoms were scheduled to be assessed are shown. Changes in dysmenorrhea, dyspareunia and pelvic pain remained significant at all monthly intervals in the 12 month follow-up period.

Source: Based on Tables T5.7-T5.8, *5.3.5.1.1, pp 388-413*

Table 12 Study 270: Mean Change from Baseline in Symptoms and Signs

	Dysmenorrhea		Dyspareunia		Pelvic Pain		Pelvic Tenderness		Induration	
Visit	DMPA-SC	Lupron	DMPA-SC	Lupron	DMPA-SC	Lupron	DMPA-SC	Lupron	DMPA-SC	Lupron
Pre-tx N, Mean (SD)	153 2.2 (0.7)	146 2.4 (0.6)	131 1.9 (0.8)	123 2.0 (0.8)	153 2.1 (0.6)	146 2.2 (0.5)	152 1.7 (0.7)	144 1.8 (0.6)	152 1.3 (0.9)	143 1.5 (0.8)
Month 1 (N, Mean change (SD); p value)	151 -1.2 (1.1) <0.001	143 -1.3 (1.1) <0.001	109 -0.7 (0.9) <0.001	105 -0.7 (0.9) <0.001	150 -0.7 (0.9) <0.001	143 -0.8 (0.8) <0.001	150 -0.5 (0.7) <0.001	141 -0.4 (0.7) <0.001	150 -0.2 (0.8) <0.001	140 -0.4 ((0.8) <0.001
Month 3 (N, Mean change (SD); p value)	146 -1.5 (1.0) <0.001	140 -2.2 (0.8) <0.001	107 -1.0 (1.1) <0.001	104 -1.2 (1.0) <0.001	146 -1.1 (0.8) <0.001	140 -1.3 (0.8) <0.001	145 -0.8 (0.8) <0.001	136 -1.0 (0.8) <0.001	145 -0.6 (0.9) <0.001	136 -0.8 (0.9) <0.001
Month 4 (N, Mean change (SD); p value)	142 -1.7 (0.9) <0.001	138 -2-2 (0.8) <0.001	106 -1.0 (1.1) <0.001	98 -1.2 (1.0) <0.001	141 -1.1 (0.9) <0.001	138 -1.3 (0.8) <0.001	141 -1.0 (0.8) <0.001	135 -1.1 (0.7) <0.001	141 -0.7 (0.9) <0.001	135 -0.9 (0.9) <0.001
Month 6 (N, Mean change (SD); p value)	137 -1.7 (1.0) <0.001	136 -2.2 (0.8) <0.001	94 -1.2 (1.0) <0.001	91 -1.4 (0.90) <0.001	136 -1.2 (0.9) <0.001	136 -1.5 (0.9) <0.001	136 -1.1 (0.9) <0.001	132 -1.3 (0.8) <0.001	136 -0.9 (1.0) <0.001	132 -1.1 (0.9) <0.001
Early W/D (N, Mean change (SD); p value)	5 -0.8 (1.3) NS	2 -1.5 (0.7) NS	4 -0.3 (0.5) NS	2 -0.5 (0.7) NS	5 -0.8 (0.4) NS	2 -1.0 (0) NS	5 -0.6 (0.9) NS	2 0 (1.4) NS	5 -0.4 (0.9) NS	2 1.0 (1.4) NS
Month 9 (N, Mean change (SD); p value)	129 -1.8 (1.0) <0.001	128 -1.4 (1.0) <0.001	90 -1.3 (1.1) <0.001	93 -1.5 (1.01) <0.001	129 -1.3 (1.1) <0.001	127 -1.4 (0.9) <0.001	128 -1.2 (0.9) <0.001	124 -1.2 (0.8) <0.001	128 -1.0 (1.0) <0.001	124 -1.1 (0.9) <0.001
Month 12 (N, Mean change (SD); p value)	120 -1.5 (1.0) <0.001	119 -1.2 (1.0) <0.001	85 -1.3 (1.3) <0.001	85 -1.4 (1.1) <0.001	120 -1.4 (0.9) <0.001	117 -1.3 (0.9) <0.001	119 -1.2 (0.9) <0.001	114 -1.1 (0.8) <0.001	119 -1.1 (1.0) <0.001	114 -1.0 (1.0) <0.001
Month 15 (N, Mean change (SD); p value)	102 -1.4 (1.0) <0.001	110 -1.3 (1.0) <0.001	75 -1.4 (1.1) <0.001	78 -1.5 (1.0) <0.001	103 -1.4 (1.0) <0.001	109 -1.4 (0.9) <0.001	102 -1.2 (0.8) <0.001	105 -1.2 (0.8) <0.001	102 -1.1 (1.0) <0.001	105 -1.0 (1.0) <0.001
Month 18 (N, Mean change (SD); p value)	97 -1.4 (1.1) <0.001	100 -1.2 (1.0) <0.001	67 -1.3 (1.2) <0.001	73 -1.4 (1.0) <0.001	98 -1.3 (1.0) <0.001	100 -1.3 (1.0) <0.001	96 -1.2 (0.9) <0.001	97 -1.2 (0.9) <0.001	96 -1.1 (1.0) <0.001	96 -1.0 (1.0) <0.001

The p-value is based on the Wilcoxon Signed Rank test of **median change** from baseline within each treatment group

The highlighted cells indicate the earliest assessment period at which the maximal mean change was attained.

Note: Only data from those follow-up assessments at which all five signs/symptoms were scheduled to be assessed are shown. Changes in dysmenorrhea, dyspareunia and pelvic pain remained significant at all monthly intervals in the treatment and 12 month follow-up periods.

Source: Based on Tables T5.7-T5.8, *5.3.5.1.2, pp 410-441*

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Medical Reviewer's Comment:

1) ***Although it is not explicitly stated, the sample sizes indicate that these are ITT-OC analyses.***
2) ***In Study 268, in the three patient-assessed pain categories, it appears that the maximum mean change in the Lupron group has been achieved by month 4 of treatment, while the DMPA-SC group continues to show greater mean change at each assessment point through the end of treatment, indicating greater latency in the DMPA-SC group in obtaining maximal treatment benefit. In Study 270, where subjects were assessed less frequently during treatment, neither group attained maximal improvement until month 6.***
3) ***In Study 268, it can be seen that the mean change (i.e., improvement) in subjects withdrawing early was generally less than that seen at month 1 and always less than that seen at the second assessment period in the continuing DMPA-SC subjects. In the Lupron group, the mean change in subjects withdrawing early usually exceeded the change seen in continuing subjects at month 1, but was less than or equal to the change seen at the second and subsequent assessment points. The number of early withdrawals in Study 270 is too small to evaluate trends.***

The next secondary outcome measure was median time to recurrence of symptoms (defined as an increase of at least one point from the value at the end of treatment on any of the five outcome categories) following discontinuation of treatment. Data was analyzed both in the subgroup of the population that had experienced improvement during treatment and in the total population. In Study 268, there was no significant difference between the treatment arms in time to recurrence; in both groups the symptoms of dysmenorrhea, dyspareunia and pelvic pain recurred at a median time of three months after stopping treatment (see Table 53). For all five outcomes, a slightly lower proportion of DMPA-SC subjects experienced recurrence. In Study 270, there were significant differences favoring DMPA-SC in recurrence of dysmenorrhea; pelvic pain also occurred significantly later when analyzing the population that experienced improvement on treatment (see Table 85). Dysmenorrhea recurred at a median of 3 months for the DMPA-SC subjects, compared to a median of 6 months for the Lupron group; pelvic pain at over 7 months for DMPA-SC and 4 months for Lupron. Proportions of subjects experiencing recurrence was slightly lower in the DMPA-SC group, except for dyspareunia, where a slightly higher percent of DMPA-SC than Lupron subjects recurred.

Medical Reviewer's Comment:

1) ***Recurrence of pelvic tenderness and induration took six months or longer, but this measure is likely affected by the greater ascertainment interval in these physician-assessed signs.***

The final set of secondary outcome measures were three quality of life scales: the Endometriosis Health Profile-30 (EHP-30), the Short Form-36 (SF-36) and the Patient Satisfaction Questionnaire (PSQ). Both treatment groups displayed significant improvement from baseline to 6 months in scores on the pre-specified subscales of the EHP-30 (Pain, Emotional Well-Being, Self-Image and Intercourse). These improvements were maintained at month 18, one year off treatment. Similarly, the three pre-specified subscales on the SF-36 (Physical Function, Role Physical and Social Functioning) all decreased significantly from baseline to 6 and 18 months in both groups. All of these results were robust whether analyzed in the ITT-OC, ITT-LOCF or EP population. On the PSQ, both groups reported significant improvements from baseline in physical health and sexual relationships at month 6. The Lupron group also reported significant improvement in emotional health at month 6, and was more likely to recommend their treatment to a friend or to consider using it in the future.

Medical Reviewer's Comment:

1) ***While the applicant indicates that both the EHP-30 and the SF-36 are validated measures, no details about the validation process, such as the population in which each questionnaire was validated, were provided. The applicant was advised during the clinical development program that quality of life measures are not generally accepted for labeling claims.***
2) ***However, DRUDP indicated that it would like to see these measures assessed for concordance with the primary efficacy data. It is the reviewer's opinion that all three measures provide support for the treatment benefit demonstrated in the primary efficacy analysis.***

6.1.5 Clinical Microbiology

This section is not applicable, as this product is not an antimicrobial.

6.1.6 Efficacy Conclusions

Overall, this reviewer concludes that adequate evidence of efficacy relative to Lupron has been demonstrated for DMPA-SC in management of pain associated with endometriosis. While ideally, both the OC and LOCF populations would provide comparable efficacy data, when they diverge, it is important to determine which is the more relevant analysis. In these trials, the LOCF analysis is conservative, assuming that those who drop out for any reason would never have received any greater treatment benefit had they stayed in treatment. The OC analysis is an accurate assessment of the benefit accrued to subjects who stay on the treatment. Among the advice given to the applicant by the FDA statistician during the development of the clinical trial protocols was that both ITT and per protocol analyses be conducted, because of concerns about the use of ITT analyses in a non-inferiority trial. As seen in Table 11 and Table 12, it is clear that the treatment effect of DMPA-SC continues to increase over the six month course of treatment; thus the OC analysis will be more representative of the actual clinical experience of patients who receive two doses of DMPA-SC.

The single analysis that failed to meet the pre-specified criteria for non-inferiority, the ITT-LOCF analysis in Study 268, was likely hampered by several logistic factors and by a factor relating to the onset of treatment benefit. First, Study 268 fell further short of its recruitment goal than did Study 270. The rate of treatment withdrawal was also greater in Study 268 than in Study 270, and particularly so in the DMPA-SC group. Both of these factors would serve to decrease the power of the analysis to reject the null hypothesis that DMPA-SC is inferior to Lupron. In addition, in the LOCF analysis, the subjects who failed to continue treatment until month 6 had data imputed from earlier points in treatment. Given that Lupron appears to provide greater benefit earlier in the treatment course than does DMPA-SC (see Table 11 and Table 12), the Lupron subjects would have more favorable data imputed.

Medical Reviewer's Comments:

1) ***Two additional factors may confound the results and possibly inflate the apparent relative treatment benefit seen in the Lupron group. One action of Lupron is induction of amenorrhea, which, by definition, will abolish the symptom of dysmenorrhea. A much greater proportion of Lupron subjects became amenorrheic, and therefore were no longer at risk for dysmenorrhea. In contrast, less than 10% of DMPA-SC subjects experienced amenorrhea in the last three months of treatment; therefore, more DMPA-SC subjects were at risk of this symptom, and might thus demonstrate a lower response rate or mean % change even if an actual decrease in this category did occur with DMPA-SC treatment.***

2) ***Additionally, in Study 268 the use of concomitant narcotics during the treatment period was slightly greater in the Lupron group; this could be expected to have an impact on diminution of their pain scores.***

The preponderance of evidence supports an efficacy finding of non-inferiority of DMPA-SC as compared to Lupron. As noted, the OC analysis is a more appropriate reflection of the experience of patients who will, at a minimum, obtain the treatment effect noted at month 3 following a single injection. Analysis of this population met the criteria for non-inferiority on at least four of five outcome categories in both trials. In addition, the criterion for judging the clinical meaningfulness of the treatment effect, which was specifically requested by DRUDP, was achieved in both trials and was robust whether the population analyzed was ITT-OC or ITT-LOCF. The remainder of the endpoints, while not expressly used to test non-inferiority of DMPA-SC compared to Lupron, support the proposition that DMPA-SC confers a clinically meaningful treatment benefit, provides significant improvement over baseline symptomatology at all months of treatment, is associated with time to symptom recurrence similar to or of longer latency than Lupron, and results in improved quality of life, as measured by pre-specified scales.

A final way of evaluating the treatment benefit of DMPA-SC is by comparing the treatment effect to historical data in a placebo-controlled study[3] of Lupron using the Biberoglu and Behrman scale. In that study, conducted in a comparable population, the primary efficacy data was obtained from the dysmenorrhea, pelvic pain, dyspareunia and pelvic tenderness categories, with induration considered as a secondary outcome. Although the planned treatment duration was 20 weeks, subjects who continued to experience severe pain after the third monthly injection were considered treatment failures and the blind was broken. Placebo subjects were then allowed to receive Lupron in an open label study. By month 4, only six of the original 31 placebo subjects remained in the blinded study; thus, only data from months 1-3 are reported in Table 13. Treatment effect sizes at months 1-3 for both treatment arms in Studies 268 and 270 are greater than in the placebo arm of the older placebo-controlled trial. However, the changes seen in the Lupron groups in the present trials are similar to those in the older trial for dysmenorrhea, pelvic pain and pelvic tenderness. The effect sizes in the DMPA-SC groups generally exceed that seen in the placebo group by about a full point (equivalent to a decrease of a full level on the 0-3 scale).

The medical reviewer was able to compared responses obtained in the placebo-controlled study with those obtained in Study 268. Evaluation of responder rates at the end of the randomized treatment period in Study 268 and the placebo-controlled study are compared in Table 14.

Table 15 demonstrates the shifts in severity category at the end of treatment in each study. The two studies differ at baseline, because only Study 268 required that subjects meet entry severity criteria of 2 or greater on dysmenorrhea, pelvic pain and dyspareunia. Nonetheless, it can be seen that the placebo group showed very little improvement in the proportion of subjects with moderate or severe symptoms at the end of treatment. In contrast, subjects receiving DMPA-SC in Study 268 showed a clear improvement in severity scores, with the vast majority of subjects' signs and symptoms rated as moderate-severe at baseline, and absent-mild at the end of treatment. It is thus clear that the treatment effects seen in response to administration of DMPA-SC are greater than what would be expected based on a placebo effect.

Table 13 Comparative Treatment Effects in Current Trials vs. Placebo-Controlled Study

Category & Visit	Placebo*		DMPA-SC 268		DMPA-SC 270		Lupron*		Lupron 268		Lupron 270	
	N	Mean Change	N	Mean Change	N	Mean Change	N	Mean Change	N	Mean Change	N	Mean Change
Dysmenorrhea												
1	20	-0.3	125	-1.3	151	-1.2	28	-1.5	132	-1.1	143	-1.3
2	20	-0.2	120	-1.3	150	-1.5	28	-2.4	125	-2.0	140	-2.2
3	20	-0.3	105	-1.5	146	-1.5	28	-2.3	117	-2.1	140	-2.2
Pelvic pain												
1	20	-0.3	126	-0.8	150	-0.7	28	-0.5	132	-0.9	143	-0.8
2	20	-0.3	119	-1.0	150	-0.8	28	-1.1	127	-1.3	140	-1.2
3	20	-0.2	106	-1.1	146	-1.1	28	-1.2	120	-1.3	140	-1.3
Dyspareunia												
1	13	-0.2	91	-0.9	109	-0.7	14	-0.3	105	-1.1	105	-0.7
2	12	-0.2	84	-1.2	108	-1.0	11	0	97	-1.4	105	-1.1
3	13	0.1	79	-1.3	107	-1.0	14	-0.2	96	-1.5	104	-1.2
Pelvic tenderness												
1	18	-0.1	126	-0.6	150	-0.5	26	-0.4	131	-0.7	141	-0.4
2	18	-0.3	120	-0.8	N/A	N/A	24	-0.7	125	-0.9	N/A	N/A
3	20	-0.3	106	-0.9	145	-0.8	27	-0.9	119	-1.1	136	-1.0

Data from Dlugi, AM et al Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo-controlled, double-blind study. Fertil Steril 54: 419-27, 1990
N/A: This measure was not assessed at month 2.
Source: Tables T5.7-T5.8, *5.3.5.1.1, pp 388-413,* Tables T5.7-T5.8, *5.3.5.1.2, pp 410-441 and reference 3*

Table 14 Comparative Responder Analysis (LOCF) in Study 268 vs. Placebo-Controlled Study

Component	Analysis	Study 268				Placebo-Controlled Study			
		DMPA-SC		Lupron		Placebo		Lupron	
		N	%	N	%	N	%	N	%
Dysmenorrhea	ITT-LOCF	135	75.6	137	92.0	21	38.1	27	96.3
Dyspareunia	ITT-LOCF	100	66.0	108	80.6	10	30.0	15	46.7
Pelvic Pain	ITT-LOCF	134	67.2	136	80.1	21	42.9	26	84.6
Pelvic Tenderness	ITT-LOCF	134	67.2	133	72.9	21	33.3	26	73.1
Induration	ITT-LOCF	105	63.8	101	82.2	N/A		N/A	

N/A: This measure was not assessed as a primary efficacy outcome in the placebo-controlled study.
Source: Table 12, *5.3.5.1.1, p 75* and Summary Action Packet for NDA 20-011

Table 15 Shift in Severity Scores in Study 268 vs. Placebo-Controlled Study

Severity Score	Study 268								Placebo-Controlled Study							
	DMPA-SC				Lupron				Placebo				Lupron			
	Baseline		EOT		Baseline		EOT		Baseline		EOT		Baseline		EOT	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Dysmenorrhea	136		136		137		137		21		21		28		28	
Absent	1	0.7	66	48.5	0	0	116	84.7	0	0	1	4.8	1	3.6	26	92.9
Mild	4	2.9	32	23.5	6	4.4	6	4.4	3	14.3	4	19	1	3.6	0	0
Moderate	73	53.7	23	16.9	77	56.2	7	5.1	9	42.9	7	33.3	12	42.9	1	3.6
Severe	58	42.6	15	11.0	54	39.4	8	5.8	9	42.9	9	42.9	14	50	1	3.6
Dyspareunia	136		136		137		137		13		13		17		17	
Absent	1	0.7	35	25.7	2	1.5	50	36.5	3	23.1	4	30.8	2	11.8	7	41.2
Mild	9	6.6	33	24.3	3	2.2	41	29.9	7	53.8	5	38.5	9	52.9	6	35.3
Moderate	64	47.1	17	12.5	64	46.7	12	8.8	3	23.1	3	23.1	5	29.4	3	17.6
Severe	45	33.1	18	13.2	51	37.2	10	7.3	0	0	1	7.7	1	5.9	1	5.9
No Intercourse	17	12.5	33	24.3	17	12.4	24	17.5	--		--		--		--	
Pelvic Pain	136		134		137		136		21		21		28		28	
Absent	0	0	36	26.9	0	0	50	36.8	0	0	2	9.5	2	7.1	12	42.9
Mild	3	2.2	49	36.6	4	2.9	52	38.2	5	23.8	4	19	7	25	13	46.4
Moderate	97	71.3	27	20.1	91	66.4	21	15.4	8	38.1	11	52.4	14	50	2	7.1
Severe	36	26.5	22	16.4	42	30.7	13	9.6	8	38.1	4	19	5	17.9	1	3.6
Pelvic Tenderness	136		136		137		137		21		21		28		28	
Absent	6	4.4	43	31.6	5	3.6	57	41.6	0	0	3	14.3	2	7.1	11	39.3
Mild	29	21.3	52	38.2	31	22.6	54	39.4	7	33.3	6	28.6	10	35.7	15	53.6
Moderate	77	56.6	36	26.5	77	56.2	22	16.1	13	61.9	12	57.1	15	53.6	2	7.1
Severe	24	17.6	5	3.7	24	17.5	4	2.9	1	4.8	0	0	1	3.6	0	0
Induration	136		136		137		137		21		21		28		28	
Absent	40	29.4	80	58.8	38	27.7	94	68.6	3	14.3	3	14.3	9	32.1	14	50
Mild	44	32.4	40	29.4	35	25.5	30	21.9	9	42.9	10	47.6	6	21.4	8	28.6
Moderate	43	31.6	13	9.6	52	38	12	8.8	8	38.1	7	33.3	10	35.7	6	21.4
Severe	9	6.6	3	2.2	12	8.8	1	0.7	1	4.8	1	4.8	3	10.7	0	0

Source: Table T5.5.3, Sponsor submission of October 7, 2004 and Summary Action Packet for NDA 20-011

The FDA statistician reviewed the two pivotal phase 3 studies, Study 268 and 270, and concluded that the results of study 270 support the non-inferiority of DMPA-SC compared to Lupron for efficacy in both the observed cases and intent-to-treat analyses, while the results of study 268 provide supportive efficacy evidence for non-inferiority of DMPA-SC. The statistical reviewer's overall conclusion is that these studies together provide sufficient evidence to support the efficacy of DMPA-SC for the signs and symptoms of endometriosis.

Medical Reviewer's Comment:

1) *is not supported by evidence.*

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data from the two pivotal phase 3 trials and from Study 267BMD, an ongoing phase 3 contraception trial containing two-year BMD safety information were reviewed. Postmarketing data for the DMPA-IM formulation was provided from September 20, 1999 up to a cut-off date of January

31, 2004. Additionally, safety data from two other phase 3 contraception studies (Studies 267 and 269), three PK/PD studies (Studies 265, 271 and 272) and three phase 4 DMPA-IM contraception studies (Studies 234, 009 and 261) were reviewed. Table 16 summarizes the trials and the safety data reviewed in this integrated summary of safety.

Table 16 Summary of Safety Data Reviewed

Study	268	270	267BMD* +	267+	269+	265	271	272	261*	234	009	Post-marketing
Phase	3	3	3	3	3	1/2: PK/PD	1/2: PK/PD	1/2: PK/PD	4	4	4	N/A
Formulation	SC	SC	SC	SC	SC	SC	SC	SC	IM	IM	IM	IM
Indication	E	E	C	C	C	S	S	S	C	C	C	E**
Duration of Tx	6 mos	6 mos	24 mos*	12 mos	12 mos	Single dose	91 days	91 days	ongoing	136 wks	24 mos	N/A
Duration of F/U	12 mos	12 mos	Continuous w/tx	None beyond tx	None beyond tx	112 days	15 days	Up to 365 days	Up to 34 mos	2 yrs	None beyond tx	9/20/99 to 1/31/04
Comparator	Leup	Leup	DMPA-IM	None	None	None	None	DMPA-IM	None	None	Lunelle	N/A
Safety data: AEs	yes	yes	yes	yes	yes	no	no	no	yes	yes	yes	yes
BMD	yes	yes	yes	no	no	no	no	no	no	no	no	no
Kupperman Index	yes	yes	no	no	no	no	no	no	no	no	no	no
Hot flushes	yes	yes	no	no	no	no	no	no	no	no	no	no
Labs	yes	yes	no	no	no	no	no	no	no	no	no	no
Vital signs	yes	yes	no	no	no	no	no	no	no	no	no	no
Bleeding patterns	yes	yes	no	no	no	no	no	no	no	no	no	no
Body weight	yes	yes	no	no	no	no	no	no	no	no	no	no

*Study is ongoing; data is presented through 1/31/04
+ Studies 267, 269 and 267BMD were reviewed thoroughly in the review of NDA 21-583 (contraception) and findings of that review were considered in this safety review.
Indication: E = Endometriosis, C = Contraception, S = Suppression of ovulation (efficacy measure)
**The IM formulation is approved for this indication in other countries.

7.1.1 Deaths

There were no deaths in any of the endometriosis trials. The only death reported in the sources noted above was one occurring in a motor vehicle collision involving a subject in Study 267.

7.1.2 Other Serious Adverse Events

Pooled data from Studies 268 and 270 for SAEs occurring in the treatment phase are presented in Table 17. Rates of SAEs and of all AEs were similar across treatment groups. The only SAEs occurring in more than a single subject during the treatment period were two cases of appendicitis in the Lupron group. Listings of SAEs in each study are presented in Table 18 and Table 19.

Table 17 Adverse Events during Treatment Phase (Studies 268 & 270)

	DMPA-SC		Lupron	
	N	%	N	%
N with AE data	282		278	
Pts w/AEs	218	77.3	208	74.8
Pts w/SAEs	8	2.8	6	2.2
Pts withdrawing due to AEs	9	3.2	11	4.0

Source: Based on Tables 8 & 9, Module 2.7.4, p 17

Medical Reviewer's Comments:

1) ***The applicant included as SAEs occurring during treatment two cases of endometriosis in the DMPA-SC group, and one case of endometriosis in the Lupron group. Since occurrence of the disease under study should not be considered adverse events, these are removed from*** Table 17, ***which was created by the reviewer, but remain in the applicant's*** Table 18 ***and*** Table 19.

2) ***The applicant presents discrepant data on subjects withdrawing due to adverse events, with Table 6 in Module 2.7.4 reporting 12 subjects (4.2%) in each treatment arm. However, these data are superseded by the sponsor's subsequent submission (see*** Table 24***) and do not change the conclusion that the withdrawal rate due to adverse events is similar in the DMPA-SC and Lupron groups.***

3) ***A total of 7 DMPA-SC subjects and 6 Lupron subjects did not have AE data available.***

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Table 18 Listing of Subjects with SAEs (Study 268)

Investigator/ Patient No.	Age (yr)	Preferred Term*	Maximum Intensity	Drug-Related	Outcome	Action Taken
DMPA-SC (Treatment Period)						
/019	30	Pelvic inflammatory disease NOS	Severe	No	Recovered	None
099	31	Calculus renal NOS	Severe	No	Recovered with sequelae	None
/093	23	Unintended pregnancy	NA	No	Recovered	Drug permanently withdrawn
DMPA-SC (Follow-up Period)						
/221	19	Injury NOS	Severe	No	Not recovered	None
/264	22	Endometrial disorder NOS	Severe	No	Recovered with sequelae	None
Leuprolide (Treatment Period)						
157	30	Endometriosis	Severe	No	Not recovered	None
101	32	Abdominal pain lower	Severe	No	Unknown	Drug permanently withdrawn
211	44	Bile duct stone	Severe	No	Recovered	None
167	35	Abdominal pain NOS	Severe	No	Recovered	None
Leuprolide (Follow-up Period)						
056	31	Arterial thrombosis limb	Severe	No	Recovered with sequelae	None
/049	41	Hysterectomy NOS	Moderate	No	Recovered	None
178	38	Optic neuritis NEC	Severe	No	Recovered with sequelae	None
/271	47	Back pain aggravated	Mode rate	No	Recovered with sequelae	None

Source: Table 39, *5.3.5.1.1, p 122*

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Table 19 Listing of Subjects with SAEs (Study 270)

Investigator/ Patient No.	Age (yr)	Preferred Term*	Maximum Intensity	Drug-Related	Outcome	Action Taken
DMPA-SC (Treatment Period)						
;a/0105	26	Endometriosis	Severe	Yes	Recovered	None
/0043	26	Gastritis NOS	Severe	No	Recovered	None
0129	33	Pulmonary embolism	Moderate	No	Recovered	None
/0051	23	Leiomyoma NOS	Severe	No	Recovered	None
/0164	30	Abdominal pain NOS	Severe	No	Recovered	None
		Endometriosis	Severe	No	Recovered	None
		Abdominal pain lower	Severe	No	Recovered	None
		Muscle cramps	Moderate	No	Recovered	None
		Intermenstrual bleeding	Moderate	No	Recovered	None
		Vomiting NOS	Moderate	No	Recovered	None
		Vaginal hemorrhage	Moderate	No	Recovered	None
J/0227	38	Gastroenteritis NOS	Severe	No	Recovered	None
DMPA-SC (Follow-up Period)						
)052	34	Pelvic pain NOS	Severe	No	Recovered	None
/0189	33	Menorrhagia	Moderate	No	Recovered	None
0098	30	Breast neoplasm NOS†	Moderate	Yes	Recovered	None
J/0102	33	Vomiting NOS	Severe	No	Recovered	None
/0249	26	Endometriosis	Severe	No	Recovered	None
		Dysmenorrhea	Severe	No	Recovered	None
Doiq/0291	31	Endometriosis	Severe	No	Recovered	None
)227	38	Uterine hemorrhage	Severe	No	Recovered	None
/0039	32	Menometrorrhagia	Moderate	No	Recovered	None
Leuprolide (Treatment Period)						
0193	33	Appendicitis	Severe	No	Recovered	None
/0041	37	Appendicitis	Severe	No	Recovered	None
)245	19	Concussion	Severe	No	Recovered	None
Leuprolide (Follow-up Period)						
0144	27	Pregnancy NOS	Severe	No	Recovered	None
/106	29	Pelvic pain NOS	Severe	No	Recovered	None
		Ovarian cyst	Moderate	No	Recovered	None
/0041	37	Vaginal prolapse	Moderate	No	Recovered	None
		Complication of delivery NOS	Moderate	No	Recovered	None
/0056	24	Abdominal pain NOS	Severe	No	Recovered with sequelae	None
0221	31	Pregnancy NOS	NA	No	Recovered	None
/0017	29	Pregnancy NOS	NA	No	Recovered	None
		Gestational diabetes	Mild	No	Recovered	None

Source: Table 41, *5.3.5.1.2, p 128*

Medical Reviewer's Comment:

1) ***The SAE of pulmonary embolism (PE) in subject #0129 is considered by the reviewer to be a questionable diagnosis. Chest x-ray is not the standard diagnostic test for PE. The subject had a number of additional diagnoses that could have accounted for her symptoms. Without further diagnostic data, it is difficult to attribute her symptoms to PE.***

Data from Study 267BMD are presented in Table 20. The only SAE occurring in more than a single subject during the treatment period was abdominal pain in the DMPA-SC group. Table 21 lists all SAEs occurring to date in this study.

Table 20 SAEs during Treatment (Study 267BMD)

	DMPA-SC		DMPA-IM	
	n	%	n	%
Total Subjects Reported	263*	100.0	266*	100.0
Total Subjects with Adverse Events	201	76.4	198	74.4
Total Subjects with Serious Adverse Events	8	3.0	4	1.5
Total Subjects with Drug-Related Adverse Events	130	49.4	136	51.1
Total Subjects with Adverse Events Leading to Discontinuation	46	17.5	59	22.2
Deaths	0	0.0	0	0.0

* Data were not available for 3 subjects in the DMPA-SC group and for 2 subjects in the DMPA-IM group; all of these subjects were lost to follow-up.

Source: Table 16, *5.3.5.3.1, p 65*

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Table 21 Listing of Subjects with SAEs (Study 267BMD)

Investigator/ Subject No.	Age (yr)	Preferred Term*	Maximum Intensity	Drug-related	Outcome	Action Taken
DMPA-SC						
— 2263	23	Thyroid carcinoma NOS	Severe	No	Recovered	None
— 2450	18	Congenital jaw malformation NOS	Moderate	No	Recovered	None
/382	28	Appendicitis	Severe	No	Recovered	None
— /2497	18	Suicide attempt	Moderate	No	Recovered	None
		Suicide attempt	Moderate	No	Recovered	Drug permanently withdrawn
- r/2422	20	Asthma aggravated	Severe	No	Recovered	None
— 2116	32	Breast cancer stage II	Severe	No	Not recovered	Drug permanently withdrawn
— /2230	23	Diverticulitis NOS	Severe	No	Recovered	None
		Abdominal pain NOS	Severe	No	Recovered	None
— /2088	23	Abdominal pain NOS	Severe	Not Reported	Unknown	None
DMPA-IM						
— /2254	24	Unintended pregnancy	Severe	Yes	Unknown	Drug permanently withdrawn
— 2311	35	Cerebrovascular accident NOS	Severe	No	Recovered with sequelae	Drug permanently withdrawn
		Cholelithiasis	Mild	No	Recovered	None
		Venous thrombosis deep limb	Severe	No	Recovered with sequelae	Drug permanently withdrawn
— 2206	26	Appendicitis	Severe	No	Recovered	None
— 2491	30	Road traffic accidient	Severe	No	Recovered	None

Source: Table 20, *5.3.5.3.1, p 87*

Medical Reviewer's Comments:

1) ***In response to a possible association of DMPA-SC with worsening depression and the suicide attempts of subject #2497, a Safety Alert Report was issued to all investigators by the applicant. This subject had a history of multiple psychiatric diagnoses and prior suicide attempts and had experienced significant losses over the course of her enrollment in the study, thus a causal association with DMPA cannot be definitively determined.***
2) ***Subject #2116 began treatment in June 2001, not having had a pre-enrollment mammogram. She received four injections, the last in — , one month later a mammogram and subsequent biopsy were performed, culminating in a diagnosis of***

Stage II invasive ductal breast cancer. It is unlikely that DMPA use was associated in a causal manner with this diagnosis 11 months after initiating treatment.

3) ***Subject #2311, aged 35, was first dosed in August 2001, and received her last dose in — — That same day, she was hospitalized for cholelithiasis and surgical gallstone removal; four days after discharge, she had a stroke and became comatose. She recovered with hemiplegic sequelae, but experienced a deep vein thrombosis (DVT) approximately two weeks following discharge from this second hospitalization. The reviewer considers that this event is possibly related to DMPA use.***

7.1.3 Dropouts and Other Significant Adverse Events

The proportions of subjects who withdrew prior to completion of the treatment and follow-up phases of the two studies are shown in Table 22 and Table 23. Overall, the proportion withdrawing for any reason was higher in the DMPA-SC group during the treatment phase, and equivalent for the two groups during follow-up. For the DMPA-SC group at both phases of the study, and the Lupron group during follow-up, the most common reason for withdrawal was listed as "consent withdrawn." Further information concerning consent withdrawal provided by the applicant results in the following refined breakdown of reasons for withdrawal, listed by study in Table 24.

Table 22 Withdrawals during Treatment Phase (Pooled Data)

Patient Disposition	DMPA-SC N = 289		Leuprolide N = 284	
	n	%	n	%
Study completion				
Completed treatment period	226	78.2	238	83.8
Did not complete treatment period	63	21.8	46	16.2
Reason for withdrawal				
Lost to follow-up	15	5.2	14	4.9
Adverse event	12	4.2	12	4.2
Protocol violation	7	2.4	10	3.5
Consent withdrawn	29	10.0	10	3.5

Source: Table 6, Module 2.7.4, p 15

Table 23 Withdrawals during Follow-up Phase (Pooled Data)

	DMPA-SC N = 226		Leuprolide N = 238	
	n	%	n	%
Total Who Completed Follow-up	136	60.2	144	60.5
Total Withdrawn	90	39.8	94	39.5
Reasons for Withdrawal:				
Adverse Event	19	8.4	15	6.3
Protocol Violation	17	7.5	20	8.4
Consent Withdrawn	36	15.9	46	19.3
Lost to Follow-up	18	8.0	13	5.5

Source: Table 1, Module 2.7.4 Update, p 4

Table 24 Studies 268 & 270: Detailed Reason for Withdrawal from Treatment

Patient Disposition	Study 268				Study 270			
	DMPA-SC N=136		Lupron N=138		DMPA-SC N=153		Lupron N=146	
	N	%	N	%	N	%	N	%
Completed Tx	88	64.7	102	73.9	138	90.2	136	93.2
Withdrew from Tx	48	35.3	36	26.1	15	9.8	10	6.8
Reason for Withdrawal								
Lost to follow-up	14	10.3	11	8.0	1	0.7	3	2.1
Adverse event	12	8.8	11	8.0	3	2.0	2	1.4
Lack of efficacy	7*	5.1	1	0.7	1***	0.7	0	0
Problems w/inv'r or site	7**	5.1	1	0.7	0	0	0	0
Protocol violation	4	2.9	7	5.1	3	2.0	3	2.1
Personal Issues	4***	2.9	3***	2.2	2#	1.3	0	0
Unknown	0	0	2***	1.4	5***	3.3	2	1.4

* 5 subjects also had concomitant AEs at the time of withdrawal
** 3 subjects also had concomitant AEs at the time of withdrawal
*** 1 subject also had concomitant AEs at the time of withdrawal
# 2 subjects also had concomitant AEs at the time of withdrawal
Source: Based on Tables 2, 3a & 3b, pp 6-8, August 31, 2004 communication from applicant

Medical Reviewer's Comments:

1) ***One DMPA-SC subject in Study 268 initially classified as "consent withdrawn" was subsequently listed as withdrawing due to "spotting, no relief of pain" and listed in both adverse event and lack of efficacy categories by the applicant. This reviewer has assigned her to the lack of efficacy category in the table above.***
2) ***Review of individual study data reveals a higher overall withdrawal rate in Study 268, which is seen across all categories of reason for withdrawal except "unknown."***
3) ***Within Study 268, there is a higher frequency of withdrawal due to lack of efficacy and problems with investigator/site in the DMPA-SC group.***

7.1.3.1 Overall profile of dropouts

Baseline data, where appropriate, and efficacy responses are compared below between subjects completing the six-month treatment period and subjects who withdrew early from treatment. Table 25 displays data on the responder rates for each group of subjects, Table 26 shows data on the composite score and Table 27 has data on the mean change in each pain category.

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Table 25 Comparison of Response Rates in Completers and Subjects who Withdrew from Treatment (ITT-OC)

Variable & Measure	Study 268				Study 270			
	DMPA-SC		Lupron		DMPA-SC		Lupron	
	C	E	C	E	C	E	C	E
Dysmenorrhea N	88	17	100	10	135	5	135	2
Month 6/ Last visit	90.9%	58.8%	97.0%	80.0%	91.1%	60.0%	97%	100%
Pelvic Pain N	86	17	101	11	136	5	136	2
Month 6/ Last visit	82.6%	41.2%	87.1%	63.6%	81.6%	80.0%	91.2%	100%
Dyspareunia N	65	11	79	9	88	4	88	2
Month 6/ Last visit	78.5%	54.5%	84.8%	77.8%	83.0%	25%	88.6%	50%
Pelvic Tenderness N	85	17	98	10	133	4	128	2
Month 6/ Last visit	76.5%	47.1%	80.6%	70.0%	81.2%	50%	85.2%	50%
Induration N	66	13	75	9	117	2	119	1
Month 6/ Last visit	74.2%	53.8%	86.7%	88.9%	71.8%	50%	79.8%	0%

C=completers, E= early withdrawals
Source: Tables T5.11.1 & T5.12.1, *5.3.5.1.1, pp 634-45, 849-53* and TablesT5.11.1 & T5.12.1, *5.3.5.1.2, pp 600-11, 831-38*

Medical Reviewer's Comment:

1) ***In Study 268, early withdrawers almost always responded less than completers in both treatment arms, but this trend was magnified in the DMPA-SC group.***
2) ***The numbers of early withdrawers in Study 270 are too small to allow reasonable comparison of response rate to those subjects who completed treatment.***

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Table 26 Baseline and Mean Change at End of Treatment in Composite Score in Completers and Subjects who Withdrew from Treatment (ITT-OC)

Variable & Measure	Study 268				Study 270			
	DMPA-SC		Lupron		DMPA-SC		Lupron	
	C	E	C	E	C	E	C	E
Composite Score N	64	11	76	8	94	4	91	2
Baseline	9.9	9.5	10.4	10.4	9.3	7.3	9.7	9.0
Month 6/ Last visit Change	-6.2	-2.7	-7.7	-6.5	-6.3	-2.5	-7.3	-2.0
Composite Score w/o Dyspareunia N	85	17	97	10	135	5	132	2
Baseline	7.5	8.1	7.9	8.3	7.4	5.4	7.8	6.5
Month 6/ Last visit Change	-4.8	-2.6	-6.0	-4.4	-5.0	-2.6	-6.0	-1.5

C=completers, E= early withdrawals
Source: Tables T5.9.1 & T5.10.1, *5.3.5.1.1, pp 448-52, 541-45* and Tables T5.9.1 & T5.10.1, *5.3.5.1.2, pp 442-5, 521-24*

Medical Reviewer's Comment:

1) ***In Study 268, with or without the inclusion of dyspareunia, early withdrawers always benefited less than completers in both treatment arms, but this trend was magnified in the DMPA-SC group.***
2) ***The numbers of early withdrawers in Study 270 are too small to allow reasonable comparison of mean change to those subjects who completed treatment.***

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Table 27 Comparison of Baseline Status and Mean Change in B&B Score in Completers and Subjects who Withdrew from Treatment

Variable & Measure	Study 268				Study 270			
	DMPA-SC		Lupron		DMPA-SC		Lupron	
	C	E	C	E	C	E	C	E
Dysmenorrhea N	88	17	100	10	137	5	136	2
Baseline	2.4	2.5	2.4	2.0	2.2	1.8	2.4	2.5
Month 6/ Last visit	-1.8	-1.1	-2.2	-1.4	-1.7	-0.8	-2.2	-1.5
Pelvic Pain N	86	17	101	11	136	5	136	2
Baseline	2.2	2.4	2.2	2.5	2.1	1.8	2.2	2.0
Month 6/ Last visit	-1.2	-0.5	-1.4	-1.2	-1.2	-0.8	-1.5	-1.0
Dyspareunia N	65	11	81	9	94	4	91	2
Baseline	2.3	2.1	2.4	2.1	1.9	1.8	2.0	2.5
Month 6/ Last visit	-1.4	-0.5	-1.6	-1.2	-1.2	-0.3	-1.4	-0.5
Pelvic Tenderness N	87	17	100	11	136	5	132	2
Baseline	1.9	1.9	1.9	1.8	1.7	1.2	1.8	1.5
Month 6/ Last visit	-1.0	-0.6	-1.3	-0.8	-1.1	-0.6	-1.3	0
Induration N	87	17	100	11	136	5	132	2
Baseline	1.1	1.3	1.3	1.6	1.4	0.6	1.5	0.5
Month 6/ Last visit	-0.7	-0.4	-1.0	-0.8	-0.9	-0.4	-1.1	1.0

C=completers, E= early withdrawals
Source: Tables T5.7 & 5.8, *5.3.5.1.1, pp 414-47* and Tables T5.7 & 5.8, *5.3.5.1.2, pp 410-41*

Medical Reviewer's Comment:

1) ***In Study 268, the mean change was always lower in the early withdrawers in both treatment arms, but the difference between completers and early withdrawers was generally greater in the DMPA-SC group.***
2) ***The number of early withdrawers in Study 270 is too small to allow reasonable comparison of mean change to those subjects who completed treatment.***
3) ***Across all three comparisons in Study 268, there is little evidence that early withdrawers consistently represented subjects with more severe disease at entry. That their response was lower than completers can be due either to their withdrawal prior to month 6, while the treatment benefit continued to rise over time, or due to the selective withdrawal of subjects who responded poorly to treatment. The fact that the discrepancy was greater in the DMPA-SC subjects, coupled with the data showing that the maximal mean change generally occurred later in the DMPA-SC group than in the Lupron group, favors the former explanation.***

7.1.3.2 Adverse events associated with dropouts

When withdrawals originally considered "consent withdrawal" are reclassified, similar proportions (5.2% in the pooled DMPA-SC groups and 4.6% in the pooled Lupron groups) in each treatment group withdrew due to adverse events in the treatment period (see Table 24). In Study 267BMD,

17.5% of subjects taking DMPA-SC and 22.5% of subjects receiving DMPA-IM withdrew from the study due to adverse events, with increased weight being the most common event leading to withdrawal. These rates are higher than those seen in the endometriosis study, as would be expected with ongoing treatment and a longer ascertainment period (i.e., 24 months vs. 6 months).

7.1.3.3 Other significant adverse events

The protocol-defined primary safety endpoint in the two pivotal trials was BMD loss after six months of treatment. Additional BMD safety data was presented from an ongoing contraception study, Study 267BMD, in which subjects had ongoing treatment, with BMD data for up to 2 years reported in the safety update. This is discussed in Section 7.1.12.1.

Additional, secondary, safety endpoints included assessment of hypoestrogenic symptoms using the Kupperman Index and patient-reported frequency and severity of hot flushes, clinical laboratory evaluations, blood pressure data and bleeding patterns (See Sections 7.1.12.2, 7.1.12.3, 7.1.7, 7.1.8 and 7.1.3.3.3, respectively). Other adverse events of concern in the DMPA-SC trials include injection site reactions and depression.

7.1.3.3.1 Injection Site Reactions

In Studies 268 and 270, a total of 13 DMPA-SC subjects (4.6%) experienced 17 injection site reactions, compared to 6 Lupron subjects (2.2%) who experienced 6 reactions. None were considered severe. All except one in each treatment arm occurred in Study 268. One DMPA-SC subject withdrew due to an injection site reaction.

In Study 267BMD, injection site reactions occurred in 8% of DMPA-SC subjects and 0.4% of DMPA-IM subjects, with a total of 26 reactions occurring. Almost half occurred at the first injection. One-third of the DMPA-SC cases were classified as "injection site atrophy," which included investigator descriptions of indentation at the site.

Medical Reviewer's Comments:

1) ***The single Lupron subject (#0041) in Study 270 who experienced an injection site reaction received the drug subcutaneously and monthly. All six Lupron subjects in Study 268 received IM Lupron.***
2) ***The applicant acknowledges that the contraceptive trials indicate a stronger association of SC administration than IM administration with injection site reactions.***

7.1.3.3.2 Depression

In the pooled data from Studies 268 and 270, 4.3% of DMPA-SC subjects and 5.8% of Lupron subjects reported AEs of depression. A single Lupron subject withdrew due to this AE.

Depression or aggravation of depression occurred in 6.8% of DMPA-SC subjects and 5.6% of DMPA-IM subjects in Study 267BMD.

Medical Reviewer's Comment:

1) ***A recent Canadian national survey[4] reports an annual incidence of self-reported depression in women of 5.7%, with highest rates in reproductive aged women. Thus, depression rates reported in these trials are within the incidence expected in the general female population.***

7.1.3.3.3 Bleeding Pattern Data

Bleeding data, derived from the patient diaries, was evaluated over 30 day intervals, beginning with receipt of the first injection of study drug. The initial interval contained the menstrual period during which the first injection was given; thus, virtually all subjects reported some bleeding. Table 28

presents data on the frequency of amenorrhea and categorical frequency of bleeding in those subjects who did not become amenorrheic. From month 2 on, the frequency of amenorrhea was much greater in the Lupron group. The proportion of subjects with frank bleeding was much greater in the DMPA-SC group than the Lupron group at all monthly intervals beyond the first. In those subjects who did not experience amenorrhea, the duration of bleeding or spotting during the last monthly interval during treatment tended to be longer in the DMPA-SC group, with over half the women experiencing bleeding that lasted longer than a typical menstrual period; the comparative proportion in the Lupron group was only 2%.

The applicant also reported subjects' characterization of their bleeding patterns during two 90-day intervals during the treatment phase. The most frequent characterizations of bleeding pattern in the DMPA-SC group were "prolonged and irregular" (27%) in the first interval and "prolonged" (23%) in the second interval, while in the Lupron group, they were "irregular" (38-43%) in the first interval and "amenorrhea" (80-84%) in the second interval.

Table 28 Bleeding Patterns by Treatment Group (Studies 268 & 270)

Outcome	30 Day Interval	DMPA-SC N=289		Lupron N=284	
		N	%	N	%
Percent of subjects with bleeding	1	240	80.5	251	89.2
	2	242	57.9	244	9.0
	3	239	52.3	239	9.2
	4	220	42.2	234	7.2
	5	207	48.3	224	4.5
	6	173	46.8	180	3.4
Percent of subjects with spotting only	1	240	13.8	251	9.6
	2	242	24.4	244	13.9
	3	239	27.2	239	5.4
	4	220	29.5	234	5.1
	5	207	27.1	224	5.8
	6	173	28.9	180	5.6
Percent of subjects with amenorrhea	1	240	5.8	251	1.2
	2	242	17.8	244	77.0
	3	239	20.5	239	85.4
	4	220	28.2	234	87.6
	5	207	24.6	224	89.7
	6	173	24.3	180	91.1
Bleeding or spotting duration at end of treatment	# days/mo	173		180	
	0		24.3		91.1
	1-7		21.4		6.7
	8-10		6.9		1.1
	11-30		47.4		1.1

Source: Based on Tables 1D, 1L, 3D & 3L, pp 5-6, 11-12, September 15, 2004 communication from applicant

In addition, AE data indicate that 4.3% of DMPA-SC subjects as compared to 0.7% of Lupron subjects experienced vagina/uterine hemorrhage classified as an adverse event during the treatment period. A single DMPA-SC subject in Study 270 reported vaginal hemorrhage as an SAE.

In Study 267BMD, bleeding events comprising "intermenstrual bleeding," "menometrorrhagia," "metrorrhagia" and vaginal hemorrhage occurred in 9.9% of DMPA-SC subjects and 12% of DMPA-IM subjects.

Medical Reviewer's Comment:

1) ***The bleeding seen in DMPA-SC subjects may impact the acceptability of the treatment; however, data from contraceptive trials and from the existing IM formulation suggest that most women will become amenorrheic on DMPA with longer duration of use.***

7.1.4 Other Search Strategies

No signals of toxicity requiring additional investigation were noted.

7.1.5 Common Adverse Events

Table 29 shows the adverse events occurring with >= 3% incidence in the two pivotal trials during the treatment or follow-up phases. Events that occurred during the treatment phase with at least twice the frequency in DMPA-SC vs. Lupron subjects were:

- abdominal pain
- fatigue
- injection site reactions
- intermenstrual bleeding
- pelvic pain
- vaginal/uterine hemorrhage

Events occurring at least twice as frequently during treatment in the Lupron group were:

- myalgia
- insomnia
- vulvovaginal dryness
- hot flushes.

During follow-up, pharyngitis, intermenstrual bleeding, menorrhagia and uterine/vaginal bleeding occurred with twice the frequency in the DMPA-SC group.

Medical Reviewer's Comment:

1) ***The 15 pregnancies occurring in the follow-up period were classified by the applicant as AEs for unknown reasons.***
2) ***Among treatment-emergent AEs, the most relevant occurrences likely to be treatment-related are injection site reactions and vaginal/uterine bleeding in the DMPA-SC subjects and hypoestrogenic symptoms (hot flushes, vulvovaginal dryness) in the Lupron subjects.***

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Table 29 Most Common Adverse Events (>= 3%) During Treatment or Follow-up

	Treatment				Follow-up			
Adverse Event	DMPA-SC		Lupron		DMPA-SC		Lupron	
	N	%	N	%	N	%	N	%
Total N	282		278		226		238	
N with at least one AE	218	77.3	208	74.8	134	59.3	128	53.8
GI Disorders								
Abdominal pain	17	6.0	8	2.9	8	3.5	9	3.7
Constipation	10	3.5	6	2.2				
Diarrhea	13	4.6	9	3.2				
Nausea	31	11.0	32	11.5	10	4.4	7	2.9
Vomiting	10	3.5	5	1.8				
General Disorders & Admin Site Conditions								
Fatigue	13	4.6	4	1.4				
Influenza	24	8.5	22	7.9	6	2.7	12	5.0
Injection site reactions	13	4.6	6	2.2				
Infections & Infestations								
Bronchitis	7	2.5	10	3.6				
Nasopharyngitis	22	7.8	22	7.9	18	8.0	13	5.5
Pharyngitis					7	3.1	2	0.8
Sinusitis	14	5.0	17	6.1	8	3.5	6	2.5
URI	12	4.3	11	4.0	8	3.5	5	2.1
UTI	9	3.2	8	2.9	7	3.0	8	3.3
Vaginitis	9	3.2	10	3.6	17	7.6	10	4.2
Musculoskeletal, Connective Tissue & Bone Disorders								
Arthralgia	17	6.0	13	4.7	7	3.1	12	5.0
Back pain	19	6.7	19	6.8	8	3.5	10	4.2
Limb pain	8	2.8	10	3.6				
Myalgia	4	1.4	10	3.6				

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Nervous System Disorders								
Dizziness	7	2.5	10	3.6				
Headache	34	12.1	41	14.7	9	4.0	11	4.6
Insomnia	6	2.1	17	6.1				
Migraine	6	2.1	9	3.2				
Pregnancy, Puerperium & Perinatal Conditions								
Pregnancy					6	2.7	9	3.8
Psychiatric Disorders								
Depression	12	4.3	16	5.8	10	4.4	13	5.5
Decreased libido	10	3.5	18	6.5				
Reproductive System & Breast Disorders								
Breast pain/tenderness	16	5.7	12	4.3	13	5.8	11	4.7
Intermenstrual bleeding	27	9.6	4	1.4	7	3.1	1	0.4
Menorrhagia					7	3.1	1	0.4
Pelvic pain	9	3.2	3	1.1	7	3.1	8	3.4
Vaginal /uterine hemorrhage	12	4.3	2	0.7	8	3.6	1	0.4
Vulvovaginal dryness	3	1.1	11	4.0				
Skin Disorders								
Acne	12	4.3	9	3.2				
Vascular Disorders								
Hot flushes	12	4.3	41	14.7				

Source: Based on Tables 11, Module 2.7.4, pp 18-19 and T3.1, Module 2.7.4 Update, pp 1-15

In Study 267BMD, 76% of DMPA-SC subjects experienced at least one adverse event, similar to the findings in the treatment phases of the endometriosis trials. The most common events (>5%) were:

- headache
- weight increased
- nasopharyngitis
- injection site reactions
- acne
- depression
- UTI
- sinusitis

7.1.5.1 Eliciting adverse events data in the development program

In Studies 268 and 270, all adverse events were recorded; however, signs and symptoms of endometriosis-associated pain, anticipated menstrual cycle changes and hypoestrogenic symptoms were not collected on the AE form of the CRF. Adverse events were defined as any untoward medical occurrence in a patient receiving study drug, regardless of potential causality. Directly observed and spontaneously reported AEs were recorded, and subjects were queried about health problems at every clinic visit. The reporting period spanned from the administration of the first dose

of study drug until the final clinic visit, except for pregnancies, which were followed until conclusion if that were the later event.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

MedDRA Version 2.3 was used to categorize AEs, which were further classified by system/organ class and preferred term. Spot-checking of categorization based on investigators' verbatim comments indicates that events were appropriately categorized.

7.1.5.3 Incidence of common adverse events

See Section 7.1.5.

7.1.5.4 Common adverse event tables

See Table 29.

7.1.5.5 Identifying common and drug-related adverse events

A summary of AEs considered drug-related by the applicant is presented in Table 30. The applicant did not consider any SAEs to be drug-related, except one event of endometriosis in a DMPA-SC subject in Study 270.

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Table 30 Drug-Related Adverse Events During Treatment in >=1% of Subjects (Studies 268 & 270)

System/Organ Class* Preferred Term	DMPA-SC		Leuprolide	
	n	%	n	%
Total Reported	282	100.0	278	100.0
Patients with at least one Drug-Related Adverse Event	137	48.6	118	42.4
Cardiac Disorders				
Palpitations	1	0.4	4	1.4
Gastrointestinal Disorders				
Abdominal distension	3	1.1	2	0.7
Nausea†	21	7.4	16	5.8
General Disorders and Administration Site Conditions				
Fatigue	6	2.1	4	1.4
Injection site reactions†	12	4.3	5	1.8
Infections and Infestations				
Vaginitis	3	1.1	4	1.4
Investigations				
Weight increased	7	2.5	7	2.5
Musculoskeletal, Connective Tissue, and Bone Disorders				
Arthralgia	3	1.1	3	1.1
Pain in limb			4	1.4
Polyarthralgia	1	0.4	4	1.4
Nervous System Disorders				
Dizziness (exc vertigo)	1	0.4	6	2.2
Formication	3	1.1	1	0.4
Headache†	20	7.1	25	9.0
Hypersomnia	6	2.1	2	0.7
Insomnia NEC	4	1.4	9	3.2
Migraine†	2	0.7	4	1.4
Paresthesia NEC			3	1.1
Psychiatric Disorders				
Anxiety†	1	0.4	3	1.1
Depression†	6	2.1	7	2.5
Irritability	2	0.7	4	1.4
Libido decreased†	9	3.2	13	4.7
Mood disorder†	4	1.4	4	1.4

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System/Organ Class* Preferred Term	DMPA-SC		Leuprolide	
	n	%	n	%
Total Reported	282	100.0	278	100.0
Reproductive System and Breast Disorders				
Breast pain/tenderness†	15	5.3	10	3.6
Galactorrhea			3	1.1
Intermenstrual bleeding	26	9.2	2	0.7
Menorrhagia	3	1.1	1	0.4
Ovarian cyst			3	1.1
Pelvic pain NOS	4	1.4		
Uterine hemorrhage	8	2.8	1	0.4
Vaginal hemorrhage	10	3.5	2	0.7
Vulvovaginal dryness	1	0.4	10	3.6
Skin & Subcutaneous Tissue Disorders				
Acne†	8	2.8	6	2.2
Alopecia	1	0.4	4	1.4
Dermatitis†	4	1.4		
Vascular Disorders				
Hot flushes NOS	12	4.3	37	13.3

*MedDRA version 2.3
†Includes more than one MedDRA preferred term. See Listing L1.12.
Source: Table 12, *2.7.4, pp 20-1*

Medical Reviewer's Comments:

1) ***As noted previously, the reviewer would not consider endometriosis to be an SAE; thus it cannot be considered a drug-related SAE. Lack of efficacy does not constitute an adverse event.***
2) ***The only drug-related AEs that are meaningfully different between the treatment groups are injection site reactions and bleeding complaints (intermenstrual bleeding, uterine/vaginal bleeding) in the DMPA-SC group and hypoestrogenic symptoms (hot flushes, vulvovaginal dryness, insomnia) in the Lupron group.***

7.1.5.6 Additional analyses and explorations

No safety signals of sufficient concern to warrant further investigation were noted.

7.1.6 Less Common Adverse Events

No additional adverse event signals of concern were noted.

7.1.7 Laboratory Findings

Laboratory assessments (hematology, serum chemistries including hepatic panels, and urinalysis) were obtained at baseline and at months 3 and 6. At selected sites in Poland and Sweden (Study 270), coagulation and lipid panels were also obtained. Neither clinically significant changes nor important differences between treatment groups were found for hematology variables. Liver function tests, specifically AST, ALT and alkaline phosphatase, tended to increase over the course of treatment in the Lupron groups, while showing little change to a slight decrease in the DMPA-SC groups. No clinically important changes in urinalysis parameters were seen in either treatment group. Baseline values and mean and median changes with treatment from the pooled studies are listed for selected tests of interest in Table 31.

Table 31 Laboratory Assays in Studies 268 and 270 (Pooled Data)

Test and Visit	Results	DMPA-SC N=289	Lupron N=284
Hematocrit (fraction)			
Baseline	N	269	261
	Mean (SD)	0.40 (0.04)	0.40 (0.03)
Month 3	N	211	216
	Mean Change (SD)	-0.001 (0.026)	-0.003 (0.025)
	Median Change	-0.003	0
Month 6	N	189	196
	Mean Change (SD)	0.002 (0.028)	0 (0.026)
	Median Change	0	0
Hemoglobin (g/L)			
Baseline	N	279	267
	Mean (SD)	132.4 (12.7)	133.6 (11.3)
Month 3	N	222	224
	Mean Change (SD)	1.1 (8.4)	0.7 (8.0)
	Median Change	0	0
Month 6	N	202	203
	Mean Change (SD)	1.8 (9.0)	1.0 (0)
	Median Change	1.5	0
AST (U/L)			
Baseline	N	283	273
	Mean (SD)	20.0 (6.1)	21.6 (8.8)
Month 3	N	237	244
	Mean Change (SD)	-0.5 (5.0)	3.5 (14.1)
	Median Change	-1.0	2.5
Month 6	N	214	223
	Mean Change (SD)	0.2 (8.1)	2.4 (9.9)
	Median Change	-1.0	2.0
ALT (U/L)			
Baseline	N	283	273
	Mean (SD)	17.8 (9.0)	20.0 (15.6)
Month 3	N	237	244
	Mean Change (SD)	0.1 (7.9)	5.4 (22.7)
	Median Change	1.0	5.0
Month 6	N	214	223
	Mean Change (SD)	1.3 (13.5)	3.8 (16.0)
	Median Change	1.0	3.0
GGT (U/L)			
Baseline	N	283	273
	Mean (SD)	19.6 (18.5)	19.0 (10.8)
Month 3	N	237	244
	Mean Change (SD)	-0.2 (10.0)	3.4 (12.9)
	Median Change	0	2.0
Month 6	N	214	223
	Mean Change (SD)	1.5 (19.1)	2.3 (9.4)
	Median Change	1.0	1.0

Alk Phos (U/L)			
Baseline	N	283	273
	Mean (SD)	73.3 (22.0)	75.4 (22.0)
Month 3	N	237	244
	Mean Change (SD)	-4.0 (10.9)	8.1 (13.1)
	Median Change	-3.0	7.5
Month 6	N	214	223
	Mean Change (SD)	-0.6 (17.0)	16.8 (14.0)
	Median Change	-2.0	15.0
Total Bili (µmol/L)			
Baseline	N	283	272
	Mean (SD)	8.81 (4.39)	8.76 (4.69)
Month 3	N	237	242
	Mean Change (SD)	0.57 (3.84)	0.14 (3.76)
	Median Change	0	0
Month 6	N	214	222
	Mean Change (SD)	0.59 (3.71)	-0.73 (3.71)
	Median Change	0	0
Creatinine (µmol/L)			
Baseline	N	283	273
	Mean (SD)	65.5 (11.6)	64.8 (12.2)
Month 3	N	237	244
	Mean Change (SD)	2.2 (9.8)	2.7 (9.6)
	Median Change	0	0
Month 6	N	214	223
	Mean Change (SD)	2.5 (10.4)	1.6 (11.0)
	Median Change	0	0

Source: Tables T1.9.1 & T1.9.3, 5.3.5.3.1, *pp 452-60, 479-85*

Medical Reviewer's Comment:

1) ***Despite increased incidence of bleeding in the DMPA-SC group, there was no demonstrable impact on hemoglobin or hematocrit.***
2) ***Inspection of laboratory data for subjects who withdrew from treatment early does not reveal any clinically relevant discrepancies from that reported for completers.***

Lipid studies were done in Study 268 under non-fasting conditions and in a subset of Study 270, fasting profiles including VLDL were conducted. Changes from baseline seen in both treatment groups were not considered clinically significant.

In addition, the Study 270 subgroup had coagulation assays done, which included platelet count, PTT, aPTT, fibrinogen, Factor VII, Factor X, ATIII, protein C and free protein S. Statistically significant differences between treatment groups in median change from baseline to end of treatment were found for Factor VII and Protein C, although the clinical relevance of these differences is unclear. Selected variables of interest are displayed in Table 32.

Table 32 Coagulation Assays in Study 270 (Subgroup)

Test and Visit	Results	DMPA-SC N=45	Lupron N=47
Platelets (10*9/L)			
Baseline	N	37	40
	Mean (SD)	266.9 (78.1)	245.1 (60.4)
Month 3	N	24	31
	Mean Change (SD)	-27.5 (56.3)	-5.0 (32.0)
	Median Change	-23.5	3.0
Month 6	N	27	26
	Mean Change (SD)	-20.1 (43.2)	10.7 (43.6)
	Median Change	-13.0	8.0
Factor VII (%)			
Baseline	N	40	43
	Mean (SD)	1.09 (0.17)	1.07 (0.13)
Month 3	N	30	38
	Mean Change (SD)	0.02 (0.25)	0.16 ((0.27)
	Median Change	0.01	0.15
Month 6	N	32	36
	Mean Change (SD)	0.11 (0.19)	0.24 (0.20)
	Median Change	0.09	0.30
Protein C (%)			
Baseline	N	40	43
	Mean (SD)	0.95 (0.21)	0.90 (0.15)
Month 3	N	30	38
	Mean Change (SD)	0.03 (0.24)	0.12 (0.22)
	Median Change	-0.02	0.06
Month 6	N	32	36
	Mean Change (SD)	0.08 (0.19)	0.23 (0.23)
	Median Change	0.06	0.23

Source: Tables T1.9.11, *5.3.5.3.1, pp 452-60, 479-85*

7.1.7.1 Overview of laboratory testing in the development program

See Section 7.1.7.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory data were reviewed for the two pivotal, comparator-controlled studies for the endometriosis indication. Other studies providing safety data were either designed for the contraception indication, reviewed for NDA 21-583, or were phase 1/2 PK/PD studies, which typically had no comparator.

7.1.7.3 Standard analyses and explorations of laboratory data

See Section 7.1.7.

7.1.7.4 Additional analyses and explorations

The more detailed analyses of lipid and coagulation profiles undertaken in a subset of Study 270 are discussed in Section 7.1.7.

7.1.7.5 Special assessments

No additional special laboratory assessments were conducted.

7.1.8 Vital Signs

In both studies, changes in seated blood pressure were small and not judged to be clinically relevant. Pooled data are presented in Table 33.

Table 33 Mean Change (SD) in Blood Pressure by Treatment Group

Visit	Systolic		Diastolic	
	DMPA-SC	Lupron	DMPA-SC	Lupron
Mean Baseline BP	113.1 (10.6)	114.3 (12.3)	71.9 (8.8)	71.7 (9.6)
Month 1	-0.7 (11.2)	-0.4 (11.5)	-0.7 (9.1)	0.7 (8.6)
Month 2	0.7 (11.7)	-0.9 (11.8)	-0.4 (9.5)	0.4 (9.6)
Month 3	-2.3 (11.1)	-1.6 (11.9)	-0.6 (9.4)	0.2 (10.2)
Month 4	-0.6 (11.4)	-1.2 (12.5)	-1.3 (9.4)	0 (10.8)
Month 5	-0.5 (10.6)	-1.8 (12.9)	-1.1 (9.7)	0 (11.0)
Month 6	-2.0 (11.6)	-3.0 (11.3)	-2.1 (9.8)	-0.6 (9.9)
Month 12	-1.7 (11.1)	-2.0 (13.7)	-1.8 (9.0)	-1.5 (10.6)
Month 18	-2.6 (11.1)	-2.5 (13.6)	-2.0 (9.7)	-1.0 (11.9)

Source: Based on Table T4.1, *5.3.5.3.1, pp 1-8*

7.1.8.1 Overview of vital signs testing in the development plan

Seated systolic and diastolic blood pressures were the only vital signs evaluated in the clinical trials.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs data were reviewed for the two pivotal, comparator-controlled studies for the endometriosis indication. Other studies providing safety data were either designed for the contraception indication, reviewed for NDA 21-583, or were phase 1/2 PK/PD studies, which typically had no comparator.

7.1.8.3 Standard analyses and explorations of vital signs data

See Section 7.1.8.

7.1.8.4 Additional analyses and explorations

No additional analyses and explorations were conducted.

7.1.9 Electrocardiograms (ECGs)

Electrocardiographic data was not obtained in any of the trials. Depo-Provera has been marketed to reproductive aged women for contraception since 1992 with no evidence of effect on ECG parameters. A search of PubMed revealed a single study[5] evaluating the effect on MPA on ECG variables, which noted a 3.9 msec shortening of the QRS interval.

7.1.10 Immunogenicity

Data on potential Immunogenicity was not submitted by the applicant. A search of PubMed on the term "medroxyprogesterone acetate AND immunogenicity" revealed no relevant publications.

7.1.11 Human Carcinogenicity

A single case of breast cancer was diagnosed during contraceptive Study 276BMD. A search of PubMed on the term "medroxyprogesterone acetate AND human carcinogenicity" revealed eight publications, dating from 1979 to 1993. The most recent article[6] reviewed the two well-conducted case-control studies available and concluded that while the use of DMPA does not increase the overall risk of breast cancer, it may be associated with an increased risk of breast cancer that is diagnosed prior to age 35.

7.1.12 Special Safety Studies

7.1.12.1 BMD Data

Change from baseline in BMD at the femur and lumbar spine was assessed after six months of treatment as the protocol-defined primary safety endpoint, and again during the 12 month follow-up period. Pooled data from the two pivotal trials demonstrated superiority of DMPA-SC over Lupron in producing less BMD loss after six months of treatment, which was sustained over follow-up. Table 34 presents the median percent change from baseline in each treatment group. At the femur, the DMPA-SC group had a median change of -0.4% after six months of treatment, and showed evidence of partial recovery by six months of follow-up (median change of -0.3%), which continued at the 18 month assessment (median change of -0.2%). The Lupron group, in contrast, had 1.9% femur bone loss at the 6 month visit, and also demonstrated some recovery at the 12 (median change of -1.6%) and 18 month (median change of -1.2%) visits. By the end of the study, the median loss of BMD at the femur was greater by 1% in the Lupron group than in the DMPA-SC group. Evaluated at the lumbar spine, the DMPA-SC group showed its maximum median decrease (-1.1%) at month 12, but was recovering toward the baseline value by month 18 (median change of -0.25%). In the Lupron group, median BMD loss at the end of treatment was 4%, vs. 1% in the DMPA-SC group, but also showed evidence of partial recovery at both months 12 (median change of -2.7%) and 18 (median change of -1.4%). At the end of the study, loss in spine BMD was higher by 1.15% in the Lupron group. Thus, at both skeletal sites and each of the three assessment times, median BMD loss was less in the DMPA-SC group. These differences were statistically significant in the individual studies (see Table 63 and Table 95).

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Table 34 Median Percent Change in BMD by Treatment Group

Visit	Results	DMPA-SC	Leuprolide
Baseline Total Femur	Total patients reported	280	281
	Baseline median (g/cm^2)	1.02	1.05
Baseline Spine	Total patients reported	280	283
	Baseline median (g/cm^2)	1.17	1.18
Month 6 Total Femur	Total patients reported	207	227
	Median percent change from baseline	-0.40	-1.90
	Range	-10.7 to 18.6	-9.0 to 18.8
Month 6 Spine	Total patients reported	208	229
	Median percent change from baseline	-1.00	-4.00
	Range	-10.5 to 5.2	-13.2 to 2.3
Month 12 Total Femur	Total patients reported	169	181
	Median percent change from baseline	-0.30	-1.60
	Range	-12.8 to 21.6	-11.3 to 18.1
Month 12 Spine	Total patients reported	168	180
	Median percent change from baseline	-1.10	-2.70
	Range	-9.9 to 9.4	-11.9 to 4.9
Month 18 Total Femur	Total patients reported	125	134
	Median percent change from baseline	-0.20	-1.20
	Range	-5.8 to 18.5	-8.4 to 13.6
Month 18 Spine	Total patients reported	124	133
	Median percent change from baseline	-0.25	-1.40
	Range	-9.4 to 9.8	-12.4 to 5.9

Note: Months 12 and 18 represent 6 and 12 months following treatment cessation, respectively
Source: Table 3, Module 2.7.4 Update, p 6

When the BMD data are examined in terms of mean percent change (Table 35), similar trends are noted, with the DMPA-SC group displaying less bone loss than the Lupron group at each bone site and each assessment period.

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Table 35 Mean (SD) Percent Change in BMD by Treatment Group

Visit	Results	DMPA-SC	Lupron
Baseline			
Femur	N	280	281
	Mean (SD)	1.04 (0.13)	1.05 (0.13)
Spine	N	280	283
	Mean (SD)	1.19 (0.13)	1.20 (0.14)
Month 6			
Femur	N	207	227
	Mean (SD)	-0.03 (3.10)	-1.83 (3.22)
Spine	N	208	229
	Mean (SD)	-1.20 (2.50)	-4.10 (2.66)
Month 12			
Femur	N	169	181
	Mean (SD)	-0.05 (3.48)	-1.59 (3.55)
Spine	N	168	180
	Mean (SD)	-1.06 (2.77)	-2.75 (2.62)
Month 18			
Femur	N	125	134
	Mean (SD)	0.39 (3.29)	-1.15 (3.34)
Spine	N	124	133
	Mean (SD)	-0.54 (2.89)	-1.48 (3.02)

Source: Table T2.1, Module 2.7.4, pp 1-4

Looking at categorical percent change in BMD, the proportions of subjects in the two groups, who had >2.4% bone loss at the femur or spine and at one or more of the three assessment periods are presented in Table 36. The Lupron group had 2-3 times the frequency of subjects with this magnitude of BMD loss at the femur at all times, compared to the DMPA-SC group. The proportions of subjects with this degree of loss at the spine were always greater in the Lupron group, particularly at the end of treatment (28.4% and 76% in the DMPA-SC and Lupron groups, respectively). The differences between the two treatment groups became less during the post-treatment follow-up period.

Table 36 Proportion with BMD Loss > 2.4% by Treatment Group and Time

Visit		Femur		Spine	
		DMPA-SC	Lupron	DMPA-SC	Lupron
Month 6	N	207	227	208	229
	% losing >2.4%	12.6%	41.4%	28.4%	76.0%
Month 12	N	169	181	168	180
	% losing >2.4%	16.6%	39.3%	31.0%	54.4%
Month 18	N	125	134	124	133
	% losing >2.4%	11.2%	32.8%	25.0%	33.1%

Note: Months 12 and 18 represent 6 and 12 months following treatment cessation, respectively
Source: Based on Table T2.2 *Module 5.3.5.3.1 Update, pp 1-4*

Change in BMD was also assessed in Study 267BMD, a contraception study in which subjects were treated with DMPA-SC or DMPA-IM every three months for up to two years. The primary safety endpoint in this study was percent change in BMD from baseline to two years of treatment. The safety update submitted by the applicant provided 24-month data on BMD for 208 subjects (106 using DMPA-SC and 102 using DMPA-IM) who have continued to use the study drugs (Table 37). As expected with ongoing use, subjects in both groups show increased bone loss over time, with

BMD change greater at the spine than at the hip, as was seen in the endometriosis trials. While bone loss in the DMPA-SC group was always less than that in the DMPA-IM group, the difference between the SC and IM formulations was statistically significant only for the spine at month 12. It appears that use of DMPA-SC for 24 months is associated with less than 5% loss of BMD at either femur or spine.

Medical Reviewer's Comments:

1) ***The data support statistical superiority of DMPA-SC over Lupron in minimizing BMD loss over six months of treatment.***
2) ***The two-year data above support the safe use of DMPA-SC for endometriosis for longer than 6 months.***

Table 37 Study 267BMD: Median Percent Change in BMD by Treatment Group

Visit	Results	DMPA-SC	DMPA-IM	p-Value*
Baseline Total Femur	Total subjects reported	264	267	
	Baseline median (g/cm^2)	1.03	1.03	0.922
Baseline Spine	Total subjects reported	264	268	
	Baseline median (g/cm^2)	1.16	1.15	0.840
Month 12 Total Femur	Total subjects reported	166	162	
	Median percent change from baseline	-1.40	-1.95	0.165
	Range	-19.9 to 4.9	-18.0 to 4.3	
Month 12 Spine	Total subjects reported	166	162	
	Median percent change from baseline	-2.35	-3.40	0.021†
	Range	-9.9 to 4.2	-10.7 to 3.5	
Month 24 Total Femur	Total subjects reported	106	101	
	Median percent change from baseline	-3.30	-3.60	0.724
	Range	-22.7 to 8.1	-18.3 to 6.6	
Month 24 Spine	Total subjects reported	106	102	
	Median percent change from baseline	-4.30	-5.00	0.191
	Range	-10.8 to 3.4	-11.8 to 4.8	

Source: 2-year report for Study 267BMD[8], Table T6.2.
* Between treatment Kruskal-Wallis test
† Statistically significant ($p \leq 0.049$)
Source: Table 4, Module 2.7.4 Update, p 9

7.1.12.2 Kupperman Index Data

The Kupperman Index measures 11 symptoms of decreased estrogen levels, which are rated 0 (none), 1 (slight), 2 (moderate) or 3 (severe), for a total score range of 0-33:

- Hot flushes
- Abnormal sensations
- Insomnia

- Nervousness
- Depression
- Vertigo
- Fatigue
- Pain in joints/muscles
- Headache
- Palpitations
- Formication

This instrument was reviewed with subjects monthly throughout the treatment phase; pooled results are displayed in Table 38. The DMPA-SC group showed a small median increase in hypoestrogenic symptoms at months 1 and 4, with a median change of 0 at all other assessments. In contrast, the Lupron subjects in the two studies displayed median increases ranging from 1 to 8 over the six months of treatment. At every assessment, both Lupron groups, regardless of whether administration was IM or SC, showed increased symptomatology from baseline, and the DMPA-SC group had smaller median changes from baseline (i.e., fewer symptoms of hypoestrogenemia) than either Lupron group at every assessment.

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Table 38 Median Change in Kupperman Index by Treatment Group

Visit		DMPA-SC† 268+270	Leuprolide (IM)† 268	Leuprolide (SC)‡ 270
Pretreatment	Total Reported	289	137	146
	Pretreatment Median	9.0	13.0	9.0
Month 1	Total Reported	275	132	142
	Pretreatment Median*	9.0	12.5	9.0
	Median Change	1.0	2.0	5.0
	Range	-26 to 27	-21 to 26	-12 to 33
Month 2	Total Reported	269	127	140
	Pretreatment Media *	9.0	12.0	9.0
	Median Change	0.0	4.0	7.0
	Range	-26 to 27	-18 to 25	-23 to 36
Month 3	Total Reported	251	120	140
	Pretreatment Median*	9.0	12.0	9.0
	Median Change	0.0	5.0	8.0
	Range	-22 to 24	-24 to 27	-22 to 36
Month 4	Total Reported	238	110	138
	Pretreatment Media *	9.0	11.5	9.0
	Median Change	0.5	3.0	8.0
	Range	-29 to 27	-26 to 29	-21 to 32
Month 5	Total Reported	228	106	137
	Pretreatment Median*	9.0	11.5	9.0
	Median Change	0 0	2.5	6.0
	Range	-25 to 20	-28 to 28	-20 to 38
Month 6 (EOT)	Total Reported	226	102	136
	Pretreatment Median*	9 0	12.0	9.0
	Median Change	0.0	1.0	6.0
	Range	-29 to 29	-32 to 30	-18 to 37

*Based on patients who had non-missing values at both pretreatment and the change visit. Pretreatment values were the randomization visit values. If a randomization visit value was missing, then the baseline value was used.
† Administered every 3 months.
‡ Administered monthly, except in the 6 patients in the Netherlands, who were dosed every 3 months.
Source: Table 21, Module 2.7.4, p 40

Medical Reviewer's Comment:

1) ***The Kupperman Index has been criticized for unjustified weighting, overlapping criteria, and suboptimal patient understanding. The applicant was informed during the development program that data based on this index were unlikely to be acceptable for labeling claims.***

7.1.12.3 Hot Flush Data

In the pooled data, DMPA-SC subjects experienced a median of 0 hot flushes daily during the 6 month treatment. Lupron subjects had a median of 0 at baseline, but increased to 2 or greater after the first month of treatment. Looking at mean values, the DMPA-SC group increased from a mean frequency of 0.37 hot flushes/day at baseline to a maximal value of 0.78/day at month 2, while the Lupron subjects increased from a baseline mean frequency of 0.36/day to a maximum of 4.55/day at month 5 (Table 39). Similarly, the average daily severity index[7] in the DMPA-SC group went from a baseline mean of 0.62 to a maximum of 1.30 at month 3, while the Lupron group increased

maximally in severity index from 0.62 at baseline to 8.84 at month 5. Hot flush frequency and severity were statistically significantly lower in the DMPA-SC group in the individual studies.

Table 39 Mean (SD) Daily Hot Flush Frequency during Treatment

Month	Value	DMPA-SC	Lupron
Baseline	N	244	252
	Mean (SD)	0.37 (0.99)	0.36 (0.77)
Month 1	N	242	253
	Mean (SD)	0.71 (1.65)	1.99 (5.34)
Month 2	N	237	241
	Mean (SD)	0.78 (2.37)	3.99 (5.41)
Month 3	N	236	231
	Mean (SD)	0.77 (2.46)	4.36 (6.07)
Month 4	N	220	226
	Mean (SD)	0.71 (1.39)	4.35 (6.71)
Month 5	N	204	221
	Mean (SD)	0.64 (1.26)	4.45 (6.77)
Month 6	N	189	202
	Mean (SD)	0.49 (1.12)	4.13 (6.54)

Source: Table T1.6.4, *5.3.5.3.1, pp 170-71*

Medical Reviewer's Comment:

1) ***The data support the superiority of DMPA-SC over Lupron in minimizing symptoms of hypoestrogenemia.***

7.1.12.4 Return of Ovulation

As women of reproductive age with endometriosis are often interested in fertility, the duration of ovulation suppression following cessation of treatment with DMPA-SC is of interest. This was examined in the PK/PD Study 272 and in a substudy of the contraceptive Study 267.

In Study 272, following administration of a single 104 mg SC dose in 39 women, the median return to ovulation, based on first occurrence of a progesterone level >= 4.7 ng/ml was 212 days, with a range of 106 to 358 days. The cumulative rate of return to ovulation by one year following a single dose was 97.4%.

Following three doses of DMPA-SC in Study 267, the median return of ovulation was 291 days, with 80% of the 15 subjects resuming ovulation by one year after the last injection interval. The 21 women who left the two contraceptive studies desiring pregnancy were followed for 485 days after their last injection; only two achieved pregnancy by that time, one conceived 310 days following the last injection and one 443 days after.

Medical Reviewer's Comment:

1) ***Endometriosis is often associated with infertility, and patients may desire pregnancy following successful treatment of their symptoms. It should be clearly communicated to potential users of DMPA-SC that they may not resume ovulation seven months or longer following their last dose.***

7.1.12.5 Body Weight Data

Subjects' body weight was monitored through the follow-up period; changes from baseline are presented in Table 40. Lupron subjects were slightly heavier at baseline. Weight gain was greater in the DMPA-SC group at the end of treatment and after six months of follow-up; however, by the end of follow-up, Lupron subjects had a slightly greater weight gain. In the pooled data, on average, DMPA-SC subjects gained 0.79 kg at the end of six months of treatment, while Lupron subjects

gained 0.59 kg. The proportion of subjects gaining more than 2.3 kg at the end of treatment was 23% in the DMPA-SC group, compared to 24.8% in the Lupron group.

Table 40 Mean Change (SD) in Body Weight (kg) by Treatment Group

Visit	Results	DMPA-SC	Lupron
Baseline	Mean weight	65.8 (15.0)	68.1 (17.1)
Month 6	Mean change	0.79 (3.1)	0.59 (3.0)
	Range	-22.5 to 11.3	-9.1 to 10.5
	N	226	239
Month 12	Mean change	1.28 (4.0)	1.10 (3.8)
	Range	-22.6 to 11.2	-8.7 to 13.2
	N	171	179
Month 18	Mean change	0.69 (4.9)	0.86 (3.9)
	Range	-30.0 to 18.6	-9.2 to 11.0
	N	136	144

Source: Based on Table T4.2, *5.3.5.3.1, pp 1-4*

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No abuse potential for this drug is expected, nor are opportunities for abuse likely, since the drug is not self-administered.

7.1.14 Human Reproduction and Pregnancy Data

In the single pregnancy occurring during the treatment period in Study 268, the pregnancy was electively terminated, so no data on fetal effects are available.

A number of studies of DMPA exposure during pregnancy exist; however, conclusions regarding the risk of various congenital anomalies are inconsistent. A search of the Reprotox database[8] last revised in August 2003 found the following summary statement: "Medroxyprogesterone use during early pregnancy is not associated with an increase in adverse pregnancy outcome. Breastfeeding women may take this medication." Two studies cited in Reprotox report an increase in low birth weight infants in pregnancies exposed to DMPA as compared to unexposed pregnancies[9, 10].

Progestin-based contraceptives in general have demonstrated in increase in the proportion of all pregnancies occurring that are ectopic. However, in the case of DMPA-IM, postmarketing surveillance does not suggest an increase in the proportion of ectopic pregnancies, in cases where contraception failed. No ectopic pregnancies occurred in the DMPA-SC trials for either the contraceptive or the endometriosis indication.

Medical Reviewer's Comments:

1) ***The current DMPA-IM label discusses avoidance of administration during pregnancy in the Warnings section, with instructions on timing of the first dose to prevent inadvertent use during early pregnancy. While this is appropriate, clear information conveying the generally reassuring data on pregnancy exposure to DMPA should be provided.***
2) ***Ectopic pregnancy and lactation are also discussed in the Warnings Section of the current DMPA-IM label. Discussion in the Warnings Section of the lack of data on the risk of ectopic pregnancy and the need to remain alert to this possibility remains appropriate. The data on use during lactation are reassuring and do not warrant inclusion of this topic under the Warnings Section.***

7.1.15 Assessment of Effect on Growth

Use of DMPA by lactating women has not shown evidence of altering the duration of lactation. Although small amounts are excreted in breast milk, children breastfed by women using DMPA display normal long-term growth and development[11, 12].

The use of DMPA by adolescents may impact the bone accretion typically occurring during this stage of life. The effect of DMPA on adolescents' BMD is the subject of ongoing study by the applicant.

7.1.16 Overdose Experience

No overdoses have been reported, nor is overdosing likely to occur, as the drug is administered in a pre-filled syringe.

7.1.17 Post-marketing Experience

The applicant included postmarketing data in the original submission and in the Periodic Safety Update Report for the period September 20, 1999 to January 31, 2004. DMPA-IM has been marketed for over 40 years, and the applicant estimates U.S. exposure to the drug at over — woman-years. As DMPA-SC is not marketed anywhere, postmarketing data relevant to the use of DMPA-IM for endometriosis, for which it is approved in other countries, was the focus of these reports. Worldwide, among patients using DMPA-IM for endometriosis, a total of 17 SAEs in 7 patients and 60 non-serious events in 24 patients were reported. According to the applicant, none of the events provided reason to reevaluate the safety of this product.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The primary studies providing safety data were the two phase 3 randomized, comparator-controlled, evaluator-blinded clinical trials for the endometriosis indication, which were conducted in the U.S. and Canada (Study 268) and in South America, Europe and Asia (Study 270). In studies 268 and 270, a total of 289 subjects exposed for six months to DMPA-SC and 284 exposed to Lupron were included in the ITT and safety populations. In addition, Study 267BMD, a randomized, comparator-controlled, evaluator-blinded trial conducted in Brazil, Canada and the U.S. for the contraception indication, enrolled 534 subjects (266 received DMPA-SC and 268 DMPA-IM), and provided 24-month BMD data on 208 subjects.

7.2.1.2 Demographics

Pooled data from Studies 268 and 270 provided the demographic information displayed in Table 41. Overall, the two groups are similar.

Table 41 Pooled Demographic Data

Characteristic	DMPA-SC N = 289	Leuprolide N = 284
Age (years)		
Mean ± SD	30.55 ± 6.64	31.47 ± 6.33
Median	29.90	31.45
Range	18.8–49.4	18.4–48.0
Race [n,(%)]		
White	209 (72.3)	208 (73.2)
Black	13 (4.5)	21 (7.4)
Asian or Pacific Islander	28 (9.7)	9 (3.2)
Mixed/Multiracial	39 (13.5)	46 (16.2)
Pretreatment Bodyweight (kg)		
Mean ± SD	65.83 ± 14.96	68.07 ± 17.05
Median	62.00	64.00
Range	42.0–124.4	35.5–168.2
BMI (kg/m^2)		
Mean ± SD	24.63 ± 5.06	25.44 ± 5.55*
Median	23.50	24.30*
Range	16.1–47.3	15.2–47.6*
≤ 25 [n,(%)]	181 (62.6)	158 (55.8)
> 25 to ≤ 30 [n,(%)]	65 (22.5)	71 (25.1)
> 30 [n,(%)]	43 (14.9)	54 (19.1)
Country Grouping (n,%)		
Asia	24 (8.3)	7 (2.5)
Europe	65 (22.5)	61 (21.5)
North America	136 (47.1)	138 (48.6)
South America	64 (22.1)	78 (27.5)

* Based on data from 283 patients
Source: Table 5, Module 2.7.4, p 14

Medical Reviewer's Comments:

1) *There are some imbalances in ethnicity (more Asians in the DMPA-SC group than in the Lupron group) and weight and BMI (higher in the Lupron group), but these are not anticipated to have a notable impact on the results of the studies.*
2) *However, there was a slight differential in the use of concomitant narcotics for pain relief in Study 268, where 35% of DMPA-SC and 38% of Lupron used codeine or hydrocodone during treatment.*

7.2.1.3 Extent of exposure (dose/duration)

Both studies 268 and 270 involved six months of treatment with 104 mg of DMPA-SC, administered once every three months. In Study 268, 138 subjects received Lupron 11.25 mg IM every three months. In Study 270, the majority of subjects (122) received a monthly dose of 3.75 mg of Lupron, administered SC. The six subjects in the Netherlands received a SC dose of 11.25 every three months, while the 18 subjects in Peru were administered 3.75 mg IM every month. Over the six-month treatment period, 86% of DMPA-SC subjects received both scheduled injections; the number of scheduled Lupron injections varied over the two studies, but, overall, 90% received all scheduled injections. Overall, 289 subjects provided data on 6-month use of DMPA-SC. An additional 116 subjects from Study 267BMD provided data on 24 months of continuous use of DMPA-SC.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

See Section 7.1.

7.2.2.1 Other studies

No other studies not previously described were submitted.

7.2.2.2 Postmarketing experience

The applicant included postmarketing data focusing on the use of DMPA-IM for endometriosis (an indication for which it is approved in other countries) for the period September 20, 1999 to January 31, 2004.

7.2.2.3 Literature

The applicant provided 15 references from the published literature in Module 5, but did not comprehensively review the literature

7.2.3 Adequacy of Overall Clinical Experience

The majority of the data submitted evaluated a six-month exposure to DMPA-SC; the effect of a longer duration of treatment was examined only in a subset of 116 subjects from Study 267BMD. The age range of women studied was representative of the target population for this indication. Small numbers of members of racial and ethnic subgroups beyond Caucasians were represented in the trials. Inclusion and exclusion criteria for subjects in the trials were appropriate for obtaining a sample that is likely to be comparable to the target population.

Medical Reviewer's Comment:

1) ***The sponsor does not indicate the anticipated duration of use of DMPA-SC for the management of endometriosis-associated pain. The data submitted provide adequate clinical experience and safety data to support a six-month course of treatment. The longer-term data available in Study 267BMD supports safety of up to three retreatment courses, when warranted by return of symptoms.***

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Data from the preclinical program were generally submitted in NDA 20-246 for the IM formulation for contraception. DMPA is a well-characterized drug product.

7.2.5 Adequacy of Routine Clinical Testing

In general, the routine evaluation of subjects on the safety parameters incorporated in the trials was adequate. The sponsor has indicated that the sensitivity of the estradiol assay was only [redacted] ag/ml.

Medical Reviewer's Comment:

1) ***The low sensitivity of the assay and the low frequency of testing for estradiol (every three months) limit the value of this potentially useful measure of the pharmacodynamic effect of DMPA-SC most relevant to the endometriosis indication.***

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The applicant submitted literature that was found by the Clinical Pharmacology reviewer to adequately characterize the metabolic pathways of MPA and address the potential for drug interactions.

7.2.7 Adequacy of Evaluations for Potential Adverse Events for any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The subject of this NDA is not a new drug. The applicant was thorough in evaluating the occurrence of known adverse events associated with DMPA, such as bone loss and weight gain.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the data were of sufficient quality to allow an adequate safety review. There was some attrition in subjects contributing data during the follow-up period, but the primary safety review focused on events occurring during the treatment phase.

7.2.9 Additional Submissions, Including Safety Update

A safety update was submitted on April 14, 2004; data from this update were incorporated into the preceding safety review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There were no signals of concern in regard to the occurrence of SAEs or changes in vital signs or laboratory evaluations associated with DMPA-SC. Selected AEs of particular relevance to this product are:

Bone loss
Data from the pivotal clinical trials indicates a clear superiority of DMPA-SC over Lupron in reducing BMD loss over the course of six months of treatment. At the end of the six-month treatment, the DMPA-SC subjects had lost a median of 0.4% at the femur and 1% at the spine, compared to Lupron subject's loss of 1.9% at the femur and 4% at the spine. These differences were statistically significant in the individual studies. Partial recovery was evident in both groups at six and 12 months following cessation of treatment, but was virtually complete after 12 months in the DMPA-SC group, while the Lupron group scores were still 1.2 to 1.4% below baseline values.

Hypoestrogenic symptoms
Diary data on hot flush frequency and severity was used to assess the extent of symptoms attributable to hypoestrogenemia. Median number and severity of daily hot flushes was statistically significantly lower in the DMPA-SC group at each month of treatment in both studies.

Injection site reactions
Injection site reactions to appear associated with SC administration of DMPA, as they were seen at higher rates with DMPA-SC than with either DMPA-IM or Lupron IM. In a number of cases, they appear as areas of indentation or induration at the injection site. However, none were rated severe, and only a single subject withdrew due to this reaction. Subjects' willingness to recommend DMPA-

SC to a friend or to consider using it again did not appear to be decreased by the occurrence of these reactions.

Bleeding
Uterine bleeding, whether minor spotting or hemorrhagic events, occurred more frequently in the DMPA-SC group. In the 90 days following the second injection, DMPA-SC subjects experienced, on average, over 30 days of spotting or bleeding, compared to fewer than 2 in the Lupron subjects. In contrast, amenorrhea occurred in about 80% of Lupron subjects by months 4-6, but in less than 10% of DMPA-SC subjects. More significant bleeding, classified as an adverse event, occurred in 4% of DMPA-SC subjects, but less than 1% of Lupron subjects.

Weight gain
Weight gain occurred in both treatment arms during the course of treatment and continued for the first six months of follow-up. By one year after discontinuing treatment, both groups had lost some weight, but had still not regained their baseline weight. Mean magnitude of the change was similar in each group, representing about 1-3/4 lb in the DMPA-SC group and 1-1/3 lb in the Lupron group at the end of treatment.

Depression
The rates of depression reported in Studies 268 and 270 were similar between DMPA-SC and Lupron, and were close to the incidence reported for females in the general population.

Delayed resumption of ovulation
Comparative data on return of ovulatory function for DMPA-SC and Lupron was not presented; however two DMPA-SC studies outside of the endometriosis trials indicate that resumption of ovulation may take about 7-10 months following cessation of treatment.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Safety data were pooled over Studies 268 and 270 for evaluation of BMD, Kupperman Index, hot flushes, estradiol levels, bleeding patterns, adverse events, laboratory evaluations, blood pressure and body weight.

7.4.1.1 Pooled data vs. individual study data

Individual study data is reported for lipid profiles, since Study 268 conducted a non-fasting profile, and Study 270 had a more extensive fasting profile done as a substudy at the sites in Poland and Sweden. Coagulation profiles were also not pooled, as Study 268 only assessed platelets, while the Study 270 substudy performed a more comprehensive panel. Data concerning the Kupperman Index and bleeding patterns were not pooled for the Lupron subjects since different routes of administration occurred in the two studies.

7.4.1.2 Combining data

Pooled data were obtained by summing the individual events in each of the two pivotal studies; no weighting was utilized.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Only a single dose level was evaluated in the clinical studies, and no PK data to explore exposure were obtained. Dose dependency of adverse findings can therefore not be determined.

7.4.2.2 Explorations for time dependency for adverse findings

Both pivotal studies examined a six-month treatment duration. The effect of longer duration of treatment on BMD was assessed in Study 267BMD, indicating that bone loss continues with ongoing treatment.

7.4.2.3 Explorations for drug-demographic interactions

An analysis by race was done for BMD, estradiol levels, AEs and change in body weight. No effect of race was evident; however, numbers of non-white subjects were low.

7.4.2.4 Explorations for drug-disease interactions

Subjects were healthy outside of their endometriosis diagnoses. Subjects with hepatic or renal dysfunction were excluded; therefore impact of DMPA-SC in patients with such concomitant illnesses cannot be assessed.

7.4.2.5 Explorations for drug-drug interactions

Drug-drug interactions were not explored in this NDA; see Section 8.2 for review of data provided in NDA 21-583.

Aminoglutethimide, a chemotherapeutic agent, may lower serum concentration of DMPA-SC; no subjects in the pivotal trials used this agent.

7.4.3 Causality Determination

Three adverse events appear causally related to drug treatment: injection site reactions and irregular bleeding in the DMPA-SC subjects and hot flushes in the Lupron subjects. Comparison of injection site reaction frequency in Study 267BMD between subjects who received DMPA SC vs. IM suggests that it is the SC route of administration that is associated with these reactions. Comparative data from Lupron subjects who received SC dosing in Study 270 is not available, as very few subjects in either treatment arm reported injection site reactions in that study.

Irregular bleeding is known to occur with the currently marketed DMPA-IM formulation and is noted in its labeling. While a majority of women using this drug for contraception will become amenorrheic over the course of a year, the current studies assessed only a six-month duration of treatment.

The occurrence of hot flushes is also a documented adverse event with use of Lupron and is labeled under Adverse Reactions.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dose for the endometriosis indication is 104 mg SC, administered into the anterior thigh or abdomen, once every three months. Duration of treatment is not discussed by the applicant. The dose recommended is based on adequate efficacy data supporting this dose, the only one evaluated in the pivotal trials. The initial dose-ranging studies were based upon the pharmacodynamic action of ovulation suppression, as measured by serum progesterone. Few data are available concerning the pharmacodynamics of DMPA-SC in suppressing estradiol, the more likely mechanism of action relevant to management of endometriosis.

Medical Reviewer's Comments:

1) ***Pharmacodynamic data concerning estradiol suppression would be of greater value than ovulation suppression data in determining the least effective dose for management of symptoms of endometriosis; however, these data are largely unavailable.***

2) ***It is possible that efficacy would be greater with a higher dose of DMPA-SC; however, this would likely minimize the superiority demonstrated over Lupron in terms of lower BMD loss. It is unlikely that a lower dose than that tested would have adequate efficacy in managing endometriosis.***
3) ***The six-month duration of the pivotal trials would limit the recommended duration of treatment to six months (two injections). The follow-up data showing near complete recovery of BMD loss after six months off treatment and the two-year data from Study 267BMD support the safety of up to three additional courses of treatment, as warranted by recurrent symptoms.***

8.2 Drug-Drug Interactions

Drug-drug interactions were not assessed in the development program for DMPA-SC. A summary based on the published literature provided by the sponsor indicates that MPA is metabolized by CYP3A4. Although the effect of CYP3A4 inducers would be of potential concern for reducing MPA levels, the literature provides no evidence of any clinically significant drug-drug interactions that would lead to contraceptive failure. Liver clearance of MPA is extensive under normal conditions, and unlikely to be increased markedly by enzyme induction.

Studies 267 and 269 for the contraceptive indication did provide subgroup analyses looking at efficacy and safety in subjects who were concomitantly using medications with CYP3A4 inducing or inhibiting properties (~10% of the pooled population). No pregnancies occurred, indicating no clinically relevant drug-drug interaction affecting efficacy. There was also no consistent effect on the number of bleeding/spotting days experienced by subjects using CYP3A4 inducers or inhibitors. The frequency of all AEs and drug-related AEs was higher in subjects using CYP3A4 inducers or inhibitors than in the total population, but there was not a consistent difference between the two subgroups (Table 42).

Table 42 Adverse Events with Concomitant Use of CYP3A4 Inhibitors/Inducers (Contraception Studies)

	Study 267		Study 267BMD-SC		Study 269	
	% Subjects AEs	% Subjects DR-AEs	% Subjects AEs	% Subjects DR-AEs	% Subjects AEs	% Subjects DR-Aes
Total	70.7 (509)	45.1 (325)	70.7 (135)	42.9 (82)	46.5 (493)	31.7 (336)
Inducers	98.1 (53)	66.7 (36)	90.0 (9)	80.0 (8)	72.7 (8)	45.5 (5)
Inhibitors	93.3 (56)	50.0 (30)	93.3 (14)	60.0 (9)	87.0 (20)	65.2 (15)

Number in parenthesis = Total N
Source: Table 2, Module 2.7.2, p 9

Medical Reviewer's Comment:

1) ***The fact that AEs were higher in both concomitant users of inhibitors and of inducers than in the total population suggests no systematic effect.***

8.3 Special Populations

Pharmacokinetic/pharmacodynamic results were obtained in Caucasian, African-American and Asian women with no significant differences noted. Similarly, no dosage adjustment is needed based upon body weight or BMI. No formal studies have evaluated PK/PD in subjects with hepatic or renal

dysfunction. The IM formulation is contraindicated in pregnancy. No adverse effects on lactation or on children exposed through breast milk have been detected.

8.4 Pediatrics

The FDA waived the requirement for pediatric studies, as this product will only be indicated for postmenarchal females.

8.5 Advisory Committee Meeting

Not applicable

8.6 Literature Review

A comprehensive review of the literature was not conducted. Individual publications reviewed are discussed and referenced throughout the body of the review.

8.7 Post-marketing Risk Management Plan

No post-marketing risk management plan is recommended.

8.8 Other Relevant Materials

DDMAC has reviewed the proposed label; currently labeling for the endometriosis indication has not been submitted.

9 OVERALL ASSESSMENT

9.1 Conclusions

The primary efficacy analysis demonstrated statistically significant protocol defined non-inferiority on four of five pain categories in Study 268 and on all five categories in Study 270, when analyzed in the ITT-OC population, thus meeting the pre-specified criteria for non-inferiority. In the ITT-LOCF population, Study 270 again demonstrated statistically significant non-inferiority on all five categories. In Study 268, however, this analysis failed to meet criteria for non-inferiority, as only one of five categories was statistically significantly non-inferior. On the composite score, used to assess the overall clinical meaningfulness of the treatment effect, both studies met the pre-set criteria for magnitude of improvement, and these results were robust over both analysis populations.

Overall, this reviewer concludes that adequate evidence of efficacy relative to Lupron has been demonstrated for DMPA-SC in management of pain associated with endometriosis. While the results of the two pivotal trials for the primary efficacy endpoint are not completely concordant, the preponderance of evidence supports a finding of non-inferiority of DMPA-SC as compared to Lupron. The remainder of the endpoints, while not expressly used to test non-inferiority of DMPA-SC compared to Lupron, support the proposition that DMPA-SC confers a clinically meaningful treatment benefit, provides significant improvement over baseline symptomatology at all months of treatment, is associated with time to recurrence similar to or of longer latency than Lupron, and results in improved quality of life, as measured by pre-specified scales. Finally, comparison of DMPA-SC treatment effects in these clinical trials with those seen in placebo subjects from a 1990 randomized, double-blind, placebo-controlled Lupron trial, indicates that the changes in the scores for painful symptoms or signs of endometriosis in DMPA-SC treated subjects are much greater than what would be attributable to a placebo effect.

[redacted] is not supported by evidence.

9.2 Recommendation on Regulatory Action

It is recommended that NDA 21-584, Depot Medroxyprogesterone Acetate for subcutaneous injection be approved for the indication of management of endometriosis-associated pain in women with endometriosis, contingent upon submission of acceptable labeling by the applicant. It is further recommended that the approved indication limit treatment duration to six months, with retreatment acceptable if warranted by recurrent symptoms, following a six-month drug-free interval. Finally, it is recommended that
not be approved.

The reviewer finds that:

- Adequate evidence of efficacy relative to Lupron has been demonstrated for DMPA-SC in management of pain associated with endometriosis.
- There is adequate evidence demonstrating superiority of DMPA-SC over Lupron in minimizing loss of bone mineral density (BMD).
- DMPA-SC provides a benefit relative to Lupron in minimizing symptoms of hypoestrogenemia resulting from treatment.
- The remaining safety data do not raise concern for a safety profile discrepant from that of the approved product, DMPA-IM.
- Considering the risk/benefit profiles of DMPA-SC and the approved comparator Lupron, there is adequate evidence that DMPA-SC has non-inferior efficacy and superior BMD safety to support approval of the indication for management of endometriosis-associated pain.
- The applicant did not submit data to suppor
- The majority of safety data relevant to BMD loss and subsequent recovery is based upon six months duration of treatment. Additional data from the DMPA-SC contraceptive trials provides information about BMD loss with two years of treatment. These data support the safety of an initial six month treatment duration and up to three additional courses of treatment, as warranted by recurrent symptoms.
- The relatively prolonged interval until return of ovulation after use of DMPA-SC must be communicated to endometriosis patients, who often desire fertility.

9.3 Recommendation on Post-marketing Actions

9.3.1 Risk Management Activity

No need for risk management activity is anticipated

9.3.2 Required Phase 4 Commitments

No phase 4 commitment is required.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

At the time of this review, the applicant has not yet submitted revised labeling. Previously, a combined label for the separate indications of contraception and endometriosis was submitted to NDA 21-583. That NDA received an approvable action pending acceptable labeling, and therefore a combined label with the contraceptive indication cannot be approved at this time.

9.5 Comments to Applicant

There are no comments to be forwarded to the applicant.

October 12, 2004

Lisa M. Soule, MD Date

Medical Officer, DRUDP

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10 APPENDICES

10.1 Clinical Trial 839-FEH-0012-268

10.1.1 Summary

Title: "Phase III Study of Depot Medroxyprogesterone Acetate Subcutaneous Injection (DMPA-SC) in Women with Endometriosis in the United States (Final Report: 6 Months of Treatment and 12 Months of Follow-Up)," dated 27 February 2004.

Two amendments were made to Study 268. The first, dated March 17, 2001, included the following changes:

- Added a primary safety endpoint (BMD loss after 6 months of treatment), which had previously been a secondary endpoint; added additional secondary safety endpoints (including Kupperman Index, hot flushes, hormone levels and outcomes research assessments)
- Extended the range of prior laparoscopic diagnosis of endometriosis from 24 to 42 months
- Modifying the entry requirement regarding "total pelvic score" so that subjects who are not sexually active must have a total of 4 or more (including 2 or more in each of the pain categories dysmenorrhea and pelvic pain)
- Changed the criterion for a clinically meaningful change in the global outcome measure from 3 points at 6 months to 4 points at six months in subjects who have all 5 categories recorded at baseline
- Changed the endpoints for which the study is powered to show superiority from BMD loss at 6 months and the Kupperman Index to powering for non-inferiority on at least four of the five signs/symptoms of endometriosis and powering for superiority on BMD loss at 6 months
- Removed the exclusion of subjects who have had surgical treatment for endometriosis
- Added the requirement that subjects diagnosed by a remote surgery must have a current vaginal sonogram and vaginal swab to rule out other etiologies for pelvic pain and gonorrhea/chlamydia
- Added diseases that may produce chronic abdominal/pelvic pain as an additional exclusion criterion
- Added a bimanual pelvic examination to assess pelvic tenderness and induration to Visits 1, 2, 3, 5 and 6
- Complete revision of the statistical analysis plan
- Other minor protocol changes

Amendment two, dated March 18, 2003, included the following changes:

- Subjects who discontinue participation will be not be asked to return for BMD assessments 6 and 12 months following discontinuation
- Removed the plan to follow subjects for pregnancy for 12 months following their termination from the study
- Eliminated the urine pregnancy test at 120 days following the last medication dose

An administrative protocol change, dated August 8, 2002, included:

- Pre-specification of four EHP-30 scales and three SF-36 scales as secondary efficacy endpoints
- Clarification of the plan to report study results at the end of 6 months of follow-up. The initial plan to keep treatment group assignments for individual patients blinded until

completion of the 12 month follow-up period was changed; treatment assignments were unblinded at the end of 6 months of follow-up.

Medical Reviewer's Comment:

1) ***While treatment assignment was unblinded for the study report after six months of follow-up, the applicant states that patient-level treatment information was not to be shared with the evaluative staff. The study was never more than evaluator-blinded, so this is unlikely to compromise the integrity of the blind.***

First patient entered: May 21, 2001

Last patient completed: September 5, 2002

Last follow-up: August 14, 2003

10.1.2 Objectives

The primary efficacy objective of this study was:

- to assess the efficacy, as determined by the reduction of endometriosis-associated pain, achieved by DMPA-SC vs. Lupron in a comparative non-inferiority study.

The primary safety objective of this study was:

- to demonstrate superiority of DMPA-SC over Lupron for minimizing bone mineral density (BMD) decline after six months of treatment.

The secondary efficacy objectives were:

- to evaluate changes from baseline in patient quality of life.
- to evaluate the time to return of endometriosis-associated symptoms during the follow-up period.

The secondary safety objectives were:

- to assess further the safety/tolerability of DMPA-SC with Lupron.

Medical Reviewer's Comments:

1) ***In DRUDP's discussions with the sponsor during development of these protocols, the term "non-inferiority" was used in discussing the trials, and, based upon the statistical methods and null hypothesis used, the two studies are in fact non-inferiority trials. Nonetheless, the applicant calls them "equivalence" trials throughout the submission.***
2) ***The applicant had indicated that comparative superiority in reduction of hot flushes over Lupron was a desired labeling claim, and had been informed that such a claim required support from an appropriately powered primary endpoint.***

10.1.3 Overall Design

This Phase 3, multinational (U.S. and Canada), multicenter, randomized, evaluator-blinded, comparator-controlled six month treatment duration, study was designed to evaluate the clinical efficacy and safety of DMPA-SC or Lupron in the treatment of subjects with signs and symptoms of endometriosis. Subjects, diagnosed by laparoscopic or other visualization of endometriotic lesions or by histopathology, were enrolled in a six-month treatment phase and a 12-month follow-up phase, during which time neither the study drug nor comparator could be used. Subjects were randomized to DMPA-SC or Lupron in a 1:1 ratio. Subjects in both groups were also given Os-Cal 500 mg tablets which they were instructed to take daily to ensure adequate calcium intake.

The study could not be double-blinded due to different routes of administration of the two drugs; however, it was evaluator-blinded, with the drug being administered by an independent injectionist who also received the study syringes. Any attempt by clinic site staff to discover a subject's randomization or route of administration was considered a protocol violation.

The study was conducted at 43 sites in the US and 7 sites in Canada. The recruitment goal was 320 subjects, 160 in each arm.

10.1.4 Study Procedures and Conduct

10.1.4.1 Schedule of Study Assessments

Subjects were screened for eligibility at Visit 0 and procedures indicated in Table 43 were performed. Subjects then fulfilled a minimum of a one-month wash-in period, during which time symptom data was recorded in a daily diary, allowing evaluation over a full menstrual cycle. At Visit 1, which occurred within 8 weeks of screening, subjects were randomized and the first dose of study medication was administered. At this visit, and at each monthly visit thereafter, efficacy and safety measures were obtained as indicated in the Schedule of Assessments. At Visit 7, the end of treatment visit, subjects also underwent BMD assessment. Subjects had follow-up telephone contact at months 7, 8, 10, 11, 13, 14, 16 and 17 to assess endometriosis-associated pain, adverse events and concomitant medication use. Follow-up clinic visits were scheduled at 9, 12, 15 and 18 months for repeat assessments, including bimanual pelvic examination, patient response questionnaires and BMD assessment at months 12 and 18.

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Table 43 Study 268: Schedule of Study Assessments

Study Activity	Visit X-Month									
	0*	1†	2 1-m	3 2-m	4 3-m	5 4-m	6 5-m	7 6-m	T‡	F§
Laparoscopy¶	X									
Informed consent	X									
Medical history	X									
Physical examination	X							X		
Pelvic examination	X	X	X	X	X	X	X	X		X
Sonogram & STD testing	X							X#		
Laboratory assays (hematology, chemistry, and urine analysis)	X				X			X		
Weight & sitting blood pressure	X	X	X	X	X	X	X	X		X
Urine pregnancy test**	X		X	X	X	X	X	X		X
Collection of patient diaries††		X	X	X	X	X	X	X		X
Pain assessment	X	X	X	X	X	X	X	X	X	X
Kupperman Index & uterine bleeding	X	X	X	X	X	X	X	X		
BMD§§	X							X		X
SHBG, serum estradiol, & progesterone		X			X			X		
EHP-30 & SF-36		X			X			X		X
PSQ		X			X			X		
Study medication injection		X			X					
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X

* Baseline visit
† Randomization and injection visit
‡ Telephone interview conducted at 7, 8, 10, 11, 13, 14, 16, and 17 months after injection
§ Follow-up visit at 9, 12, 15, and 18 months after injection
¶ First-time diagnostic laparoscopy must be performed before this visit.
# Vaginal sonogram performed at visit 7 if clinically indicated.
** Urine pregnancy test required 104 days after the last dose, regardless of time of study discontinuation.
†† Patient diary (endometriosis-impact diary including bleeding pattern information) was distributed monthly during the treatment period and every 3 months during the follow-up period (no bleeding pattern information was collected during follow-up).
§§ BMD evaluated using dual energy x-ray absorptiometry (DXA) at visits 0, 7, and at the follow-up visits at 12 and 18 months.
Abbreviations: BMD = bone mineral density, EHP-30 = Endometriosis Health Profile Questionnaire, F = follow-up visit, m = month; PSQ = Patient Satisfaction Questionnaire, SF-36 = Short Form-36 (quality of life questionnaire), SHBG = sex hormone binding globulin, STD = sexually transmitted disease, T = telephone follow-up

10.1.5 Study Drug

10.1.5.1 Dose Selection

The drug studied was DMPA-SC, 104 mg/0.65 ml, administered subcutaneously every three months. This dose was chosen based on a phase 1/2 study which determined the minimal SC dose that effectively suppressed ovulation for more than 90 days. The dose of Lupron was that recommended in its package insert for the effective treatment of endometriosis.

Medical Reviewer's Comment:

1) ***The dose selection was not directly based on the drug's effect on endometriosis. While suppression of ovulation is a useful pharmacodynamic measure for DMPA's contraceptive indication, it is a surrogate marker of unproven validity for the drug's utility for the endometriosis indication.***

10.1.5.2 Choice of Comparator

The comparator used was Lupron acetate, 11.25 mg, administered intramuscularly every three months. This drug is a synthetic GnRH analog approved for the treatment of endometriosis. Lupron was chosen due to its efficacy in relieving the signs and symptoms of endometriosis. It is given by a similar route of administration (IM injection vs. SC injection) and in the same dosing frequency as DMPA-SC.

10.1.5.3 Assignment to Study Drug

Subjects were randomized to DMPA-SC or Lupron in a 1:1 ratio. DMPA-SC was manufactured by Pharmacia, provided in a pre-filled syringe and was administered subcutaneously into the anterior thigh or abdomen. Lupron was purchased from TAP Pharmaceuticals provided in a prefilled dual-chamber syringe and administered intramuscularly into the gluteal muscle. Each drug was administered within the first five days of a normal menstrual period at Visit 1 and subsequently at 91 +/- 7 day intervals.

10.1.6 Patient Population

Subjects in this study were women with surgically diagnosed endometriosis with significant and chronic pelvic pain. Pain symptoms used as both entry criteria and outcome measures were rated according to the Biberoglu and Behrman Scale[1] presented in Table 3.

10.1.7 Inclusion and Exclusion Criteria

Inclusion Criteria

- Premenopausal women between 18-49 years
- Willing to use nonhormonal barrier contraception for 18 months
- Persistent symptoms associated with laparoscopically diagnosed endometriosis (preferably confirmed by biopsy pathology)
    - Patient experienced return of pain to its previous level within 30 days of surgery where only a diagnostic laparoscopy was performed, and within 3 months of surgery if surgical treatment was performed during the laparoscopy
    - Recurrent pain following diagnostic laparoscopy must have persisted for at least 3 months
    - Subjects with more remote laparoscopy must have had vaginal sonography and vaginal cultures to rule out other possible etiologies of chronic pelvic pain
- Total score of 6 or greater in the following 5 categories: dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness and induration. The total score must include a total of at least 2 in each

of the categories of dysmenorrhea, dyspareunia, and pelvic pain. If a patient is sexually inactive for reasons other than endometriosis, the total score must be 4 or greater, with at least 2 in each of the categories of dysmenorrhea and pelvic pain.
- Normal results on a Pap test within the last 6 months
- Normal results on a mammogram within the last 12 months (for subjects 35 or older)
- Provide informed consent
- Willing and able to comply with study-specific procedures

Exclusion Criteria
- Pregnant or breastfeeding
- Known breast cancer or mammographic results suspicious of breast cancer or requiring 6-month follow-up
- Hysterectomy and/or bilateral oophorectomy
- Current or recent use of hormonal agents (Wash out periods: 2 months for oral contraceptives, 6 months for Danazol, 12 months for GnRHa or DMPA-IM)
- BMD with both lumbar spine and femur T-scores below -1.0, or history of pathologic or compression fractures
- Abnormal cervical cytology within 6 months; ASCUS and ASCUS favoring reactive changes allowed
- Presence of disease state that could cause chronic abdominal/pelvic pain, including inflammatory bowel disease, fibromyalgia and interstitial cystitis. Large uterine fibroids palpated on bimanual examination were required to be ruled out as the source of the pain.
- Active or history of hepatic or renal disease (AST, ALT or total bilirubin >= 2.5x the upper limit of normal; creatinine > 1.8 mg/dl)
- History of severe hypersensitivity or virilization due to an endocrine disorder, hormone or Danazol therapy
- Well-documented history of thrombotic event (stroke, DVT or pulmonary embolus)
- Anticoagulant therapy or any drug therapy within the past 6 months that could suppress the hypothalamic-pituitary axis
- Uncontrolled hypertension (>180/110)
- Insulin-dependent or poorly controlled non-insulin-dependent diabetes
- Undiagnosed abnormal vaginal bleeding
- Concurrent use of other investigational medications
- Any condition that might cause the subject to be unable to comply with study instructions
- Use of aminoglutethimide

10.1.7.1 Demographics and Baseline Disease Characteristics

Fifty US and Canadian sites each enrolled 1 to 22 subjects. All 274 subjects randomized received at least one dose of study medication and therefore constitute the ITT population (136 DMPA-SC, 138 Lupron), which was used for safety and efficacy assessments. The "evaluable patient population," defined as subjects who received their 3 and 6-month injections/visits within 7 days of the expected date, consisted of 141 subjects (65 DMPA-SC, 76 Lupron).

Demographic characteristics are summarized in Table 44. There were significant differences between the groups on mean age, with the DMPA-SC group being almost 3 years younger, and on age distribution, with DMPA-SC subjects being over-represented in the <25 year old category and under-represented in the >35 year old category.

Medical Reviewer's Comment:

1) ***The younger mean age in the DMPA-SC group might be associated with disease of shorter duration, which could be less refractory to treatment. However, this is not supported by data in*** Table 45 ***which demonstrates equivalent levels of severity. Information on the interval since diagnosis in each group would be of interest.***

Table 44 Study 268: Demographic Characteristics of ITT Population

Characteristic	DMPA-SC N = 136	Leuprolide N = 138	P-value*
Age (yr)			
Mean ± SD	29.16 ± 6.29	32.09 ± 6.56	0.0002*
Range	19.2 - 45.4	19.4 - 48.0	
<25, n (%)	41 (30.1)	23 (16.7)	0.0058*
25 -35, n (%)	73 (53.7)	75 (54.3)	
>35 (n,%)	22 (16.2)	40 (29.0)	
Race, n (%)			
White	123 (90.4)	114 (82.6)	0.1772
Black	10 (7.4)	15 (10.9)	
Asian/Pacific Islander	1 (0.7)	1 (0.7)	
Mixed/Multiracial	2 (1.5)	8 (5.8)	
Weight (kg)			
Mean, ± SD	70.66 ± 16.56	73.84 ± 19.14	0.1428
Range	45.4 - 124.4	41.7 - 168.2	
Height (cm)†			
Mean ± SD	165.36 ± 6.62	164.88 ± 7.22	0.5651
Range	149.9 - 180.3	147.3 - 188.0	
Body Mass Index (kg/m^2)†			
Mean ± SD	25.83 ± 5.89	27.14 ± 6.22	0.0748
Range	17.8 - 47.3	17.3 - 47.6	
≤25, n (%)	73 (53.7)	61 (44.5)	0.3181
>25 to ≤30, n (%)	31 (22.8)	37 (27.0)	
>30, n (%)	32 (23.5)	39 (28.5)	

* T-tests were chi-square and ANOVA; significance at $p \leq 0.05$
† N=137 for leuprolide group
Source: Table 6, *5.3.5.1.1, p 65*

The baseline status of subjects' signs and symptoms of endometriosis is summarized in Table 45. There were no significant differences among the treatment arms in the frequency or severity of any of the individual components, nor in the composite score, whether or not dyspareunia was included in the composite.

Table 45 Study 268: Baseline Characteristics of ITT Population

Component Severity	DMPA-SC n (%)†	Leuprolide n (%)†	P-Value‡
Dysmenorrhea			
Absent	1 (0.7)	0	0.649
Mild	4 (2.9)	6 (4.4)	
Moderate	73 (53.7)	77 (56.2)	
Severe	58 (42.6)	54 (39.4)	
Total reported	136	137	
Dyspareunia			
Absent	1 (0.7)	2 (1.5)	0.447
Mild	9 (6.6)	3 (2.2)	
Moderate	64 (47.1)	64 (46.7)	
Severe	45 (33.1)	51 (37.2)	
Not Applicable§	17 (12.5)	17 (12.4)	
Total reported	136	137	
Pelvic Pain			
Mild	3 (2.2)	4 (2.9)	0.673
Moderate	97 (71.3)	91 (66.4)	
Severe	36 (26.5)	42 (30.7)	
Total reported	136	137	
Pelvic Tenderness			
None	6 (4.4)	5 (3.6)	0.985
Mild	29 (21.3)	31 (22.6)	
Moderate	77 (56.6)	77 (56.2)	
Severe	24 (17.6)	24 (17.5)	
Total reported	136	137	
Induration			
None	40 (29.4)	38 (27.7)	0.502
Mild	44 (32.4)	35 (25.5)	
Moderate	43 (31.6)	52 (38.0)	
Severe	9 (6.6)	12 (8.8)	
Total reported	136	137	
Composite¶			
Mean ± SD	10.0 ± 1.9	10.3 ± 1.9	0.260
Range	5 – 15	5 – 15	
Total reported	119	120	
Composite¶ Excluding Dyspareunia			
Mean ± SD	7.7 ± 1.8	7.8 ± 1.7	0.554
Range	3 - 12	3 – 12	
Total reported	136	137	

* Pretreatment values were the randomization visit values. If a randomization visit value was missing, then the baseline visit value was used.
† % = (n/total reported) x 100
‡ Statistical tests were chi-square and ANOVA, significance defined at p≤0 05
§ No intercourse for reasons other than pain.
¶ Composite is the sum of dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and induration scores, with absent/none=0, mild=1 moderate=2, and severe=3.
Abbreviations: ITT = intent-to-treat, SD = standard deviation

Source: Table 7, *5.3.5.1.1, p 67*

Medical Reviewer's Comments:

1) ***As recommended by DRUDP, the proportion of sexually inactive subjects at baseline is <20%.***
2) ***Review of*** Table 45 and Table 54 ***indicates that, on average, the levels of severity requested by DRUDP for enrollment were also met.***

10.1.7.2 Withdrawals, compliance, and protocol violations

Ninety-nine DMPA-SC (73%) and 94 Lupron subjects (68%) discontinued the trial prior to completing the full 18 months. Fewer than half of the total withdrawals occurred during the treatment phase; the percentage was higher in the DMPA-SC group (35% of DMPA-SC and 26% of Lupron withdrawals occurred during treatment). Reasons for withdrawal during the treatment phase and during follow-up are shown in Table 46 and Table 47, respectively. In total, 12 DMPA-SC subjects and 11 Lupron subjects withdrew due to adverse events during the treatment phase (see Section 10.1.9.2).

Table 46 Study 268: Detailed Reason for Withdrawal from Treatment

Patient Disposition	Study 268			
	DMPA-SC N=136		Lupron N=138	
	N	%	N	%
Completed Treatment	88	64.7	102	73.9
Withdrew from Treatment	48	35.3	36	26.1
Reason for Withdrawal				
Lost to follow-up	14	10.3	11	8.0
Adverse event	12	8.8	11	8.0
Lack of efficacy	7*	5.1	1	0.7
Problems w/investigator or site	7**	5.1	1	0.7
Protocol violation	4	2.9	7	5.1
Personal Issues	4***	2.9	3***	2.2
Unknown	0	0	2***	1.4

* 5 subjects also had concomitant AEs at the time of withdrawal
** 3 subjects also had concomitant AEs at the time of withdrawal
*** 1 subject also had concomitant AEs at the time of withdrawal
Source: Based on Tables 2, 3a & 3b, pp 6-8, August 31, 2004 communication from applicant

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Table 47 Study 268: Reasons for Withdrawal during 12 Months' Follow-up by Group

Reason for Withdrawal from Follow-up	DMPA-SC N = 88		Leuprolide N = 102		Total N = 190	
	n	%	n	%	n	%
Adverse Event	10	11.4	8	7.8	18	9.5
Protocol Violation	10	11.4	13	12.7	23	12.1
Consent Withdrawn	22	25.0	30	29.4	52	27.4
Lost to Follow-up	9	10.2	7	6.9	16	8.4
Total Withdrawn	51	58.0	58	56.9	109	57.4

Source: Table T1.9, *5.3.5.1.1, p 159*

Medical Reviewer's Comment:

1) ***No additional information clarifying the reason for withdrawal of consent during the follow-up period was provided.***

Subjects who withdrew prior to completing six months of treatment did not have consistently greater baseline severity scores than those who completed treatment (Table 48).

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Table 48 Study 268: Comparison of Baseline Status in Completers and Subjects who Withdrew from Treatment

Variable & Measure	Study 268			
	DMPA-SC		Lupron	
	All	Early	All	Early
Dysmenorrhea N	88	17	100	10
Baseline	2.4	2.5	2.4	2.0
Pelvic Pain N	86	17	101	11
Baseline	2.2	2.4	2.2	2.5
Dyspareunia N	65	11	81	9
Baseline	2.3	2.1	2.4	2.1
Pelvic Tenderness N	87	17	100	11
Baseline	1.9	1.9	1.9	1.8
Induration N	87	17	100	11
Baseline	1.1	1.3	1.3	1.6
Composite Score N	64	11	76	8
Baseline	9.9	9.5	10.4	10.4
Composite Score w/o Dyspareunia N	85	17	97	10
Baseline	7.5	8.1	7.9	8.3

Source: Tables T5.7, T5.8, T5.9.1 & T5.10.1, *5.3.5.1.1, pp 414-47, 448-52, 541-45*

Compliance was based upon receipt of the initial injection of study medication at the randomization visit, and receipt of the second dose at the month 3 visit, to occur within 91 +/- 7 days of the randomization visit. Compliance was 92% in the DMPA-SC group and 93% in the Lupron group.

Protocol violations included:

- Deviations in entry criteria
  - 29 violations occurred in 25 DMPA-SC subjects
  - 27 violations occurred in 23 Lupron subjects
- Failure to withdraw subjects who developed withdrawal criteria
  - 1 violation occurred in 1 DMPA-SC subject
  - 2 violations occurred in 2 Lupron subjects
- Treatment deviations (incorrect administration or wrong study medication)
  - 3 violations occurred in 3 DMPA-SC subjects
  - 2 violations occurred in 2 Lupron subjects
- Use of excluded concomitant medication
  - 4 violations occurred in 4 DMPA-SC subjects
  - 3 violations occurred in 3 Lupron subjects

Medical Reviewer Comment:

1) ***The majority of the entry criteria violations related to 44 subjects who did not meet the severity criteria at the baseline and/or randomization visits. Relatively little impact on study results is attributed to these violations, as 26 of these subjects withdrew early from treatment.***

10.1.8 Efficacy

10.1.8.1 Key Efficacy Assessments

The clinical efficacy variables were based on the five symptoms/signs from the Biberoglu and Behrman scale[1] (Table 3) and were evaluated at baseline and all scheduled visits. A positive response was defined as an improvement of at least one point in the score for each category after six months of treatment as compared to baseline. During the follow-up period, the three pain scores (dysmenorrhea, dyspareunia and pelvic pain) were assessed monthly by asking subjects to rate their pain over the previous month. Subject recall was facilitated by use of a daily diary which was brought to each visit. The two signs of endometriosis (induration and pelvic tenderness) were evaluated during a pelvic exam at months 9, 12, 15 and 18 of the follow-up period, as well as at monthly exams during the treatment phase. Any non-endometriosis-related medical condition interfering with pain analysis was listed as an adverse event, and the pelvic pain category rated as non-applicable for that time interval.

Efficacy analysis was done on both the Intent to Treat (ITT) and the Evaluable Patient (EP) populations. The former was defined as all subjects who received at least one dose of study medication; the latter as all subjects who received their three and six-month injection/visits within +/- 7 days of the expected date and who did not use any excluded concomitant medications [no subjects were excluded on this basis]. In the ITT population, both last-observation-carried forward (LOCF) and observed case (OC) analyses were done; in the EP population, only the OC analyses was conducted. With LOCF analysis, where there was no data after the baseline visit, the baseline data were imputed for all subsequent time periods; with OC analysis, only the collected data were used.

Medical Reviewer's Comment:

1) ***In the DMPA-SC group, 11 subjects withdrew prior to the month 1 assessment, compared to five subjects receiving Lupron. In both these cases, baseline data was imputed for all assessments of treatment effect.***

10.1.8.2 Pharmacokinetic Assessments

Pharmacokinetic sampling was not done in this study.

Medical Reviewer's Comment:

1) ***Data on estradiol suppression was collected, which ideally could be used for pharmacodynamic assessment; however, the low sensitivity — pg/ml) of the assay and the infrequent sampling renders this data of little utility.***

10.1.8.3 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint was demonstration of non-inferiority of DMPA-SC compared to Lupron in the reduction of endometriosis-associated pain, as determined by ratings on the five pain signs/symptoms. A responder analysis was used, comparing the proportion of subjects in each treatment arm who improved at least one point from baseline in each of the five categories. Non-inferiority was defined where the lower bound of the 96% two-sided confidence interval for the difference between the two drugs' improvement rates was not worse than -20%. In order for DMPA-SC to be considered clinically non-inferior, statistical non-inferiority was required on at least four of the five signs/symptoms evaluated, and an overall clinically meaningful improvement over baseline was required, as demonstrated by an improvement of at least 4 points over baseline in the total composite score. In those subjects who were sexually inactive for reasons unrelated to endometriosis, dyspareunia scores were missing values, and the clinically meaningful criterion was modified to an improvement of at least 3 points in the remaining four categories.

Response rates on each outcome measure at each month of treatment are shown in Table 49. Analysis of the five signs and symptoms of endometriosis in the ITT-OC population at month 6 as compared to baseline showed that DMPA-SC was statistically non-inferior to Lupron on four of the 5 outcome measures (dysmenorrhea, dyspareunia, pelvic pain and pelvic tenderness). Statistically significant non-inferiority on induration was not demonstrated. Although the response rate on DMPA-SC was less than that on Lupron on every outcome measure and at almost every assessment time during the treatment period, the pre-specified criterion for statistical non-inferiority was met for four of five outcome measures.

At month 6, results in the EP population were consistent, although only three of the outcome measures were statistically non-inferior (dysmenorrhea, pelvic pain and pelvic tenderness). In the ITT-LOCF analysis, only pelvic tenderness met the criteria for statistical non-inferiority, a result the applicant attributes in part to the greater frequency of early treatment discontinuation in the DMPA-SC group and the longer delay in achieving amenorrhea and hence perhaps greater persistence of dysmenorrhea in the DMPA-SC group.

At month 12, six months after cessation of treatment, the statistical non-inferiority of DMPA-SC was maintained in the ITT-OC analysis on four of five outcomes, although not all the same ones demonstrated at the end of treatment (dysmenorrhea, pelvic pain, pelvic tenderness and induration). At this time, a higher response rate for DMPA-SC than for Lupron was demonstrated on all four variables. In the EP analysis at 12 months, statistical non-inferiority was maintained on dysmenorrhea, pelvic pain and pelvic tenderness. Analysis using the ITT-LOCF population was not done for time periods beyond the six months of treatment.

At month 18, non-inferiority was shown in the ITT-OC analysis on all five outcomes with DMPA-SC's response rate exceeding Lupron on all variables except pelvic pain. At 18 months, analysis of the EP population found statistical non-inferiority of DMPA-SC compared to Lupron for dysmenorrhea, dyspareunia and pelvic tenderness.

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Table 49 Study 268: Response of Signs and Symptoms of Endometriosis by Month and Treatment Group (ITT Observed Case Analysis)

Component Visit	DMPA-SC		Leuprolide		P-Value‡	96% CI
	Total Reported	n (%)†	Total Reported	n (%)†		
Dysmenorrhea						
Month 1	125	94 (75.2)	132	96 (72.7)	<0.001§	-8.77, 13.72
Month 2	120	93 (77.5)	125	118 (94.4)	0.237	-25.80, -8.00
Month 3	105	90 (85.7)	117	113 (96.6)	0.008§	-18.69, -3.05
Month 4	94	86 (91.5)	109	105 (96.3)	<0.001§	-11.82, 2.14
Month 5	87	78 (89.7)	104	102 (98.1)	<0.001§	-15.68, -1.16
Month 6 (EOT)	88	80 (90.9)	100	97 (97.0)	<0.001§	-13.30, 1.12
Month 12	51	37 (72.5)	64	42 (65.6)	<0.001§	-10.79, 24.64
Month 18	36	24 (66.7)	44	27 (61.4)	0.009§	-16.79, 27.40
Dyspareunia						
Month 1	90	59 (65.6)	103	68 (66.0)	0.002§	-14.53, 13.60
Month 2	84	68 (81.0)	95	78 (82.1)	<0.001§	-13.10, 10.80
Month 3	78	60 (76.9)	94	78 (83.0)	0.012§	-18.69, 6.58
Month 4	73	56 (76.7)	84	72 (85.7)	0.039	-21.84, 3.84
Month 5	64	49 (76.6)	76	64 (84.2)	0.034	-21.52, 6.22
Month 6 (EOT)	65	51 (78.5)	79	67 (84.8)	0.018§	-19.72, 7.02
Month 12	35	28 (80.0)	45	38 (84.4)	0.036	-22.23, 13.34
Month 18	29	27 (93.1)	29	22 (75.9)	<0.001§	-1.74, 36.22
Pelvic Pain						
Month 1	126	82 (65.1)	132	85 (64.4)	<0.001§	-11.54, 12.91
Month 2	119	90 (75.6)	127	106 (83.5)	0.009§	-18.38, 2.72
Month 3	106	79 (74.5)	120	101 (84.2)	0.027	-20.71, 1.43
Month 4	95	73 (76.8)	110	91 (82.7)	0.006§	-17.46, 5.69
Month 5	86	66 (76.7)	106	88 (83.0)	0.009§	-18.27, 5.72
Month 6 (EOT)	86	71 (82.6)	101	88 (87.1)	0.002§	-15.42, 6.27
Month 12	51	37 (72.5)	64	44 (68.8)	0.003§	-13.71, 21.31
Month 18	37	29 (78.4)	44	35 (79.5)	0.019§	-19.86, 17.53
Pelvic Tenderness						
Month 1	125	72 (57.6)	130	78 (60.0)	0.002§	-15.07, 10.27
Month 2	118	77 (65.3)	121	87 (71.9)	0.013§	-18.96, 5.67
Month 3	104	74 (71.2)	116	86 (74.1)	0.002§	-15.36, 9.39
Month 4	95	71 (74.7)	106	84 (79.2)	0.005§	-16.73, 7.72
Month 5	83	58 (69.9)	103	79 (76.7)	0.022	-20.25, 6.61
Month 6 (EOT)	85	65 (76.5)	98	79 (80.6)	0.005§	-16.66, 8.38
Month 12	49	36 (73.5)	62	45 (72.6)	0.007§	-16.53, 18.31
Month 18	35	25 (71.4)	44	29 (65.9)	0.007§	-15.97, 27.01
Induration						
Month 1	96	51 (53.1)	99	62 (62.6)	0.068	-23.97, 4.97
Month 2	86	49 (57.0)	92	71 (77.2)	0.511	-34.38, -6.01
Month 3	79	56 (70.9)	89	71 (79.8)	0.047	-22.56, 4.78
Month 4	69	46 (66.7)	80	67 (83.8)	0.339	-31.5, -2.67
Month 5	61	44 (72.1)	77	65 (84.4)	0.138	-26.82, 2.25
Month 6 (EOT)	66	49 (74.2)	75	65 (86.7)	0.128	-26.12, 1.27
Month 12	37	30 (81.1)	50	40 (80.0)	0.007§	-16.53, 18.69
Month 18	27	24 (88.9)	35	31 (88.6)	0.006§	-16.31, 16.95

* Response (ie, improvement) defined as a decrease of at least 1 point in the score relative to pretreatment (primary endpoint was the response at month 6).

The p values tests the null hypothesis: DMPA-SC % improved – Lupron % improved is <= -20%

At baseline, DMPA-SC N=136, Lupron N=138

Source: Table 10, *5.3.5.1.1, p 73*

Table 50 compares results at the end of treatment reached by the ITT-OC analysis, which is the primary analysis reported by the applicant, with the ITT-LOCF and EP analyses. On the applicant's primary analysis, non-inferiority is demonstrated on four endpoints, missing only on induration, thus satisfying the pre-set criteria (non-inferiority on four of five endpoints) for overall DMPA-SC non-inferiority to Lupron. On the ITT-LOCF analysis, statistical non-inferiority is shown only for pelvic tenderness. The EP analysis also fails to meet the overall threshold for non-inferiority, meeting criteria only for dysmenorrhea, pelvic pain and pelvic tenderness.

Table 50 Study 268: Response at 6 Months: Comparison of Three Analyses

Component	Analysis	DMPA-SC		Lupron			
		N	%	N	%	p-value	96% CI
Dysmenorrhea	ITT-OC	88	90.9	100	97.0	<0.001	-13.3, 1.12
	ITT-LOCF	135	75.6	137	92.0	0.206	-25.39, -7.44
	EP	65	87.7	75	97.3	0.01	-18.85, -0.44
Dyspareunia	ITT-OC	65	78.5	79	84.8	0.018	-19.72, 7.02
	ITT-LOCF	100	66.0	108	80.6	0.185	-27.05, -2.06
	EP	47	78.7	59	86.4	0.05	-23.03, 7.59
Pelvic Pain	ITT-OC	86	82.6	101	87.1	0.002	-15.42, 6.27
	ITT-LOCF	134	67.2	136	80.1	0.093	-23.89, -2.08
	EP	63	82.5	76	86.8	0.005	-16.96, 8.35
Pelvic Tenderness	ITT-OC	85	76.5	98	80.6	0.005	-16.66, 8.38
	ITT-LOCF	134	67.2	133	72.9	0.005	-17.26, 5.73
	EP	63	79.4	73	84.9	0.014	-19.12, 7.99
Induration	ITT-OC	66	74.2	75	86.7	0.128	-26.12, 1.27
	ITT-LOCF	105	63.8	101	82.2	0.394	-30.78, -5.95
	EP	50	74.0	55	90.9	0.336	-31.94, -1.88

N = Total reported; % = % improved (i.e., with >=1 point decrease in score relative to baseline)
p-value tests the H_0 that DMPA-SC % improved – Lupron % improved <= -20%. Statistical non-inferiority concluded if p <0.02.
CI = 96% confidence intervals around point estimate of difference in improvement rate between DMPA-SC and Lupron
Source: Based on Tables 10-12, *5.3.5.1.1, pp 73-75*

Medical Reviewer's Comments:

1) ***The FDA statistical review of the protocols for Studies 268 and 270 in January 2001 noted that the sponsor proposed that the ITT-LOCF analysis would be considered the primary analysis. However, the reviewer also noted that the ICH E9 guidelines express concern about the role of ITT analyses in equivalence trials, as they may not be conservative. The FDA statistician recommended that a per protocol (PP) analysis also be performed, with a goal of demonstrating consistent results between the ITT-LOCF and the PP analyses. In this study, the EP analysis would seem least useful, as it is overly restrictive and sacrifices data (i.e., eliminates subjects from the analysis) based on late administration of the study drugs. This is unwarranted, since both study drugs are depot formulations that allow for "late" administration. The ITT-OC analysis would seem closest to the FDA-requested PP analysis, as it includes all subjects who have data at baseline and the 6 month primary outcome period.***
2) ***The applicant attributes the discrepancy between the ITT-OC and ITT-LOCF analyses to the greater proportion of DMPA-SC subjects who terminated the study prior to completing the 6 months of treatment, as compared to the Lupron subjects. The greater latency in***

achieving amenorrhea in the DMPA-SC group would also have limited the improvement seen in dysmenorrhea.

A composite score was also used to evaluate the clinical meaningfulness of the treatment results, with the criterion for meaningful change set at a mean decrease from baseline of at least 4 points. At the end of treatment, a statistically and clinically significant change from baseline was seen in each treatment group in the ITT-OC population: a mean decrease of 6.2 points in the DMPA-SC group, and a mean decrease of 7.7 points in the Lupron group. Results were consistent in the EP and ITT-LOCF analyses, with respective mean decreases of 6.4 (DMPA-SC) and 7.9 (Lupron) and 4.9 (DMPA-SC) and 6.9 (Lupron) in these two analyses.

The improvement in the composite score remained statistically and clinically significant at 6 months of follow-up, with decreases of 4.9 points and 5.7 points in the DMPA-SC and Lupron groups, respectively, in the ITT-OC analysis. The comparative change in the EP analysis was -5.3 (DMPA-SC) and -5.7 (Lupron), and in the ITT-LOCF analysis, -4.9 (DMPA-SC) and -6.9 (Lupron). At 12 months of follow-up, the mean decreases were 5.3 and 5.1, for DMPA-SC and Lupron, respectively, in the ITT-OC analysis, and 5.3 and 5.7 in the EP analysis, thus, continuing to meet the threshold for clinical as well as statistical significance. There were no additional analyses using the ITT-LOCF population at months 12 or 18.

Results for the ITT-OC analyses for each month on treatment are displayed in Table 51. The confidence interval for the difference between treatment group mean changes indicates that the decrease in the Lupron group was statistically greater at months 2 through 6 than that in the DMPA-SC group. Comparative data for the three populations analyzed are presented in Table 52.

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Table 51 Study 268: Mean Change in Composite Score by Time and Treatment Group

Visit		DMPA-SC	Leuprolide	95% CI†	
				Lower	Upper
Month 1	Total reported	90	105		
	Pretreatment mean (SD)‡	10.0 (2.0)	10.3 (1.9)		
	Mean change (SD)	-4.0 (2.9)	-4.2 (2.9)	-0.6	1.1
	Within group test§	<0.001	<0.001		
Month 2	Total reported	84	94		
	Pretreatment mean (SD)‡	9.9 (1.9)	10.3 (2.0)		
	Mean change (SD)	-4.7 (2.8)	-6.2 (2.4)	0.8	2.3
	Within group test§	<0.001	<0.001		
Month 3	Total reported	79	92		
	Pretreatment mean (SD)‡	10.1 (1.8)	10.3 (1.8)		
	Mean change (SD)	-5.2 (2.9)	-6.7 (2.7)	0.7	2.3
	Within group test§	<0.001	<0.001		
Month 4	Total reported	72	84		
	Pretreatment mean (SD)‡	9.9 (1.8)	10.4 (1.8)		
	Mean change (SD)	-5.7 (3.0)	-7.3 (2.6)	0.7	2.5
	Within group test§	<0.001	<0.001		
Month 5	Total reported	61	75		
	Pretreatment mean (SD)‡	10.0 (1.8)	10.3 (1.8)		
	Mean change (SD)	-5.7 (3.3)	-7.7 (2.5)	1.0	3.0
	Within group test§	<0.001	<0.001		
Month 6 (EOT)	Total reported	64	76		
	Pretreatment mean (SD)‡	9.9 (1.8)	10.4 (1.8)		
	Mean change (SD)	-6.2 (3.4)	-7.7 (2.6)	0.5	2.6
	Within group test§	<0.001	<0.001		
Month 12	Total reported	35	44		
	Pretreatment mean (SD)‡	9.7 (2.1)	10.4 (2.0)		
	Mean change (SD)	-4.9 (3.6)	-5.7 (2.8)	-0.7	2.2
	Within group test§	<0.001	<0.001		
Month 18	Total reported	27	30		
	Pretreatment mean (SD)‡	9.7 (2.2)	10.3 (1.9)		
	Mean change (SD)	-5.3 (3.0)	-5.1 (3.1)	-1.8	1.5
	Within group test§	<0.001	<0.001		

* Composite score includes dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and induration. The composite was not assessed at a visit if a component was not assessed at that visit (primary efficacy timepoint was month 6).

† 95% CI for the difference between treatment group mean changes.

Source: Table 13, *5.3.5.1.1, p 77*

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Table 52 Study 268: Change in Composite Score: Comparison of Three Analyses

Time Period	Analysis Population	DMPA-SC		Lupron		Threshold for Clinical Meaningfulness
		N	Change	N	Change	
Month 6 (End of Treatment)	ITT-OC	64	-6.2	76	-7.7	-4
	ITT-LOCF	100	-4.9	109	-6.9	-4
	EP	46	-6.4	55	-7.9	-4
Month 12 (6 mo F/U)	ITT-OC	35	-4.9	44	-5.7	-4
	EP	31	-5.3	35	-5.7	-4
Month 18 (12 mo F/U)	ITT-OC	27	-5.3	30	-5.1	-4
	EP	26	-5.3	22	-5.7	-4
Composite Score Excluding Dyspareunia						
Month 6 (End of Treatment	ITT-OC	85	-4.8	97	-6.0	-3
	ITT-LOCF	134	-3.9	136	-5.3	-3
	EP	62	-4.9	72	-6.2	-3
Month 12 (6 mo F/U)	ITT-OC	50	-3.8	61	-4.0	-3
	EP	45	-4.0	49	-4.0	-3
Month 18 (12 mo F/U)	ITT-OC	35	-3.7	44	-3.9	-3
	EP	34	-3.7	34	-4.0	-3

Source: Based on Tables 13-18, *5.3.5.1.1, pp 77-82*

A pre-specified alternate analysis of the composite score involved eliminating dyspareunia, so that subjects who were not sexually active for reasons unrelated to endometriosis could contribute to the analysis. Excluding dyspareunia from the composite score, in the ITT-OC analysis, the mean decrease in the composite score at the end of treatment was 4.8 points in the DMPA-SC group and 6.0 points in the Lupron group, surpassing the threshold for clinical significance that was set at decrease of 3 in the composite score excluding dyspareunia. These changes remained clinically significant at month 12, with mean changes of -3.8 and -4.0 in the DMPA-SC and Lupron groups, respectively, and at month 18, with changes of -3.7 and -3.9, respectively. Again, examination of the confidence intervals shows that the difference between treatment group mean changes was significant, favoring Lupron, at months 2 through 6. Table 52 also shows the relative results from the ITT-OC, EP and ITT-LOCF analyses.

There were no marked differences noted in subgroup analyses of composite score for BMI, age and race.

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Medical Reviewer's Comments:

1) ***The composite score data was available on only 47% of the DMPA-SC subjects and 55% of Lupron subjects by the end of treatment; by 6 months of follow-up, it was calculated on only 26% of DMPA-SC subjects and 31% of Lupron subjects. The composite score was calculated only where all five components were available; it appears that the drop off at 6 and 12 months was due primarily to missing data on dyspareunia and induration. No explanation is provided as to why fewer subjects had scores for induration than for pelvic tenderness; both would have been rated during the pelvic examination***
2) ***The composite score Ns when dyspareunia is excluded are inconsistent with Ns for the individual outcome measures; e.g., while 85 DMPA-SC and 97 Lupron subjects had composite score data at month 6 and 50 DMPA-SC and 60 Lupron subjects had composite score data at month 12, only 66 DMPA-SC and 75 Lupron subjects had induration data available at month 6, and only 37 and 49, respectively, at 12 months.***

10.1.8.4 Secondary Efficacy Endpoint Analysis

Secondary endpoints were:

- Time to recurrence of symptoms following treatment discontinuation
- The proportion of women in each treatment arm who experienced an improvement from baseline in each of the five categories, at each study visit
- Change from baseline in patient quality of life

Time to symptom recurrence, defined as increase of at least one point in the scales for dysmenorrhea, dyspareunia and pelvic pain during the follow-up period was compared between treatment arms using a Kaplan-Meier survival analysis. Additional analyses of each of the five signs/symptoms of endometriosis were also done.

Time to symptom recurrence/worsening (defined as an increase of at least one point from the value at the end of treatment on any of the five outcome categories) was evaluated during the 12 month follow-up period off treatment. The three patient-reported symptoms of dysmenorrhea, dyspareunia and pelvic pain were evaluated monthly in the follow-up period; the physician-assessed signs, pelvic tenderness and induration, were evaluated at 3-monthly intervals following treatment cessation (months 9, 12, 15 and 18). Results are displayed in Table 53. The three symptoms tended to recur or worsen approximately three months after the end of treatment; while there appeared to be greater latency in the return of the two signs; it is likely that this is due to longer ascertainment intervals. Only those subjects who had experienced improvement during treatment were included in this analysis. Over half of subjects in each group experienced exacerbation of the three symptoms once treatment was stopped. Smaller proportions, on the order of 20-50%, had worsening of pelvic tenderness or induration. There were no significant differences between the DMPA-SC and Lupron groups.

The mean change and the significance of the change in each sign/symptom from baseline at each month of treatment and follow-up was tested in each treatment group; the data are in Table 54. Each category showed significant decrease from pretreatment levels at each month assessed and in each treatment group.

Medical Reviewer's Comment:

1) ***It is not explicitly stated, but it appears that these analyses were only conducted using the ITT-OC population. No data are presented for EP or ITT-LOCF.***

2) ***Subjects who withdrew early from treatment generally had improvement scores about 50% less than completers in the DMPA-SC group. The difference between completers and early withdrawers was less in the Lupron group (see*** Table 27***).***

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Table 53 Study 268: Time to Recurrence Following Discontinuation of Treatment

Sign/Symptom	DMPA-SC	Leuprolide	P-Value*
Dysmenorrhea			
Total reported†	80	97	
No. (%) of patients with event	58 (72.5)	80 (82.5)	
No. (%) of patients censored‡	22 (27.5)	17 (17.5)	
Median time (days)§	101	96	0.107
25th, 75th percentile (days)	59, 154	64, 134	
Dyspareunia			
Total reported†	53	70	
No. (%) of patients with event	33 (62.3)	46 (65.7)	
No. (%) of patients censored‡	20 (37.7)	24 (34.3)	
Median time (days)§	97	106	0.913
25th, 75th percentile (days)	35, 281	64, 230	
Pelvic Pain			
Total reported†	71	88	
No. (%) of patients with event	48 (67.6)	68 (77.3)	
No. (%) of patients censored‡	23 (32.4)	20 (22.7)	
Median time (days)§	96	99	0.591
25th, 75th percentile (days)	33, 219	37, 183	
Pelvic Tenderness			
Total reported†	65	79	
No. (%) of patients with event	30 (46.2)	42 (53.2)	
No. (%) of patients censored‡	35 (53.8)	37 (46.8)	
Median time (days)§	184	184	0.855
25th, 75th percentile (days)	97, 407	95, 367	
Induration			
Total reported†	49	65	
No. (%) of patients with event	13 (26.5)	25 (38.5)	
No. (%) of patients censored‡	36 (73.5)	40 (61.5)	
Median time (days)§	--	365	0.359
25th, 75th percentile (days)	181, --	111, --	

* P value is based on log-rank test; significance defined at $p \leq 0.05$
† Includes only those patients whose symptoms had improved between pretreatment and month 6 (EOT).
‡ A patient was censored if the symptom had not worsened either at the time of leaving the study or at the end of the 12-month follow-up period.
§ Kaplan-Meier estimate of median time to return of symptoms.
-- No median or 75th percentile value because it had not been achieved during the 12-month follow-up period (eg no available median because at least half of the patients had not reached that endpoint yet).
Source: Table 19, *5.3.5.1.1, p 84*

Table 54 Study 268: Mean Change from Baseline in Symptoms and Signs

	Dysmenorrhea		Dyspareunia		Pelvic Pain		Pelvic Tenderness		Induration	
Visit	DMPA-SC	Lupron	DMPA-SC	Lupron	DMPA-SC	Lupron	DMPA-SC	Lupron	DMPA-SC	Lupron
Pre-tx N, Mean (SD)	136 2.4 (0.6)	137 2.4 (0.6)	119 2.3 (0.6)	120 2.4 (0.6)	136 2.2 (0.5)	137 2.3 (0.5)	136 1.9 (0.7)	137 1.9 (0.7)	136 1.2 (0.9)	137 1.3 (1.0)
Month 1 (N, Mean change (SD); p value)	125 -1.3 (1.0) <0.001	132 -1.1 (1.0) <0.001	91 -0.9 (1.0) <0.001	105 -1.1 (1.0) <0.001	126 -0.8 (0.9) <0.001	132 -0.9 (0.9) <0.001	126 -0.6 (0.7) <0.001	131 -0.7 (0.9) <0.001	126 -0.3 (0.9) <0.001	131 -0.5 ((0.8) <0.001
Month 2 (N, Mean change (SD); p value)	120 -1.3 (1.0) <0.001	125 -2.0 (0.9) <0.001	84 -1.2 (1.0) <0.001	97 -1.4 (1.0) <0.001	119 -1.0 (0.8) <0.001	127 -1.3 (0.9) <0.001	120 -0.8 (0.9) <0.001	125 -0.9 (0.8) <0.001	120 -0.5 (0.9) <0.001	125 -0.8 (0.9) <0.001
Month 3 (N, Mean change (SD); p value)	105 -1.5 (0.9) <0.001	117 -2.1 (0.8) <0.001	79 -1.3 (1.2) <0.001	96 -1.5 (1.0) <0.001	106 -1.1 (0.8) <0.001	120 -1.3 (0.9) <0.001	106 -0.9 (0.9) <0.001	119 -1.1 (0.9) <0.001	106 -0.6 (0.9) <0.001	119 -0.8 (1.0) <0.001
Month 4 (N, Mean change (SD); p value)	94 -1.7 (0.9) <0.001	109 -2-2 (0.7) <0.001	73 -1.3 (1.1) <0.001	86 -1.6 (1.0) <0.001	95 -1.1 (0.9) <0.001	110 -1.4 (1.0) <0.001	96 -1.0 (0.9) <0.001	109 -1.2 (1.0) <0.001	96 -0.6 (0.9) <0.001	109 -0.9 (0.9) <0.001
Month 5 (N, Mean change (SD); p value)	87 -1.7 (0.9) <0.001	104 -2-2 (0.7) <0.001	64 -1.3 (1.1) <0.001	78 -1.6 (1.0) <0.001	86 -1.2 (0.9) <0.001	106 -1.4 (1.0) <0.001	86 -0.9 (1.1) <0.001	105 -1.2 (1.0) <0.001	85 -0.7 (0.9) <0.001	105 -0.9 (0.9) <0.001
Month 6 (N, Mean change (SD); p value)	88 -1.8 (0.9) <0.001	100 -2.2 (0.8) <0.001	65 -1.4 (1.2) <0.001	81 -1.6 (1.0) <0.001	86 -1.2 (0.9) <0.001	101 -1.4 (0.9) <0.001	87 -1.0 (0.9) <0.001	100 -1.3 (0.9) <0.001	87 -0.7 (1.0) <0.001	100 -1.0 (1.0) <0.001
Early w/d (N, Mean change (SD) p value)	17 -1.1 (1.1) 0.002	10 -1.4 (0.8) 0.008	11 -0.5 (1.3) NS	9 -1.2 (1.0) 0.016	8 -0 6 (0.7) NS	12 -0.7 (0.9) NS	17 -0.6 (0.9) 0.031	11 -0.8 (1.1) NS	17 -0.4 (0.9) NS	11 -0.8 (0.6) 0.008
Month 9 (N, Mean change (SD); p value)	61 -1.4 (1.0) <0.001	76 -1.4 (1.0) <0.001	44 -1.2 (1.0) <0.001	55 -1.8 (1.1) <0.001	61 -1.0 (0.9) <0.001	77 -1.2 (0.9) <0.001	62 -0.8 (1.0) <0.001	75 -1.2 (0.9) <0.001	62 -0.7 (0.9) <0.001	75 -1.0 (0.9) <0.001
Month 12 (N, Mean change (SD); p value)	51 -1.1 (1.0) <0.001	64 -0.9 (1.0) <0.001	35 -1.2 (1.0) <0.001	46 -1.5 (1.1) <0.001	51 -1.1 (1.0) <0.001	64 -1.1 (0.9) <0.001	50 -1.0 (1.1) <0.001	62 -1.0 (0.9) <0.001	50 -0.7 (0.9) <0.001	61 -1.0 (1.0) <0.001
Month 15 (N, Mean change (SD); p value)	38 -1.0 (0.9) <0.001	46 -0.8 (0.9) <0.001	30 -1.4 (0.9) <0.001	32 -1.5 (1.1) <0.001	38 -0.9 (0.7) <0.001	46 -1.2 (0.8) <0.001	37 -1.0 (1.0) <0.001	45 -1.1 (0.9) <0.001	37 -0.9 (0.9) <0.001	45 -1.1 (1.0) <0.001
Month 18 (N, Mean change (SD); p value)	36 -0.8 (0.8) <0.001	44 -0.8 (0.9) <0.001	29 -1.5 (0.9) <0.001	30 -1.3 (1.0) <0.001	37 -1.0 (0.8) <0.001	44 -1.1 (0.8) <0.001	36 -0 8 (1.1) <0.001	44 -1.0 (0.9) <0.001	35 -1.0 (0.9) <0.001	44 -1.0 (0.9) <0.001

* The p-value is based on the Kruskal-Wallis evaluation of **median change** from baseline within each treatment group

Note: Only data from those follow-up assessments where all five signs/symptoms were assessed are shown. Changes in dysmenorrhea, dyspareunia and pelvic pain remained significant at all monthly intervals in the 12 month follow-up period.

Source: Based on Tables T5.7-T5.8, *5.3.5.1.1, pp 388-413*

Quality of life was measured by outcomes research assessment measures, the EHP-30 and the SF-36, and by the Patient Satisfaction Questionnaire (PSQ) and the daily diary. The EHP-30 is an

endometriosis-specific measure containing 30 items on a 5-point Likert scale, rating the frequency of manifestations of endometriosis over the past four weeks. Four scales of the EHP-30 were specified as endpoints and analyzed hierarchically (pain, sexual intercourse, emotional well-being and self-image). The SF-36 is a global quality of life measure, evaluating 36 items relative to their status one year before. Three scales of this instrument were specified as endpoints and analyzed hierarchically (role-physical, social function and physical function). Subjects also completed the PSQ, rating their response to and satisfaction with the assigned treatment. Finally, the daily diary was used to collect information relating to daily productivity as it was affected by endometriosis symptoms.

Overall, results on the secondary endpoints were similar between the DMPA-SC and Lupron groups, although no formal criteria for statistical non-inferiority were defined.

Data from the EHP-30 is in Table 55. The DMPA-SC group demonstrated significant decreases from baseline in the four pre-specified subscales at the end of treatment, and these changes were maintained at 12 months of follow-up. Similar results were seen in the Lupron group. Results in both groups were consistent when the ITT-LOCF and EP populations were analyzed.

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Table 55 Study 268: EH-30 Subscale Means (SD) and Change from Randomization

EHP-30 Scale		DMPA-SC		
		Randomization	Month 6	Month 18
Pain‡	Total reported	133	104	49
	Mean (SD)	49.02 (16.71)	21.68 (23.06)	29.55 (22.12)
	T-Test of change from randomization		<0.001†	<0.001†
Control and powerlessness	Total reported	133	104	49
	Mean (SD)	61.09 (23.80)	27.62 (29.23)	33.84 (29.76)
	T-Test of change from randomization		<0.001†	<0.001†
Social support	Total reported	134	104	49
	Mean (SD)	49.81 (23.45)	30.95 (27.67)	29.97 (26.97)
	T-Test of change from randomization		<0.001†	<0.001†
Emotional well-being‡	Total reported	134	104	49
	Mean (SD)	43.83 (18.56)	28.66 (20.65)	27.47 (19.13)
	T-Test of change from randomization		<0.001†	<0.001†
Self-image‡	Total reported	134	104	49
	Mean (SD)	42.66 (26.63)	30.69 (29.06)	28.40 (28.56)
	T-Test of change from randomization		0.001†	0.008†
Intercourse‡	Total reported	116	86	38
	Mean (SD)	62.64 (25.10)	41.35 (30.56)	38.29 (30.28)
	T-Test of change from randomization		<0.001†	<0.001†

* A lower mean score indicates greater improvement.
† T-test significance defined as $p \leq 0.05$
‡ Prespecified scale
Source: Table 20, *5.3.5.1.1, p 86*

Medical Reviewer's Comments:

1) *While the applicant indicates that both the EHP-30 and the SF-36 are validated measures, no details about the validation process, such as the population in which each questionnaire was validated, were provided. The applicant was advised during the clinical development program that quality of life measures are not generally accepted for labeling claims.*
2) *Data at follow-up which appears to show an ongoing decrease in symptomatology is likely to be biased by the withdrawal from follow-up of those subjects who failed to achieve or maintain symptom improvement.*

The SF-36 data for the DMPA-SC group are displayed in Table 56. The three pre-specified subscales all showed significant improvement from randomization to the end of treatment, which was maintained at 12 months' follow-up. Similar results were seen in the Lupron group. Again, results in both groups were consistent when the ITT-LOCF and EP populations were analyzed.

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Table 56 Study 268: SF-36 Subscale Means and Change from Randomization

SF-36 Scale		DMPA-SC		
		Randomization	Month 6	Month 18
Physical function‡	Total reported	135	103	49
	Mean (SD)	69.61 (21.66)	82.61 (18.84)	81.33 (21.72)
	T-Test of change from randomization		<0.001†	0.001†
Role physical‡	Total reported	135	103	49
	Mean (SD)	31.73 (34.17)	66.02 (41.40)	55.10 (44.77)
	T-Test of change from randomization		<0.001†	0.001†
Bodily pain	Total reported	135	104	49
	Mean (SD)	39.00 (16.34)	61.26 (24.56)	56.18 (23.67)
	T-Test of change from randomization		<0.001†	<0.001†
General health	Total reported	133	104	49
	Mean (SD)	56.05 (21.70)	62.67 (22.64)	64.61 (21.52)
	T-Test of change from randomization		<0.001†	0.016†
Vitality	Total reported	135	104	49
	Mean (SD)	38.11 (18.56)	47.39 (22.24)	50.10 (23.75)
	T-Test of change from randomization		<0.001†	0.007†
Social functioning‡	Total reported	135	104	49
	Mean (SD)	56.94 (22.94)	72.12 (25.49)	70.66 (26.83)
	T-Test of change from randomization		<0.001†	0.038†
Role emotional	Total reported	134	103	49
	Mean (SD)	54.23 (41.62)	67.31 (40.15)	68.03 (40.23)
	T-Test of change from randomization		0.036†	0.149
Mental health	Total reported	135	104	49
	Mean (SD)	62.47 (18.05)	70.27 (17.34)	70.78 (16.58)
	T-Test of change from randomization		0.002†	0.124

* A higher mean score indicates greater improvement.
† T-test significance defined as $p \leq 0.05$
‡ Prespecified scale
Source: Table 21, *5.3.5.1.1, p 88*

The Patient Satisfaction Questionnaire evaluated patient-perceived improvements in status and satisfaction with the treatment at 3 month intervals during the treatment phase. Both groups indicated significant improvements in physical health and sexual relationship at both months 3 and 6, and in emotional health by month 6 (Table 57). The DMPA-SC group was slightly less willing to recommend their treatment to a friend or to consider using it in the future (results based on a 10 point scale).

Table 57 Study 268: Patient Satisfaction Questionnaire Data

PSQ Item	Visit Mean (SD) N						T-Test of Change			
	Randomization		Month 3		Month 6		Randomization to Month 3		Randomization to Month 6	
	DMPA-SC	LPLD	DMPA-SC	LPLD	DMPA-SC	LPLD	DMPA-SC	LPLD	DMPA-SC	LPLD
Emotional Health	6.01 (1.97) 134	5.73 (2.04) 137	6.30 (2.05) 107	6.21 (2.27) 121	6.50 (1.98) 103	6.67 (2.23) 109	.209	.047*	.148	.001*
Physical Health	5.60 (1.90) 134	5.29 (2.02) 137	6.60 (1.79) 107	6.42 (2.20) 121	6.50 (1.96) 103	7.09 (1.89) 109	< .001*	< .001*	< .001*	< .001*
Sexual Relationship	5.02 (2.21) 106	4.61 (2.52) 113	5.85 (2.37) 81	5.52 (2.78) 97	6.05 (2.56) 81	5.95 (2.82) 85	.044*	.008*	.003*	.001*
Injection Anxiety	4.84 (3.00) 134	4.99 (3.27) 137	3.49 (2.63) 106	3.99 (3.08) 121			< .001*	.002*		
Injection Pain	3.88 (2.50) 130	3.15 (2.73) 134	3.92 (2.41) 106	3.48 (2.66) 120			.773	.264		
Recommend to a Friend			7.68 (2.43) 107	8.13 (2.31) 120	7.33 (2.57) 103	8.53 (2.03) 109				
Consider in the Future			7.61 (2.63) 107	7.82 (2.59) 121	6.85 (3.06) 103	7.67 (2.93) 109				

Source: Table T16.3.1, *5.3.5.1.1, p 1949*

Finally, the daily diary that subjects completed detailing the impact of endometriosis on their daily lives was evaluated. Both groups showed significant improvement at the end of treatment in:

- Mean hours of work missed and mean % of work hours missed
- Mean hours of housework missed and mean % of housework hours missed
- Work productivity in work and housework

Medical Reviewer's Comment:

1) Although subjects in both groups showed significant improvements in amount of work/housework missed, they also had significantly decreased hours of work/housework scheduled; thus the apparent improvement may result from lowering the demands upon them.

10.1.9 Safety

10.1.9.1 Safety Measurements

All participants who received at least one dose of study medication were included in the summaries and listings of safety data (N=274). Adverse events were monitored from the administration of the first dose of study medication until the final study visit with the exception of pregnancy, which was followed until conclusion. Any untoward event occurring after this monitoring period that the investigator assessed as possibly related to the study drug was also recorded as an adverse event. Adverse events were categorized according to the Medical Dictionary for Regulatory Action (MedDRA) and were summarized by organ system and preferred term. Safety analyses were conducted with no imputation of missing data.

The following safety measurements were evaluated:

- BMD assessments done at Visit 0 (baseline) and at months 6, 12 and 18; these measures were made from the spine (L1-4) and the proximal femur (femoral neck and total femur) using dual energy x-ray absorptiometry (DXA) scanners.
- The Kupperman Index global weighted score[13] evaluating hypoestrogenemic symptoms, reviewed by the same investigator with the subject at each visit
- Occurrence of hot flushes as recorded in the daily diary. Subjects recorded the number of mild, moderate and severe hot flushes, or absence of this symptom, daily. Definitions were derived from the February 1997 FDA Guidance pertaining to vasomotor symptoms
- Changes in sex hormone binding globulin (SHBG), serum estradiol and progesterone, measured at visits 1, 4 and 7
- Reports of adverse events; not to include anticipated changes in subjects' menstrual cycles, although such changes were recorded in the subject diary
- Any pregnancy occurring or discovered during the treatment period or within 120 days after the last dose, with follow-up until the conclusion of the pregnancy
- Laboratory assessment (hematology, serum chemistries including hepatic and lipid panels and urinalysis, done at baseline and at months 3 and 6
- Blood pressure, assessed at each study visit, through follow-up
- Body weight and BMI, measured at each study visit, through follow-up
- Uterine bleeding diaries, evaluated at each study visit during the treatment phase

10.1.9.1.1 Extent of exposure

Number of injections for the two groups is displayed in Table 58. A greater proportion of the DMPA-SC group than the Lupron group failed to receive both scheduled injections, consistent with the higher withdrawal from treatment rate seen in the DMPA-SC group.

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Table 58 Study 268: Treatment Exposure by Group

Number of Injections	DMPA-SC N = 136		Leuprolide N = 138		Total N = 274	
	n	%	n	%	n	%
One	31	22.8	20	14.5	51	18.6
Two	105	77.2	118	85.5	223	81.4
Total Reported	136	100.0	138	100.0	274	100.0

10.1.9.2 Adverse Events

10.1.9.2.1 Serious adverse events

Deaths: there were no deaths through the 12 months of follow-up.

Premature termination due to adverse events: According to the reclassification of reasons for withdrawal from treatment, 12 DMPA-SC subjects (8.8 %) and 11 Lupron subjects (8.0%) terminated prematurely from the study during the treatment phase because of adverse events. All adverse events leading to withdrawals are listed in Table 59.

Medical Reviewer's Comment:

1) ***Six of the 11 subjects from the DMPA-SC group who withdrew reported vaginal bleeding as an associated AE. In the Lupron group, none reported bleeding, and the AEs associated with withdrawal were more diverse..***

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Table 59 Study 268: Treatment Withdrawals due to Adverse Events

Subject #	MedDRA Term	Treatment group	Drug-related	SAE
060	Insomnia	DMPA-SC	Yes	No
127	Tension	DMPA-SC	Yes	No
	Mood swings	DMPA-SC	Yes	No
	Intermenstrual bleeding	DMPA-SC	Yes	No
263	Acne	DMPA-SC	Yes	No
	Injection site reaction	DMPA-SC	Yes	No
153	Intermenstrual bleeding	DMPA-SC	Yes	No
256	Vaginal hemorrhage	DMPA-SC	Yes	No
	Dizziness	DMPA-SC	No	No
	Fatigue	DMPA-SC	No	No
238	Libido decreased	DMPA-SC	No	No
093	Unintended pregnancy	DMPA-SC	Yes	No
057	"Spotting"	DMPA-SC	*	No
208	"Decreased libido, sore joints"	DMPA-SC	*	No
052	"Bleeding"	DMPA-SC	*	No
063	"Bleeding"	DMPA-SC	*	No
101	Lower abdominal pain	Lupron	No	Yes
219	Breast lump (R)	Lupron	Yes	No
	Breast lump (L)	Lupron	Yes	No
258	Migraine aggravated	Lupron	Yes	No
	Headache aggravated	Lupron	Yes	No
270	Pain in limb	Lupron	Yes	No
	Fatigue	Lupron	Yes	No
194	Hot flushes	Lupron	Yes	No
046	Nausea	Lupron	No	No
	Social avoidant behavior	Lupron	Yes	No
	Decreased interest	Lupron	Yes	No
	Dysmenorrhea	Lupron	Yes	No
	Libido decreased	Lupron	Yes	No
181	Headache	Lupron	Yes	No
	Nausea	Lupron	Yes	No
	Dizziness	Lupron	Yes	No
008	Hot flushes	Lupron	Yes	No
	Libido decreased	Lupron	Yes	No
252	Hypoesthesia	Lupron	Yes	No
	Migraine	Lupron	Yes	No
	Vision blurred	Lupron	Yes	No
247	Mood swings	Lupron	*	No
266	Depression	Lupron	*	No

*Subjects in **bold** were reclassified regarding reason for withdrawal from "consent withdrawn" to "adverse event" – drug-relatedness was not determined by the applicant for these subjects.
One subject from the DMPA-SC group is unaccounted for in the line-listings of subjects who withdrew due to adverse events.
Source: Appendix 3.12.3, *5.3.5.1.1, pp 8143-47* and Tables 2, 3a & 3b, pp 6-8, August 31, 2004 communication from applicant

Serious adverse events: There were three DMPA-SC and four Lupron group subjects who experienced serious adverse events during the treatment period. An additional two SAEs in the DMPA-SC group and four SAEs in the Lupron group occurred in the follow-up period. One of the SAEs occurring in each group resulted in withdrawal, and no SAEs were considered to be treatment related. All SAEs occurring during the 18-month study period are listed in Table 60; the overall rate was 3.8% in the DMPA-SC group and 5.9% in the Lupron group.

Table 60 Study 268: Serious Adverse Events during Treatment and Follow-up

Investigator/ Patient No.	Age (yr)	Preferred Term*	Maximum Intensity	Drug-Related	Outcome	Action Taken
DMPA-SC (Treatment Period)						
[redacted]019	30	Pelvic inflammatory disease NOS	Severe	No	Recovered	None
[redacted]/099	31	Calculus renal NOS	Severe	No	Recovered with sequelae	None
[redacted]093	23	Unintended pregnancy	NA	No	Recovered	Drug permanently withdrawn
DMPA-SC (Follow-up Period)						
[redacted]221	19	Injury NOS	Severe	No	Not recovered	None
[redacted]264	22	Endometrial disorder NOS	Severe	No	Recovered with sequelae	None
Leuprolide (Treatment Period)						
[redacted]157	30	Endometriosis	Severe	No	Not recovered	None
[redacted]101	32	Abdominal pain lower	Severe	No	Unknown	Drug permanently withdrawn
[redacted]211	44	Bile duct stone	Severe	No	Recovered	None
[redacted]167	35	Abdominal pain NOS	Severe	No	Recovered	None
Leuprolide (Follow-up Period)						
[redacted]056	31	Arterial thrombosis limb	Severe	No	Recovered with sequelae	None
[redacted]/049	41	Hysterectomy NOS	Moderate	No	Recovered	None
[redacted]178	38	Optic neuritis NEC	Severe	No	Recovered with sequelae	None
[redacted]271	47	Back pain aggravated	Mode rate	No	Recovered with sequelae	None

Source: Table 39, *5.3.5.1.1, p 122*

Medical Reviewer's Comments:

1) ***Classification of unintended pregnancy (Subject #093), endometriosis (Subject #157) and a surgical procedure (Subject #049) as SAEs is not warranted.***
2) ***Subject #167's SAE was initially considered treatment-related; this was changed in the updated study report submitted April 14, 2004, with no explanation. A query to the applicant provided no additional information supporting this change.***

10.1.9.2.2 Frequent adverse events

Adverse event data from the treatment phase was unavailable for six DMPA-SC and three Lupron subjects, making the respective denominators 130 and 135. At least one adverse event was reported during the treatment phase by 87% and 85% of the DMPA-SC and Lupron groups, respectively. The most frequent (>5%) adverse events in both groups were:

- Diarrhea
- Nausea
- Influenza
- Nasopharyngitis

- Sinusitis
- Upper respiratory tract infection
- Back pain
- Headache

Events occurring at >5% frequency only in the DMPA-SC group were:

- Sore throat
- Fatigue
- UTI
- Injection site reaction
- Hypersensitivity
- Arthralgia
- Intermenstrual bleeding
- Pelvic pain
- Acne

Events occurring at >5% frequency only in the Lupron group were:

- Pain in limb
- Insomnia
- Decreased libido
- Hot flushes

Events occurring at significantly different rates (chi-square p<=0.05) in the two groups (DMPA vs. Lupron) were:

- Hot flushes NOS (2.3 vs. 11.9%)
- Hypersensitivity NOS (seasonal allergies and latex reaction) (5.4 vs. 0 %)
- Injection site reaction, NOS (6.9 vs. 0%)
- Toothache (0 vs. 3.7%)
- Pelvic pain NOS (6.2 vs. 1.5%)

Overall, adverse events occurring frequency >5% in either group are reported in Table 61.

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Table 61 Study 268: Treatment-Emergent Adverse Events Occurring in >=5% of Subjects

Adverse Event	DMPA-SC		Lupron		Between-Treatment p-value
	N	%	N	%	
Headache NOS	16	12.3	20	14.8	NS
Nasopharyngitis	16	12.3	15	11.1	NS
Sinusitis NOS	12	9.2	13	9.6	NS
Nausea	11	8.5	18	13.3	NS
Influenza	11	8.5	13	9.6	NS
URI NOS	10	7.7	11	8.1	NS
Arthralgia	10	7.7	6	4.4	NS
Acne NOS	9	6.9	6	4.4	NS
Fatigue	9	6.9	4	3.0	NS
Injection site reaction NOS	9	6.9	0	0	0.002
Back pain	8	6.2	12	8.9	NS
Diarrhea NOS	8	6.2	7	5.2	NS
Pelvic pain NOS	8	6.2	2	1.5	0.046
Sore throat NOS	7	5.4	5	3.7	NS
UTI NOS	7	5.4	5	3.7	NS
Intermenstrual bleeding	7	5.4	2	1.5	NS
Hypersensitivity NOS	7	5.4	0	0	0.006
Pain in limb	5	3.8	7	5.2	NS
Insomnia NEC	4	3.1	10	7.4	NS
Hot flushes NOS	3	2.3	16	11.9	0.003
Libido decreased	3	2.3	8	5.9	NS

Source: Based on Table T12.1.1, *5.3.5.1.1, pp 1840-1855*

Medical Reviewer's Comment:

1) The hypersensitivity reactions comprise 6 seasonal allergies and one latex reaction.

The frequency of adverse events considered to be drug-related was similar in both groups (48% in the DMPA-SC group, 45% in the Lupron group); by system, there were significantly higher frequencies of psychiatric disorders (p=0.016) and vascular disorders (p=0.01) in the Lupron group. Looking at depressive disorders specifically, 3.9% of the DMPA-SC group and 6.7% of the Lupron group experienced "depressed mood" or "depression NEC.".

Racial subgroups were evaluated for adverse events; however, small numbers of non-white subjects precluded statistical comparisons. Analysis by age or BMI category was not reported.

In the follow-up period, adverse events were reported by 66% of DMPA-SC subjects and 59% of Lupron subjects; however, the population described includes only 88 DMPA-SC and 102 Lupron subjects who completed follow-up. The most frequent adverse events in both groups were:

- Sinusitis (9.1% DMPA-SC, 4.9% Lupron)
- Nasopharyngitis (8.0% DMPA-SC, 8.8% Lupron)
- URI (6.8% DMPA-SC, 4.9% Lupron)
- Influenza (4.5% DMPA-SC, 5.9% Lupron)
- Depression (5.7% DMPA-SC, 4.9% Lupron)
- UTI (5.7% DMPA-SC, 2.9% Lupron)

No other adverse events occurred in >5% of subjects.

10.1.9.2.3 Injection site reactions

In Study 268, a total of 12 DMPA-SC subjects (7.5%) experienced 13 injection site reactions, compared to 5 Lupron subjects (2.2%) who experienced 5 reactions. None was considered severe. One DMPA-SC subject withdrew due to an injection site reaction.

Medical Reviewer's Comment:

1) ***The overall event "injection site reactions" was aggregated from 6 MedDRA terms, including bruising, inflammation, edema, pain, urticaria and "injection site reaction NOS", which was typically described as indentation or induration at the site. Nine DMPA-SC subjects and no Lupron subjects experienced this latter event.***

10.1.9.3 Bone Mineral Density

Change from baseline in bone mineral density at the femur and lumbar spine was the primary safety measure in this study. The mean BMD measurements in each treatment group, at each skeletal site and each time period are shown in Table 62. Data at month 6 was available for only 59% of DMPA-SC subjects who had baseline measurements and for 72% of Lupron subjects.

Table 62 Study 268: Mean (SD) BMD Scores at each Visit by Treatment Group

Visit	Femur BMD		Spine BMD	
	DMPA-SC	Lupron	DMPA-SC	Lupron
Baseline	**1.01 (0.12)**	**1.01 (0.12)**	**1.14 (0.13)**	**1.17 (0.15)**
N	131	138	132	138
Month 6 (End of Treatment)	1.02 (0.12)	0.99 (0.12)	1.13 (0.13)	1.11 (0.15)
N	77	98	77	98
Month 12 (6 month post-tx follow-up)	1.03* (0.12)	0.99* (0.12)	1.16 (0.15)	1.11 (0.14)
N	50	64	51	63
Month 18 (12 month post-tx follow-up)	1.03 (0.12)	0.98 (0.11)	1.15 (0.14)	1.11 (0.13)
N	32	42	31	42

* Between-treatment Kruskal-Wallis p<=0.05
Source: based on Table T7.1.1., *5.3.5.1.1, pp 1168-1071*

Median percent changes at month 6 (end of treatment), month 12 (6 months off treatment) and month 18 (12 months off treatment) are displayed in Table 63. The Lupron subjects showed a statistically significant decrease in BMD at both measurement sites after 6 months of treatment, while the DMPA-SC subjects showed a statistically significant decrease only in lumbar spine BMD. The magnitude of the change from baseline was statistically significantly less at both sites in the DMPA-SC group as compared to the Lupron group. At month 12, 6 months off study medication, only about 38% of DMPA-SC subjects had follow-up data to compare to baseline; as did 46% of Lupron subjects. The DMPA-SC subjects had none to small and nonsignificant decreases from baseline at the femur and lumbar sites, respectively, indicating recovery from the bone loss seen at 6 months. The Lupron subjects again showed statistically significant decreases from baseline at both sites, with minimal to no recovery from the status at 6 months. Again, the difference between treatment groups was

statistically significant at both sites, favoring DMPA-SC. By month 18, bone loss at both sites in the DMPA-SC group showed full recovery, although only 24% of the original group had data at this time period. In the Lupron group, 30% of the original subjects had data, and these subjects continued to show statistically significant bone loss from baseline, although there was evidence of partial recovery. The difference between the treatment arms remained statistically significant at both sites, indicating statistical superiority of DMPA-SC over Lupron in minimizing bone loss after six months of treatment.

Medical Reviewer's Comment:

1) ***The attrition in number of subjects providing BMD data at 6, 12 and 18 months is due in part to the protocol amendment that rescinded the requirement to obtain BMD measurements on subjects withdrawing early from treatment. This likely accounts for the lower proportion of DMPA-SC subjects who have BMD data as compared to Lupron subjects, as the withdrawal rate was higher in the DMPA-SC group.***

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Table 63 Study 268: BMD Median Percent Change from Baseline Median by Treatment Group

Visit		DMPA-SC	Leuprolide	P-Value* Between Treatments
Baseline	**Femur Total BMD (g/cm^2)**			
	Total reported	131	138	
	Baseline median	0.98	0.99	0.926
	Spine Total BMD (g/cm^2)			
	Total reported	132	138	
	Baseline median	1.11	1.15	0.091
Month 6 (EOT)	**Femur Total BMD (g/cm^2)**			
	Total reported	77	98	
	Baseline median†	1.00	0.98	
	Median % change	-0.30	-1.65	<0.001
	Within group test‡	0.063	<0.001	
	Spine Total BMD (g/cm^2)			
	Total reported	77	98	
	Baseline median†	1.12	1.15	
	Median % change	-1.10	-3.95	<0.001
	Within group test‡	<0.001	<0.001	
Month 12	**Femur Total BMD (g/cm^2)**			
	Total reported	50	64	
	Baseline median†	1.01	0.98	
	Median % change	-0.25	-1.60	0.002
	Within group test‡	0.223	<0.001	
	Spine Total BMD (g/cm^2)			
	Total reported	51	63	
	Baseline median†	1.15	1.14	
	Median % change	0.00	-3.20	<0.001
	Within group test‡	0.176	<0.001	
Month 18	**Femur Total BMD (g/cm^2)**			
	Total reported	32	42	
	Baseline median†	0.99	0.98	
	Median % change	0.00	-1.30	0.004
	Within group test‡	0.573	<0.001	
	Spine Total BMD (g/cm^2)			
	Total reported	31	42	
	Baseline median†	1.12	1.10	
	Median % change	0.20	-1.70	0.021
	Within group test‡	0.759	<0.001	

* Kruskal-Wallis test, significance defined at $p \leq 0.05$
† Based on patients who had non-missing values at both baseline and the change visit.
‡ Wilcoxon signed rank test, significance defined at $p \leq 0.05$
Abbreviations: BMD = bone mineral density, EOT = end of treatment, ITT = intent-to-treat
Source: Table 25, *5.3.5.1.1, p 97*

Table 64 Study 268: Mean (SD) Percent Change in BMD by Treatment Group

Visit	Results	DMPA-SC	Lupron
Baseline			
Femur	N	131	138
	Mean (SD)	1.01 (0.12)	1.01 (0.12)
Spine	N	132	138
	Mean (SD)	1.14 (0.13)	1.17 (0.15)
Month 6			
Femur	N	77	98
	Mean (SD)	-0.32 (1.75)	-1.85 (2.57)
Spine	N	77	98
	Mean (SD)	-1.27 (2.29)	-3.91 (2.60)
Month 12			
Femur	N	50	64
	Mean (SD)	-0.26 (1.79)	-1.73 (2.77)
Spine	N	51	63
	Mean (SD)	-0.46 (2.79)	-2.89 (2.88)
Month 18			
Femur	N	32	42
	Mean (SD)	0.24 (2.14)	-1.65 (2.84)
Spine	N	31	42
	Mean (SD)	-0.14 (2.91)	-1.63 (2.92)

Source: Table T7.2.1, *5.3.5.1.1*, pp 1181-5

When the BMD data are examined in terms of mean percent change (Table 64), similar trends are noted, with the DMPA-SC group displaying less bone loss than the Lupron group at each bone site and each assessment period.

Categorical analysis of the median percent change showed similar trends, as displayed in Table 65. At each evaluation time and each skeletal site surveyed, the proportion experiencing bone loss of >= 2.5% was two- to six-fold higher in the Lupron group. However, even in the DMPA-SC group, almost one-quarter of subjects assessed still had >= 2.5% bone loss at the spine a year after treatment ended.

Medical Reviewer's Comment:

1) ***The significance of a 2.5% BMD loss is difficult to determine without information on the precision of the BMD measurement technique used.***

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Table 65 Study 268: BMD Percent Change from Baseline Category by Treatment Group

Change from baseline to:	% change	Femur BMD		Spine BMD	
		DMPA-SC	Lupron	DMPA-SC	Lupron
Month 6 (End of Treatment)	>=+0.1%	42%	22%	27%	9%
	-2.4 to 0%	49%	43%	48%	14%
	<=-2.5 %	9%	35%	25%	77%
	N evaluated	77	98	77	98
Month 12 (6 month post-tx follow-up)	>=+0.1%	42%	27%	49%	15%
	-2.4 to 0%	48%	34%	26%	26%
	<=-2.5 %	10%	39%	26%	60%
	N evaluated	50	62	51	62
Month 18 (12 month post-tx follow-up)	>=+0.1%	47%	24%	55%	24%
	-2.4 to 0%	47%	38%	23%	36%
	<=-2.5 %	6%	38%	23%	40%
	N evaluated	32	42	31	42

Source: based on Tables 26 & 27, *5.3.5.1.1, pp 99-100*

Evaluation of bone effects by looking at the percent of subjects with osteopenia (i.e., with a T-score <-1), showed relatively little change at either site at the end of treatment in the DMPA-SC group, while the Lupron group showed about three- to four-fold increases over baseline at each site at the end of treatment (Table 66).

The shift in T-score category (defined in 0.5 increments) was also evaluated, with the finding that over both times and sites, the Lupron group had about two to three times the rate of subjects dropping to a lower T-score category than did the DMPA-SC group.

Table 66 Study 268: BMD T-scores <-1 by Treatment Group

Visit	T-Score Femur Total (Less Than -1)		T-Score Spine Total (Less Than -1)	
	DMPA-SC n/N (%)	Leuprolide n/N (%)	DMPA-SC n/N (%)	Leuprolide n/N (%)
Baseline	2/131 (1.5)	7/138 (5.1)	5/132 (3.8)	5/138 (3.6)
Month 6 (EOT)	1/77 (1.3)	14/98 (14.3)	4/77 (5.2)	15/98 (15.3)
Month 12	1/50 (2.0)	6/64 (9.4)	2/51 (3.9)	6/63 (9.5)
Month 18	1/32 (3.1)	4/42 (9.5)	3/31 (9.7)	2/42 (4.8)

Source: Table 28, *5.3.5.1.1, p 101*

No subject in either group experienced osteoporotic fractures, nor did any have T-scores meeting the definition of osteoporosis (T-score <2.5).

Subgroup analyses were conducted on age, BMI, and race. No markedly different patterns were noted in any subgroup.

Medical Reviewer's Comments:

1) ***Although the categorical percent change analysis obscures the evaluation of subjects with neutral effects on BMD by collapsing subjects with no change in BMD into a category ranging down to a -2.4% change,*** Table 65 ***shows that DMPA-SC subjects were almost***

twice as likely as Lupron subjects to show an increase in BMD over the course of treatment.

2) ***The data on T-score changes are difficult to interpret due to small Ns in the follow-up period.***
3) ***On the primary endpoint, percent change in BMD, as well as the secondary BMD endpoints, the data clearly demonstrate the superiority of DMPA-SC over Lupron in minimizing the loss of BMD during the six month treatment course.***

10.1.9.4 Hypoestrogenic Symptoms

Symptoms of pharmaceutically lowered estrogen levels were assessed by three secondary safety endpoints: the Kupperman Index, a patient diary recording occurrence and severity of hot flushes, and reproductive hormone levels. The Kupperman Index, which measures 11 symptoms of decreased estrogen levels, was reviewed with subjects monthly throughout the treatment phase; median changes from baseline are displayed in Table 67. The Lupron group showed significant increases in symptoms of hypoestrogenemia from baseline at each month except the final month of treatment. The DMPA-SC group did not increase significantly from baseline at any time point, and had significantly lower symptomatology scores than the Lupron subjects at every time point.

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Table 67 Study 268: Median Changes in Kupperman Index by Treatment Group

Visit		DMPA-SC	Leuprolide	P-Value* Between Treatments
Pretreatment	Total reported	136	137	
	Pretreatment median	10.5	13.0	0.056
Month 1	Total reported	125	132	
	Pretreatment median†	10.0	12.5	
	Median change	0.0	2.0	0.011
	Within group T-test‡	0.322	<0.001	
Month 2	Total reported	120	127	
	Pretreatment median†	11.0	12.0	
	Median change	-1.0	4.0	<0.001
	Within group T-test‡	0.597	<0.001	
Month 3	Total reported	106	120	
	Pretreatment median†	11.0	12.0	
	Median change	-1.0	5.0	<0.001
	Within group T-test‡	0.229	<0.001	
Month 4	Total reported	96	110	
	Pretreatment median†	10.0	11.5	
	Median change	0.5	3.0	0.001
	Within group T-test‡	0.806	<0.001	
Month 5	Total reported	87	106	
	Pretreatment median†	9.0	11.5	
	Median change	-2.0	2.5	0.002
	Within group T-test‡	0.104	0.005	
Month 6 (EOT)	Total reported	88	102	
	Pretreatment median†	9.5	12.0	
	Median change	-2.0	1.0	0.002
	Within group T-test‡	0.004	0.135	

* Kruskal-Wallis test, significance defined at $p \leq 0.05$

† Based on patients who had non-missing values at both pretreatment and the change visit. Pretreatment values were the randomization visit values. If a randomization visit value was missing, then the baseline visit value was used.

‡ Wilcoxon signed rank test, with significance defined at $p \leq 0.05$.

Note: Higher scores indicate increased symptoms of hypoestrogenemia.
Source: Table 30, *5.3.5.1.1, p 100*

Mean monthly scores on the Kupperman Index are shown in Table 68. The between group difference became significant at month 1 and persisted throughout the treatment period. After an initial increase in the first month of treatment, the DMPA-SC group experienced a small numeric decrease in mean symptom scores, falling below baseline by month 3. The Lupron group reported an increase in mean symptom scores that peaked at month 2, then declined throughout the remainder of treatment, but never reached the baseline level and remained higher than those in the DMPA-SC subjects.

Table 68 Study 268: Mean (SD) Kupperman Index Scores by Month and Treatment Group

Visit	DMPA-SC	Lupron	Between-group p-value*
Baseline	11.1 (7.9)	13.3 (9.7)	0.10
Month 1	12.4 (8.1)	16.8 (8.9)	<0.001
Month 2	11.7 (8.4)	18.4 (10.2)	<0.001
Month 3	11.0 (7.8)	17.9 (9.7)	<0.001
Month 4	10.7 (6.6)	16.8 (9.8)	<0.001
Month 5	9.5 (7.2)	15.7 (9.4)	<0.001
Month 6	8.8 (6.3)	14.5 (9.8)	<0.001

* The p-value is based on the Kruskal-Wallis evaluation of medians
Source: Based on Table T9.1, *5.3.5.1.1, pp 1457-9*

Medical Reviewer's Comments:

1) ***The Kupperman Index has been criticized for unjustified weighting, overlapping criteria, and suboptimal patient understanding. The sponsor was clearly informed that outcomes based on the Kupperman Index were unlikely to be acceptable for labeling claims.***
2) ***The DMPA-SC group had only 65% of subjects completing the Kupperman Index by the end of treatment; the Lupron group had 74%. It is possible that patients who withdrew from treatment did so in part due to greater hypoestrogenemic symptomatology.***

Daily diaries were kept by subjects, recording frequency and severity of hot flushes. Median hot flush frequency data are presented in Table 69 and mean hot flush severity data are in Table 70. The DMPA-SC subjects experienced new onset of hot flushes in the first 3 months of treatment; but by month 4, the median number of hot flushes was zero. The Lupron group experienced significantly more frequent hot flushes at each month of treatment, reaching a peak at month 3, but never resolving completely. In the worst month for each group, the median and range of daily hot flush frequency were 0.055 (0-8) in the DMPA-SC group (month 1) and 2.9 (0-41) in the Lupron group (month 3). Severity of hot flushes was also considered; these data appear in Table 70. At each month of treatment, average severity scores for the Lupron subjects were two- to five-fold higher than those for the DMPA-SC subjects.

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Table 69 Study 268: Median Hot Flush Frequency by Month and Treatment Group

Diary Reference Month*	Average Daily Number	DMPA-SC	Leuprolide	P-Value† Between Treatments
Pretreatment	Total reported	116	126	
	Median	0.000	0.000	0.871
	Range	0.00 - 4.14	0.00 - 3.53	
Month 1	Total reported	110	119	
	Median	0.055	0.800	<0.001
	Range	0.00 - 8.00	0.00 - 23.81	
Month 2	Total reported	105	115	
	Median	0.030	2.900	<0.001
	Range	0.00 - 4.29	0.00 - 35.96	
Month 3	Total reported	105	110	
	Median	0.030	2.880	<0.001
	Range	0.00 - 5.33	0.00 - 40.73	
Month 4	Total reported	90	102	
	Median	0.000	2.440	<0.001
	Range	0.00 - 6.00	0.00 - 31.60	
Month 5	Total reported	78	98	
	Median	0.000	2.600	<0.001
	Range	0.00 - 5.82	0.00 - 26.73	
Month 6 (EOT)	Total reported	69	87	
	Median	0.000	1.900	<0.001
	Range	0.00 – 5.75	0.00 - 35.40	

* 30-day intervals after the start of treatment. Pretreatment is the interval before the start of treatment.

Source: Table 31, *5.3.5.1.1, p 106*

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Table 70 Study 268: Mean (SD) Average Daily Hot Flush Severity* by Month and Treatment Group

Visit	DMPA-SC	Lupron	Between-group p-value**
Baseline	0.24 (0.46)	0.26 (0.46)	0.75
Month 1	0.39 (0.58)	0.74 (0.67)	<0.001
Month 2	0.35 (0.52)	1.31 (0.85)	<0.001
Month 3	0.35 (0.57)	1.31 (0.89)	<0.001
Month 4	0.38 (0.64)	1.29 (0.85)	<0.001
Month 5	0.35 (0.58)	1.31 (0.92)	<0.001
Month 6	0.24 (0.53)	1.16 (0.91)	<0.001

*Average daily severity is calculated as the sum of daily [weighted severity (1x #mild, 2x #moderate, 3x #severe)/# hot flushes that day]/# days with data recorded. For example, a subject experiencing four mild hot flushes each day of the month would have a severity score of 1.
** The p-value is based on the Kruskal-Wallis evaluation of medians
Source: Based on Table T10.3, *5.3.5.1.1, pp 1779-81*

Medical Reviewer's Comment:

1) ***Both the mean values for daily hot flush severity and median data for hot flush frequency demonstrate lower rates in the DMPA-SC group.***

Levels of estradiol, progesterone and sex hormone binding globulin (SHBG) were assessed monthly throughout the treatment phase. Table 71 presents estradiol levels measured at baseline, and months 3 and 6 of the treatment phase. Compared to baseline, both groups showed changes in estradiol at month 3, with the DMPA-SC group showing an increase in mean estradiol. The Lupron group, which showed a decrease in mean estradiol, was significantly lower than the DMPA-SC group. This between-group difference persisted at month 6, at which time the Lupron group remained significantly lower than baseline, while the DMPA-SC group showed a minor, nonsignificant decrease from baseline.

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Table 71 Study 268: Change in Estradiol Levels by Treatment Group

Visit		DMPA-SC	Leuprolide	P-Value* Between Treatments
Estradiol, Unconjugated (pg/mL)				
Randomization	Total reported	131	132	
	Randomization mean (SD)	62.9 (29.4)	76.5 (70.3)	
	Randomization median	56.0	56.5	0.474
Month 3	Total reported	99	112	
	Randomization mean (SD)†	64.2 (31.5)	77.6 (74.9)	
	Randomization median†	56.0	56.0	
	Mean change (SD)	13.7 (61.3)	-30.7 (75.5)	
	Median change	0.0	-12.0	<0.001
	Within group T-test‡	0.050	<0.001	
Month 6 (EOT)	Total reported	80	98	
	Randomization mean (SD)†	64.5 (30.5)	71.3 (51.9)	
	Randomization median†	57.5	55.5	
	Mean change (SD)	-1.4 (40.9)	-27.2 (52.7)	
	Median change	0.0	-11.0	<0.001
	Within group T-test‡	0.840	<0.001 *	

* Kruskal-Wallis test, significance defined at $p \leq 0.05$
† Based on patients who had non-missing values at both randomization and the change visit.
‡ Wilcoxon signed rank test, significance defined at $p \leq 0.05$
Source: Table 33, *5.3.5.1.1, p 108*

Medical Reviewer's Comment:

1) P-values reported in Table 71 ***have not been corrected for multiple comparisons.***

Estradiol levels below 41 pg/ml may be associated with increased incidence of bone loss[Error! Bookmark not defined.] and vasomotor symptoms. The proportion of subjects in each treatment group experiencing estradiol levels below this threshold are displayed in Table 72. In the DMPA-SC group, there was no increase from baseline in the frequency of the low estradiol category at month 3, and only a minor increase (26% to 33%) at month 6; in contrast, in the Lupron group, there was an increase from 29% at baseline to 70% at month 3, and further increase to 77% at month 6. The Lupron group had a significantly higher proportion of hypoestrogenemic subjects than the DMPA-SC group at both treatment months assessed.

Table 72 Study 268: Estradiol Levels <41 pg/ml by Treatment Group and Time

Visit	Estradiol Category	DMPA-SC N = 136		Leuprolide N = 138		Total N = 274		Between Treatment Test +	
		n	%	n	%	n	%	P-Value	*
Randomization	< 41 pg/mL	34	26.0	38	28.8	72	27.4	0.606	
	>= 41 pg/mL	97	74.0	94	71.2	191	72.6		
	Total Reported	131	100.0	132	100.0	263	100.0		
	Not Reported	2		1		3			
Month 3	< 41 pg/mL	26	25.7	80	69.6	106	49.1	<0.001	*
	>= 41 pg/mL	75	74.3	35	30.4	110	50.9		
	Total Reported	101	100.0	115	100.0	216	100.0		
	Not Reported	3		3		6			
Month 6 (EOT)	< 41 pg/mL	27	32.9	77	77.0	104	57.1	<0.001	*
	>= 41 pg/mL	55	67.1	23	23.0	78	42.9		
	Total Reported	82	100.0	100	100.0	182	100.0		
	Not Reported	4		2		6			
Early TRT Disc	< 41 pg/mL	5	33.3	8	66.7	13	48.1	0.085	
	>= 41 pg/mL	10	66.7	4	33.3	14	51.9		
	Total Reported	15	100.0	12	100.0	27	100.0		
	Not Reported	1				1			

Source: Table T8.3, *5.3.5.1.1, p 1456*

Mean progesterone and SHBG levels decreased slightly from baseline at 3 and 6 months in both groups; the groups did not differ significantly.

Medical Reviewer's Comment:

1) ***The sponsor has indicated that the sensitivity of the estradiol assay was only — This greatly limits the utility of these measurements and particularly limits the significance and interpretation of mean values.***

10.1.9.5 Laboratory Values and Urinalysis

The serum chemistry, hematology, and urinalysis test results were reviewed. Selected mean values at intervals during the treatment period and at the time early withdrawal are presented in Table 73. Two subjects experienced elevated ALT values greater than 2.5 times the upper limit of normal during the treatment phase and after normal baseline values: one DMPA-SC subject (#104) had ALT values of 17 U/L at baseline, 23 U/L at month 3 and 169 U/L at month 6; one Lupron subject (#245) had a baseline value of 25 U/L increase to 96 U/L at month 3, then decrease to 57 U/L at month 6. The laboratory changes in general were not deemed clinically significant, and no subject discontinued due to abnormal laboratory values. No clinically relevant changes in urinalyses results were noted in either group.

Table 73 Study 268: Mean (SD) Laboratory Safety Variables

Lab Test		DMPA-SC N=136		Lupron N=138	
		N	Mean (SD)	N	Mean (SD)
Hematocrit (fraction)	Baseline	133	0.40 (0.03)	128	0.40 (0.03)
	Month 3	97	0.40 (0.03)	113	0.40 (0.03)
	Month 6	85	0.40 (0.03)	94	0.40 (0.03)
	Early w/d	14	0.40 (0.04)	11	0.40 (0.02)
Hemoglobin (g/L)	Baseline	133	134.1 (10.9)	130	133.9 (10.9)
	Month 3	97	135.2 (8.9)	113	134.7 (10.1)
	Month 6	85	135.4 (9.0)	94	134.0 (9.4)
	Early w/d	14	131.3 (12.8)	11	136.5 (8.6)
Plats (10^9/L)	Baseline	132	276.7 (72.7)	126	281.5 (55.4)
	Month 3	96	272.4 (56.4)	111	288.7 (58.1)
	Month 6	81	268.5 (62.6)	90	286.3 (62.9)
	Early w/d	14	264.7 (52.1)	10	269.0 (55.8)
AST (U/L)	Baseline	132	18.8 (4.3)	133	19.8 (6.2)
	Month 3	103	18.5 (4.3)	117	23.2 (9.3)
	Month 6	86	19.5 (9.0)	101	22.5 (7.3)
	Early w/d	15	19.1 (5.2)	12	25.1 (9.5)
ALT (U/L)	Baseline	132	16.1 (7.9)	133	17.7 (12.3)
	Month 3	103	17.1 (7.1)	117	23.8 (14.1)
	Month 6	86	19.8 (18.4)	101	22.1 (13.8)
	Early w/d	15	17.3 (7.1)	12	25.6 (16.0)
GGT (U/L)	Baseline	132	18.8 (15.3)	133	19.7 (11.7)
	Month 3	103	21.3 (18.0)	117	23.0 (15.1)
	Month 6	86	23.4 (33.7)	101	21.7 (16.5)
	Early w/d	15	15.5 (3.4)	12	24.8 (16.5)
Alk Phos (U/L)	Baseline	132	71.4 (20.3)	133	73.6 (21.0)
	Month 3	103	70.8 (23.6)	117	82.1 (21.0)
	Month 6	86	73.4 (33.1)	101	89.4 (23.0)
	Early w/d	15	71.9 (22.2)	12	78.3 (23.0)
Total Bili (µmol/L)	Baseline	132	8.6 (4.8)	133	8.3 (4.6)
	Month 3	103	8.9 (4.4)	117	8.0 (4.4)
	Month 6	86	8.4 (3.9)	101	7.1 (4.2)
	Early w/d	15	8.1 (4.0)	12	9.6 (5.2)
Creatinine (µmol/L)	Baseline	132	66.6 (10.5)	133	64.6 (10.9)
	Month 3	103	68.4 (11.5)	117	66.5 (10.4)
	Month 6	86	68.0 (12.6)	101	66.4 (11.2)
	Early w/d	15	68.9 (10.1)	12	64.8 (7.8)
Glucose (mmol/L)	Baseline	132	4.9 (0.8)	133	4.9 (0.8)
	Month 3	103	4.9 (0.9)	117	4.9 (1.0)
	Month 6	86	4.9 (1.6)	101	4.8 (1.0)
	Early w/d	15	4.7 (0.9)	12	5.0 (0.8)
Total Cholesterol (mmol/L)	Baseline	132	4.76 (0.90)	133	4.97 (0.94)
	Month 3	103	4.64 (0.77)	117	5.23 (0.97)
	Month 6	86	4.64 (0.88)	101	5.14 (0.91)
	Early w/d	15	4.64 (0.96)	12	5.42 (0.92)
Triglycerides (mmol/L)	Baseline	132	1.37 (1.06)	133	1.44 (0.97)
	Month 3	103	1.35 (0.89)	117	1.73 (1.36)
	Month 6	86	1.36 (1.05)	101	1.72 (1.04)
	Early w/d	15	1.31 (0.63)	12	1.76 (1.49)

Lab Test		DMPA-SC N=136		Lupron N=138	
		N	Mean (SD)	N	Mean (SD)
HDL (mmol/L)	Baseline	132	1.28 (0.33)	133	1.23 (0.35)
	Month 3	103	1.20 (0.31)	117	1.28 (0.38)
	Month 6	86	1.17 (0.34)	101	1.30 (0.38)
	Early w/d	15	1.21 (0.29)	12	1.32 (0.36)
LDL (mmol/L)	Baseline	132	2.87 (0.78)	133	3.08 (0.80)
	Month 3	103	2.85 (0.68)	117	3.19 (0.80)
	Month 6	86	2.85 (0.74)	101	3.08 (0.78)
	Early w/d	15	2.83 (0.91)	12	3.26 (0.48)

Source: Tables T13.1, T13.4, T13.7, and T13.10, *5.3.5.1.1, pp 1982-4 , 2078-85 , 2036-48 , 2102*

Medical Reviewer's Comments:

1) ***Despite increased incidence of bleeding in the DMPA-SC group, there was no demonstrable impact on hemoglobin or hematocrit.***
2) ***Inspection of laboratory data for subjects who withdrew from treatment early does not reveal any clinically relevant discrepancies from that reported for completers.***

10.1.9.6 Pregnancies

One subject in each group became pregnant during the study. The DMPA-SC pregnancy was detected two months after her first injection, with a sonographic estimated date of conception ten weeks after injection. This pregnancy was considered a SAE, and the subject was withdrawn from the study. The pregnancy was electively terminated at 6 weeks' gestation. The Lupron pregnancy was reported at month 12, more than nine months following the second injection. The pregnancy was delivered uneventfully by caesarian section approximately 16 months after the last injection.

Medical Reviewer's Comments:

1) ***No information is provided about the condition of the terminated fetus or the neonate.***

10.1.9.7 Vital Signs

Seated blood pressure was assessed at each study visit through the follow-up period. There were no significant between-group differences and the only significant change over time was a decrease of 2 mm Hg in systolic blood pressure in the Lupron group at month 6.

10.1.9.8 Weight and BMI

Weight was assessed at baseline, monthly during the treatment phase and every three months during follow-up. There were no significant differences between groups at any time point through month 18. Table 74 presents weight data at major evaluation points. In both groups, statistically significant weight gain from baseline was first demonstrated at month 4, and both groups remained heavier than baseline at all follow-up visits, although the difference was no longer statistically significant at the month 18 visit.

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Table 74 Study 268: Mean (SD) Weight (kg) by Treatment Group and Time

Visit	DMPA-SC Mean (SD)	N	Within-group change from baseline p-value*	Lupron Mean (SD)	N	Within-group change from baseline p-value*
Baseline	70.3 (16.4)	136	--	73.4 (19.1)	137	--
Treatment						
Month 1	70.7 (16.9)	126	NS	73.6 (19.1)	132	NS
Month 2	71.4 (17.4)	120	NS	73.7 (19.4)	126	NS
Month 3	72.2 (17.6)	105	NS	74.0 (19.5)	119	NS
Month 4	70.9 (17.0)	96	0.004	74.3 (20.0)	110	0.008
Month 5	71.6 (17.3)	86	0.015	73.6 (19.6)	106	NS
Month 6	71.3 (16.8)	88	0.001	74.1 (19.9)	103	0.008
Post-Treatment						
Month 9	73.6 (17.6)	61	0.024	75.0 (17.8)	77	0.001
Month 12	74.4 (16.2)	51	0.014	75.9 (18.2)	63	0.003
Month 15	74.9 (17.6)	37	0.014	76.3 (19.8)	46	0.024
Month 18	74.6 (18.1)	37	NS	76.4 (20.6)	44	NS

* The p-value is based on the Kruskal-Wallis or Wilcoxon signed rank evaluation of medians
Source: Based on Tables T14.3 and T14.4, *5.3.5.1.1, pp 2128-2136*

Medical Reviewer's Comment:

1) ***Absolute weight gain at the end of treatment was similar in the DMPA-SC (1.0 kg) and Lupron groups (0.7 kg). Interpretation of the persistent weight gain noted in both groups following completion of treatment is not possible in the absence of data on the natural history of weight gain over one year in women not using hormonal medications.***

10.1.9.9 Vaginal Bleeding

Subjects kept daily diaries recording bleeding and spotting over the six month treatment period. The data were summarized in six 30-day intervals, beginning with the receipt of the first injection of study drug. The initial interval contained the menstrual period during which the first injection was given; thus, virtually all subjects reported some bleeding. Table 75 presents data on the frequency of amenorrhea and categorical frequency of bleeding in those subjects who did not become amenorrheic. From month 2 on, the frequency of amenorrhea was much greater in the Lupron group. The proportion of subjects with frank bleeding (not spotting) was much greater in the DMPA-SC group than the Lupron group at all monthly intervals beyond the first. In those subjects who did not experience amenorrhea, the duration of bleeding or spotting at the last monthly interval during treatment tended to be longer in the DMPA-SC group, with almost half the women experiencing bleeding that lasted longer than a typical menstrual period; the comparative proportion in the Lupron group was only 1%.

The applicant also reported subjects' characterization of their bleeding patterns during two 90-day intervals during the treatment phase. The most common categorizations of bleeding pattern in the DMPA-SC group were "prolonged and irregular" over the first interval and "prolonged" over the second interval. In the Lupron group, the most frequent categorizations were "irregular" and "amenorrhea," respectively, at the first and second intervals.

Table 75 Study 268: Bleeding Patterns by Treatment Group

Outcome	30 Day Interval	DMPA-SC N=136		Lupron N=138	
		N	%	N	%
Percent of subjects with bleeding	1	109	78.0	119	89.9
	2	107	60.8	116	10.4
	3	106	52.8	110	8.2
	4	90	43.4	104	6.7
	5	80	48.8	98	4.1
	6	69	43.5	81	1.2
Percent of subjects with spotting only	1	109	13.8	119	9.2
	2	107	22.4	116	15.5
	3	106	25.5	110	4.5
	4	90	27.8	104	6.7
	5	80	30.0	98	6.1
	6	69	31.9	81	6.2
Percent of subjects with amenorrhea	1	109	8.3	119	0.8
	2	107	16.8	116	74.1
	3	106	21.7	110	87.3
	4	90	28.9	104	86.5
	5	80	21.3	98	89.8
	6	69	24.6	81	92.6
Bleeding or spotting duration at end of treatment	# days/mo	69		81	
	0		24.6		92.6
	1-7		26.1		6.2
	8-10		8.7		1.2
	11-30		40.6		0

Source: Based on Tables T268.0 & T268.1, pp 35-36 & 43-44, September 15, 2004 communication from applicant

Medical Reviewer's Comment:

1) ***Attainment of amenorrhea was almost 4-fold higher in the Lupron group by the end of treatment; this effect will result in complete resolution of dysmenorrhea.***

10.1.10 Reviewer's assessment of efficacy and safety

Efficacy

In the primary efficacy analysis, non-inferiority of DMPA-SC compared to Lupron in reduction of signs and symptoms of endometriosis from baseline to the end of treatment at month 6 was evaluated using a responder analysis on each of the 5 variables on the Biberoglu and Behrman scale. Response was defined as the proportion of subjects in each treatment arm who improved at least one point from baseline in each of the five categories. Non-inferiority was defined where the lower bound of the 96% two-sided confidence interval for the difference between the two drugs' improvement rates exceeded -20%. In order for DMPA-SC to be considered clinically non-inferior, statistical non-inferiority was required on at least four of the five signs/symptoms evaluated.

Three populations were analyzed; the ITT-OC analysis was considered primary by the applicant, but ITT-LOCF and EP analyses were also presented. The results in this study were discrepant. In the ITT-OC population, the criteria for statistical non-inferiority were met on four of five outcome measures, the pre-specified threshold for overall non-inferiority, failing only on induration. However, both the ITT-LOCF and EP populations failed to meet this threshold; with fewer than four of the

outcome measures demonstrating non-inferiority. On the ITT-LOCF analysis, statistical non-inferiority was shown only for pelvic tenderness. The EP analysis (considered by this reviewer to be of least importance) met non-inferiority criteria only for dysmenorrhea, pelvic pain and pelvic tenderness.

In addition, evidence of an overall clinically meaningful improvement over baseline was required, as demonstrated by an improvement of at least 4 points over baseline in the total composite score. In those subjects who were sexually inactive for reasons unrelated to endometriosis, dyspareunia scores were missing values, and the clinically meaningful criterion was modified to an improvement of at least 3 points in the remaining four categories. At the end of treatment, all three analysis populations demonstrated clinically meaningful change in the composite score, both with and without dyspareunia included, exceeding the specified thresholds for change.

Evaluated individually as secondary endpoints, each symptom/sign of endometriosis showed significant improvement in each treatment group from baseline to each assessment period. There were no significant differences between treatments in time to recurrence of symptoms following cessation of treatment. These secondary endpoints, however, were not used to formally evaluate non-inferiority of DMPA-SC to Lupron.

In summary, this study met the pre-specified criteria for demonstrating non-inferiority compared to Lupron in reducing the signs and symptoms associated with endometriosis, using an observed case population, with no imputed data. This is similar to what the FDA had requested as a per protocol analysis. Using, an analysis in which subjects who withdrew before completing treatment had values from early in the course of treatment (or even from baseline) imputed at the end of treatment evaluation, the non-inferiority criteria were not met. The pre-specified criteria for determining the clinical meaningfulness of the symptomatic improvement were met for all populations analyzed. Secondary efficacy endpoints consistently showed a benefit accruing to treatment with DMPA-SC. This trial is therefore considered to support a finding of efficacy of DMPA-SC in treating endometriosis.

Safety:

There were no deaths and few serious adverse events in this study. Discontinuations due to AEs during the treatment period were similar (12 and 11 subjects in the DMPA-SC and Lupron groups, respectively). The overall frequency of adverse events was similar between the treatment groups, with the exception of injection site reactions, which were higher in the DMPA-SC group. Laboratory and vital signs data show no worrisome trends.

The primary safety endpoint was percent change from baseline in BMD measurement after six months of treatment, with a goal of demonstrating superiority of DMPA-SC over Lupron in minimizing bone loss. Percent decrease in BMD was significantly less in the DMPA-SC group at both the femur and spine sites, and at all assessment periods. Comparative median percent changes in BMD at the end of treatment were -0.30% and -1.65% at the femur in the DMPA-SC and Lupron groups, respectively, and -1.10% and -3.95% at the spine in the respective groups. Once treatment was discontinued, the DMPA-SC group showed recovery beginning at 6 months off treatment, with return to baseline status at month 12 for the spine and month 18 for the femur, while the Lupron group showed minimal improvement in femur BMD even 12 months after stopping treatment, and improvement that did not approach baseline in the spine measurement.

Secondary safety endpoints included the experience of hypoestrogenic symptoms, as measured by the Kupperman Index, frequency and severity of hot flushes and levels of estradiol, progesterone and SHBG. Bleeding patterns and the prevalence of amenorrhea were also assessed. These various measures support the proposition that DMPA-SC confers less suppression of estrogen (and therefore

fewer hypoestrogenemic side effects) than does Lupron. Regarding bleeding, the Lupron had a significantly higher rate of amenorrhea by the second treatment interval, while the frequency of bleeding was significantly greater at both intervals in the DMPA-SC group.

Overall Risk-Benefit Assessment:

Although the efficacy results varied according to the population analyzed, results from the most relevant analysis demonstrate non-inferiority of DMPA-SC relative to Lupron in management of painful symptoms of endometriosis. The safety profile of DMPA-SC was reassuring, with few serious adverse events and no worrisome signals in laboratory or vital signs values. DMPA-SC offers benefits over the current approved treatment in reducing bone mineral density loss over the course of treatment, and in minimizing bothersome symptoms of hypoestrogenemia. Side effects more common to DMPA-SC include injection site reactions and vaginal bleeding; these may affect tolerability of the treatment, but do not represent serious safety concerns.

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10.2 Clinical Trial 839-FEH-0012-270

10.2.1 Summary

Title: "Depot Medroxyprogesterone Acetate Subcutaneous Injections for Reduction of Endometriosis-Associated Pain in European, Latin American and Asian Women. A Phase III, Randomized, Parallel Group, Multinational, Multicenter Study Including Assessments of Bone Mineral Density and Coagulation and Lipid Profiles Substudies (Final Report: 6 Months of Treatment and 12 Months of Follow-Up)," dated March 16, 2004.

Two amendments were made to Study 270. The first, dated March 27, 2001, included the following changes:

- Changed the Lupron comparator from intramuscular to subcutaneous injection
- Added a primary safety endpoint (BMD loss after 6 months of treatment); added additional secondary safety endpoints (including Kupperman Index, hot flushes, hormone levels and outcomes research assessments)
- Clarified the definition of the primary efficacy endpoint
- Extended the range of prior laparoscopic diagnosis of endometriosis from 24 to 42 months
- Added Latin America to the centers included
- Modifying the entry requirement regarding "total pelvic score" so that subjects who are not sexually active must have a total of 4 or more (including 2 or more in each of dysmenorrhea and pelvic pain categories)
- Changed the criterion for a clinically meaningful change in the global outcome measure from 3 points to 4 points at six months in subjects who have all 5 categories recorded at baseline
- Restricted secondary endpoints evaluating the effect on coagulation and lipid profiles tests to the DMPA-SC group only
- Removed the exclusion of subjects who have had surgical treatment for endometriosis
- Added the requirement that subjects diagnosed by a remote surgery must have a current vaginal sonogram and vaginal swab to rule out other etiologies for pelvic pain and gonorrhea/chlamydia; if cultures are positive, subjects cannot enter until 3 months following treatment
- Added diseases that may produce chronic abdominal/pelvic pain as an additional exclusion criterion
- Added a bimanual pelvic examination to assess pelvic tenderness and induration to Visits 1, 2 and 5
- Complete revision of the statistical analysis plan
- Other minor protocol changes

Amendment two, dated March 24, 2003, included the following changes:

- Subjects who discontinue participation will be not be asked to return for BMD assessments 6 and 12 months following discontinuation
- Removed the plan to follow subjects for pregnancy for 12 months following their termination from the study
- Added urine pregnancy testing at each 3-monthly clinic visit during the follow-up phase

An administrative protocol change was made August 10, 2002 to:

- Prespecify four scales on the EHP-30 and three on the SF-36 as secondary endpoints to be analyzed hierarchically
- Clarification of the plan to report study results at the end of 6 months of follow-up. The initial plan to keep treatment group assignments for individual patients blinded until completion of the 12 month follow-up period was changed; treatment assignments were unblinded at the end of 6 months of follow-up.

Medical Reviewer's Comment:

1) ***While treatment assignment was unblinded for the study report after six months of follow-up, the applicant states that patient-level treatment information was not to be shared with the evaluative staff. The study was never more than evaluator-blinded, so this is unlikely to compromise the integrity of the blind.***

First patient entered: July 1, 2001

Last patient completed: August 12, 2002

Last follow-up: August 11, 2003

10.2.2 Objectives

The primary efficacy objective of this study was:

- to assess non-inferiority in the reduction of endometriosis-associated pain achieved by DMPA-SC compared to Lupron.

The primary safety objective of this study was:

- to demonstrate superiority of DMPA-SC over Lupron for minimizing bone mineral density (BMD) decline after six months of treatment.

The secondary efficacy objectives were:

- to evaluate changes from baseline in patient quality of life.
- to evaluate the time to return of endometriosis-associated symptoms during the follow-up period.

The secondary safety objectives were:

- to assess further the safety/tolerability of DMPA-SC with Lupron.

Medical Reviewer's Comment:

1) ***In DRUPD discussions with the sponsor during development of these protocols, the term "non-inferiority" was used in discussing the trials, and, based upon the statistical methods and null hypothesis used, the two studies are in fact non-inferiority trials. Nonetheless, the applicant calls them "equivalence" trials throughout the submission.***
2) ***The applicant had indicated that comparative superiority in reduction of hot flushes over Lupron was a desired labeling claim, and had been informed that such a claim required support from an appropriately powered primary endpoint.***

10.2.3 Overall Design

This Phase 3, multinational, multicenter, randomized, evaluator-blinded, comparator-controlled six month treatment duration, study was designed to evaluate the clinical efficacy and safety of DMPA-SC or Lupron in the treatment of subjects with signs and symptoms of endometriosis. Subjects, diagnosed by laparoscopic or other visualization of endometriotic lesions or by histopathology, were

enrolled in a six-month treatment phase and a 12-month follow-up phase, during which time neither the study drug nor comparator could be used. Subjects were randomized to DMPA-SC or Lupron in a 1:1 ratio. Subjects in both groups were also given Os-Cal 500 mg tablets which they were instructed to take daily to ensure adequate calcium intake.

The study was evaluator-blinded, with the drug being administered by an independent injectionist who also received the study syringes. Any attempt by clinic site staff to discover a subject's randomization or route of administration was considered a protocol violation.

The study was conducted at 37 sites in Europe (Hungary, Italy, the Netherlands, Poland, Sweden), Latin America (Brazil, Chile, Mexico, Peru), Asia (Indonesia, Thailand) and New Zealand. The recruitment goal was 320 subjects, 160 in each arm.

10.2.4 Study Procedures and Conduct

10.2.4.1 Schedule of Study Assessments

Subjects were screened for eligibility at Visit 0 and procedures indicated in Table 76 were performed. Subjects then fulfilled a minimum of a one-month wash-in period, during which time symptom data was recorded in a daily diary, allowing evaluation over a full menstrual cycle. At Visit 1, which occurred within 8 weeks of screening, subjects were randomized and the first dose of study medication was administered. At this visit, and at each monthly visit thereafter, efficacy and safety measures were obtained as indicated in the Schedule of Assessments. At Visit 7, the end of treatment visit, subjects also underwent BMD assessment. Subjects had follow-up telephone contact at months 7, 8, 10, 11, 13, 14, 16 and 17 to assess endometriosis-associated pain, adverse events and concomitant medication use. Follow-up clinic visits were scheduled at 9, 12, 15 and 18 months for repeat assessments, including bimanual pelvic examination, patient response questionnaires and BMD assessment at month 12 and 18. At each follow-up visit, subjects also returned an endometriosis-impact diary completed over the month prior to the visit.

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Table 76 Study 270: Schedule of Study Assessments

Study Activity	Visit X-Month									
	0*	1†	2 1-m	3 2-m	4 3-m	5 4-m	6 5-m	7 6-m	T‡	F§
Laparoscopy¶	X									
Informed consent	X									
Inclusion/exclusion criteria	X									
Medical history	X									
Demographic data & height	X									
Physical examination	X							X		
Pelvic examination	X	X	X		X	X		X		X
Confirmation of eligibility		X								
Cervical cytology & mammogram (≥35 years)‖	X									
Pelvic sonogram**	X							X		
Sexually transmitted disease testing	X									
Laboratory assays (hematology, chemistry, and urine analysis)	X				X			X		
Coagulation & lipid tests††	X				X			X		
Weight & sitting blood pressure	X	X	X	X	X	X	X	X		X
Urine pregnancy test	X		X	X	X	X	X	X		X
Collection and/or distribution of patient diary‡‡		X	X	X	X	X	X	X		X
Pain assessment	X	X	X	X	X	X	X	X	X	X
Kupperman Index	X	X	X	X	X	X	X	X		
BMD§§	X							X		X
SHBG, serum estradiol, & progesterone		X			X			X		
EHP-30 & SF-36		X			X			X		X
PSQ		X			X			X		
Injection of DMPA-SC		X			X					
Injection of leuprolide		X	X¶¶	X¶¶	X	X¶¶	X¶¶			
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X

* Baseline visit.
† Randomization and injection visit.
‡ Telephone interview conducted at months 7, 8, 10, and 11 months.
§ Follow-up visit at months 9 and 12.
¶ First-time diagnostic laparoscopy must be performed before this visit.
‖ Unless done within the past 12 months.
** For patients who had had a laparoscopic exam within the last 42 months before study entry.
†† Selected countries only.
‡‡ Patient diary (endometriosis-impact diary including bleeding pattern information) was distributed monthly during the treatment period and every 3 months during the follow-up period (no bleeding pattern information was collected during follow-up).
§§ BMD evaluated using dual energy x-ray absorptiometry (DXA) at visits 0, 7, and at the follow-up visit at 12 months.
¶¶ Injection of leuprolide 3.75 mg for patients at all study sites except the Netherlands.

Source: Table 2, *5.3.5.1.2, pp 31-32*

10.2.5 Study Drug

10.2.5.1 Dose Selection

The drug studied was DMPA-SC, 104 mg/0.65 ml, administered subcutaneously every three months. This dose was chosen based on a phase 1/2 study which determined the minimal SC dose that effectively suppressed ovulation for more than 90 days. The dose of Lupron was 11.25 mg SC every three months in the Netherlands (N=6), 3.75 mg IM monthly in Peru (N=18), and 3.75 mg SC monthly in all other countries.

Medical Reviewer's Comment:

1) ***The dose selection was not directly based on the drug's effect on endometriosis. While suppression of ovulation is a useful pharmacodynamic measure for DMPA's contraceptive indication, it is a surrogate marker of unproven validity for the drug's utility for the endometriosis indication.***

10.2.5.2 Choice of Comparator

The comparator used was Lupron acetate administered subcutaneously (IM in Peru) every one to three months, according to local practice and product labeling in the respective countries. This drug is a synthetic GnRH analog approved for the treatment of endometriosis. Lupron was chosen due to its efficacy in relieving the signs and symptoms of endometriosis. It was administered at the approved dose and route of administration in each participating locality.

10.2.5.3 Assignment to Study Drug

Subjects were randomized to DMPA-SC or Lupron in a 1:1 ratio. DMPA-SC was manufactured by Pharmacia, provided in a pre-filled syringe and was administered subcutaneously into the anterior thigh or abdomen. Lupron was purchased locally in prefilled dual-chamber syringes containing either 3.75 or 11.25 mg, and administered subcutaneously (intramuscularly in the 18 subjects from Peru). DMPA-SC was administered within the first five days of a normal menstrual period at Visit 1 and subsequently at 91 +/- 7 day intervals, while in most subjects, the 3.75 mg dose of Lupron was injected within the first five days of a normal menstrual period at Visit 1 and subsequently at one-month intervals. In the 6 subjects receiving Lupron from the Netherlands, the 11.75 mg dose was injected at 91-day intervals.

10.2.6 Patient Population

Subjects in this study were women with surgically diagnosed endometriosis with significant and chronic pelvic pain. Pain symptoms used as both entry criteria and outcome measures were rated according to the Biberoglu and Behrman Scale[1] presented in Table 3.

10.2.7 Inclusion and Exclusion Criteria

Inclusion Criteria

- Premenopausal women between 18-49 years
- Willing to use nonhormonal barrier contraception for 18 months
- Persistent symptoms associated with laparoscopically diagnosed endometriosis (preferably confirmed by biopsy pathology)
    - Where only a diagnostic laparoscopy was performed, patients fulfilling the pain criteria could be enrolled
    - Where surgical treatment was performed during the laparoscopy, recurrent pain must have persisted for at least 3 months

  - Subjects with more remote laparoscopy must have had vaginal sonography and vaginal cultures to rule out other possible etiologies of chronic pelvic pain
- Total score of 6 or greater in the following 5 categories: dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness and induration. The total score must include a total of at least 2 in the categories of dysmenorrhea, dyspareunia, and pelvic pain. If a patient is sexually inactive for reasons other than endometriosis, the total score must be 4 or greater, with at least 2 in the categories of dysmenorrhea and pelvic pain.
- Normal results on a Pap test within the last 12 months
- Normal results on a mammogram within the last 12 months (for subjects 35 or older)
- Provide informed consent
- Willing and able to comply with study-specific procedures

Exclusion Criteria

- Pregnant or breastfeeding
- Known breast cancer or mammographic results suspicious of breast cancer or requiring 6-month follow-up
- Current or recent use of hormonal agents (wash out periods: 2 months for oral contraceptives, 6 months for Danazol, 12 months for GnRHa or DMPA-IM)
- BMD with both lumbar spine and femur T-scores below -1.0, or history of pathologic or compression fractures
- Abnormal cervical cytology within 12 months; ASCUS and ASCUS favoring reactive changes allowed
- Presence of disease state that could cause chronic abdominal/pelvic pain, including inflammatory bowel disease, fibromyalgia and interstitial cystitis. Large uterine fibroids palpated on bimanual examination were required to be ruled out as the source of the pain.
- Active or history of hepatic or renal disease (AST, ALT or total bilirubin >= 2.5x the upper limit of normal; creatinine > 1.8 mg/dl)
- History of severe hypersensitivity or virilization due to an endocrine disorder, hormone or Danazol therapy
- Well-documented history of thrombotic event (stroke, DVT or pulmonary embolus)
- Anticoagulant therapy or any drug therapy within the past 6 months that could suppress the hypothalamic-pituitary axis
- Uncontrolled hypertension (>180/110)
- Insulin-dependent or poorly controlled non-insulin-dependent diabetes
- Undiagnosed abnormal genital bleeding
- Concurrent use of other investigational medications
- Any condition that might cause the subject to be unable to comply with study instructions
- Use of aminoglutethimide

Medical Reviewer's Comment:

1) ***Women with hysterectomy and/or oophorectomy were not excluded from this study. It is unclear if any such subjects were entered.***

10.2.7.1 Demographics and Baseline Disease Characteristics

Thirty-seven sites in 12 countries each enrolled 1 to 24 subjects, with Brazil and Poland contributing the largest number of patients, 59 each. All but one of the 319 subjects randomized received at least one dose of study medication; however, all data (N=19) from one site were excluded, resulting in an ITT population of 299 (153 DMPA-SC, 146 Lupron), which was used for safety and efficacy

assessments. The "evaluable patient population," defined as patients who received their 3 and 6-month injections/visits within 7 days of the expected date, consisted of 205 subjects (105 DMPA-SC, 100 Lupron).

Demographic characteristics are summarized in Table 77. There were significant differences between the groups on race, with the DMPA-SC group having a higher proportion of Asian/Pacific Islanders and the Lupron group having a slightly higher proportion of white subjects.

Table 77 Study 270: Demographic Characteristics of ITT Population

Characteristic	DMPA-SC N = 153	Leuprolide N = 146	P-value*
Age (yr)			
Mean ± SD	31.79 ± 6.72	30.88 ± 6.06	0.223
Range	18.8 - 49.4	18.4 - 44.6	
<25, n (%)	23 (15.0)	29 (19.9)	0.392
25 to ≤35, n (%)	95 (62.1)	80 (54.8)	
>35 (n, %)	35 (22.9)	37 (25.3)	
Race, n (%)			
White	86 (56.2)	94 (64.4)	0.009
Black	3 (2.0)	6 (4.1)	
Asian/Pacific Islander	27 (17.6)	8 (5.5)	
Mixed/Multiracial	37 (24.2)	38 (26.0)	
Weight (kg)			
Mean ± SD	61.54 ± 11.87	62.61 ± 12.64	0.452
Range	42.0 - 119.8	35.5 - 105.0	
Height (cm)			
Mean ± SD	161.49 ± 7.92	161.89 (7.81)	0.663
Range	144.0 - 185.0	146.0 - 180.0	
Body Mass Index (kg/m^2)			
Mean ± SD	23.57 ± 3.91	23.85 ± 4.29	0.548
Range	16.1 - 35.0	15.2 - 37.6	
≤25, n (%)	108 (70.6)	97 (66.4)	0.594
>25 to ≤30, n (%)	34 (22.2)	34 (23.3)	
>30, n (%)	11 (7.2)	15 (10.3)	

* Statistical tests were chi-square and ANOVA; significance defined at p≤0.05

Source: Table 6, *5.3.5.1.21, p 68*

The baseline status of subjects' signs and symptoms of endometriosis is summarized in Table 78. There were no significant differences among the treatment arms in the frequency or severity of any of the individual components; however, the composite score was significantly higher in the Lupron group, whether or not dyspareunia was included in the composite.

Table 78 Study 270: Baseline Characteristics of ITT Population

Component Severity	DMPA-SC n	DMPA-SC %†	Leuprolide n	Leuprolide %†	P-Value‡
Dysmenorrhea					
Absent	3	2.0	1	0.7	0.288
Mild	10	6.5	6	4.1	
Moderate	88	57.5	76	52.1	
Severe	52	34.0	63	43.2	
Total reported	153	100	146	100	
Dyspareunia					
Absent	11	7.2	8	5.5	0.647
Mild	21	13.7	13	8.9	
Moderate	71	46.4	70	47.9	
Severe	28	18.3	32	21.9	
Not applicable§	22	14.4	23	15.8	
Total reported	153	100	146	100	
Pelvic Pain					
Absent	0	0	0	0	0.085
Mild	24	15.7	11	7.5	
Moderate	97	63.4	99	67.8	
Severe	32	20.9	36	24.7	
Total reported	153	100	146	100	
Induration					
None	32	21.1	18	12.6	0.221
Mild	47	30.9	49	34.3	
Moderate	61	40.1	67	46.9	
Severe	12	7.9	9	6.3	
Total reported	152	100	143	100	
Pelvic Tenderness					
None	6	3.9	4	2.8	0.174
Mild	43	28.3	29	20.1	
Moderate	90	59.2	103	71.5	
Severe	13	8.6	8	5.6	
Total reported	152	100	144	100	
Composite¶					
Mean ± SD	9.3 ± 2.4		9.8 ± 1.8		0.039
Range	3 – 14		6 – 14		
Total reported	131		122		
Composite¶ (Excluding Dyspareunia)					
Mean ± SD	7.4 ± 1.9		7.8 ± 1.6		0.025
Range	2 – 12		4 – 11		
Total reported	152		143		

* Pretreatment values were the randomization visit values. If a randomization visit value was missing, then the baseline visit value was used.
† % = (n/total reported) x 100
‡ Statistical tests were chi-square and ANOVA; significance defined at p≤0.05
§ No intercourse for reasons other than pain.
¶ Composite is the sum of dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and induration scores, with absent/none = 0, mild = 1, moderate = 2, and severe = 3.

Source: Table 7, *5.3.5.1.2, p 69*

Medical Reviewer's Comments:

1) ***The higher mean composite scores at baseline in the Lupron group might signify subjects with more severe disease. However, the chi-square tests evaluating severity categories of the individual signs/symptoms between groups were not significantly different.,***
2) ***As recommended by DRUDP, the proportion of sexually inactive subjects at baseline is <20%.***
3) ***Review of*** Table 78 ***and*** Table 86 ***indicates that, on average, the levels of severity requested by DRUDP for enrollment were also met.***

10.2.7.2 Withdrawals, compliance, and protocol violations

Fifty-four (35%) DMPA-SC and 46 (32%) Lupron subjects discontinued the trial over the total time of 18 months. Approximately one-third of the total withdrawals occurred during the treatment phase; the percentage was higher in the DMPA-SC group [15 (10%) DMPA-SC, 10 (7%) Lupron]. Reasons for withdrawal during the treatment phase and during follow-up are shown in Table 79 and Table 80, respectively. In total, 3 DMPA-SC and 2 Lupron subjects withdrew due to adverse events during the treatment phase (see Section 10.2.9.2).

Table 79 Study 270: Study 270: Detailed Reason for Withdrawal from Treatment

Patient Disposition	Study 270			
	DMPA-SC N=153		Lupron N=146	
	N	%	N	%
Completed Tx	138	90.2	136	93.2
Withdrew from Tx	15	9.8	10	6.8
Reason for Withdrawal				
Lost to follow-up	1	0.7	3	2.1
Adverse event	3	2.0	2	1.4
Lack of efficacy	1*	0.7	0	0
Problems w/inv'r or site	0	0	0	0
Protocol violation	3	2.0	3	2.1
Personal issues	2**	1.3	0	0
Unknown	5*	3.3	2	1.4

* 1 subject also had concomitant AEs at the time of withdrawal
** 2 subjects also had concomitant AEs at the time of withdrawal
Source: Based on Tables 2, 3a & 3b, pp 6-8, August 31, 2004 communication from applicant

Table 80 Study 270: Reasons for Withdrawal during Follow-up by Group

Reason for Discontinuation	DMPA-SC N (%)	Lupron N (%)
Total patients completing treatment	138 (100)	136 (100)
Total discontinued patients	39 (28.3	36 (26)
Adverse Event	9 (6.5)	7 (5.1)
Protocol violation	7 (5.1)	7 (5.1)
Consent withdrawn	14 (10.1)	16 (11.8)
Lost to follow-up	9 (6.5)	6 (4.4)

Source: Based on Figure 1, *5.3.5.1.2, p 62*

Medical Reviewer's Comment:

1) ***No additional information clarifying the reason for withdrawal of consent during the follow-up period was provided.***

Compliance was based upon receipt of the initial injection of study medication at the randomization visit, and, for DMPA-SC and the subjects receiving Lupron in the Netherlands, receipt of the second dose at the month 3 visit, to occur within 91 +/- 7 days of the randomization visit. For all other Lupron subjects, compliance entailed receipt of subsequent doses at one month intervals. Compliance with these time intervals was 91.6% in the DMPA-SC group and 84-92% per month in the monthly dosing Lupron subjects.

Medical Reviewer's Comment:

1) ***The overall proportion of subjects receiving all expected injections is not reported for the Lupron group. However, if the proportion of Lupron subjects receiving the expected number of injections is calculated including the six subjects in the Netherlands who received both of the two scheduled injections, the exposure rate is 93.8% as compared to 93.5% of the DMPA-SC subjects (see*** Table 90***).***

Protocol violations included:

- Deviations in entry criteria
  - 18 violations occurred in 17 DMPA-SC subjects
  - 11 violations occurred in 11 Lupron subjects
- Failure to withdraw subjects who developed withdrawal criteria
  - 3 violations occurred in 3 DMPA-SC subjects
  - 2 violations occurred in 2 Lupron subjects
- Treatment deviations (incorrect administration or wrong study medication)
  - 2 violations occurred in 2 DMPA-SC subjects
  - no violations occurred in Lupron subjects
- Use of excluded concomitant medication (use of estrogen [Estrofem and emergency contraception] during trial)
  - 1 violation occurred in 1 DMPA-SC subject
  - 1 violation occurred in 1 Lupron subject

Data from one site (Investigator 50623, Indonesia, N=19) were eliminated from analysis due to data quality issues. Specifically, information from the daily diary could not be verified, as the source material had been discarded and the existing data was unreliable due to transcription errors and multiple transcriptions, sometimes by non-study personnel; the integrity of the evaluator-blinding was compromised, as the unblinded injectionist was also the study nurse who transcribed the diary records; and the treatment blind was broken early in the study and review of efficacy results from this site revealed them to be discrepant with other sites' results.

Medical Reviewer's Comment:

1) ***Entry criteria violations were typically minor violations that should have relatively little impact on study results.***
2) ***The administration of the "wrong study medication" in two DMPA-SC subjects actually consisted of their being given DMPA-SC from a different study, but in the same dose and route of administration.***

10.2.8 Efficacy

10.2.8.1 Key Efficacy Assessments

The clinical efficacy variables were based on the five symptoms/signs from the Biberoglu and Behrman scale[1] (Table 3) and were evaluated at baseline and all scheduled visits. A positive response was defined as an improvement of at least one point in the score for each category after six months of treatment as compared to baseline. During the follow-up period, the three pain scores (dysmenorrhea, dyspareunia and pelvic pain) were assessed monthly by asking subjects to rate their pain over the previous month. Subject recall was facilitated by use of a daily diary which was brought to each visit. The two signs of endometriosis (induration and pelvic tenderness) were evaluated during a pelvic exam at months 9, 12, 15 and 18 in the follow-up period, as well as at monthly exams during the treatment phase. Any non-endometriosis-related medical condition interfering with pain analysis was listed as an adverse event, and the pelvic pain category rated as non-applicable for that time interval.

Efficacy analysis was done on both the Intent to Treat (ITT) and the Evaluable Patient (EP) populations. The former was defined as all subjects who received at least one dose of study medication; the latter as all subjects who received their three and six-month injection/visits within +/- 7 days of the expected date and who did not use any excluded concomitant medications (i.e., aminoglutethimide). In the ITT population, both last-observation-carried forward (LOCF) and observed case (OC) analyses were done; in the EP population, only the OC analyses was conducted.

10.2.8.2 Pharmacokinetic Assessments

Pharmacokinetic sampling was not done in this study.

Medical Reviewer's Comment:

1) ***Data on estradiol suppression was collected, which ideally could be used for pharmacodynamic assessment; however, the low sensitivity of the assay (~ pg/ml) and the infrequent sampling renders this data of little utility.***

10.2.8.3 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint was demonstration of non-inferiority of DMPA-SC compared to Lupron in the reduction of endometriosis-associated pain, as determined by ratings on the five pain signs/symptoms. A responder analysis was used, comparing the proportion of subjects in each treatment arm who improved at least one point from baseline in each of the five categories. Non-inferiority was defined where the lower bound of the 96% two-sided confidence interval for the difference between the two drugs' improvement rates was no worse than -20%. In order for DMPA-SC to be considered clinically non-inferior, statistical non-inferiority was required on at least four of the five signs/symptoms evaluated, with a p value < 0.02 required for significance on any given category, and an overall clinically meaningful improvement over baseline was required, as demonstrated by an improvement of at least 4 points over baseline in the total composite score. In those subjects who were sexually inactive for reasons unrelated to endometriosis, dyspareunia scores were missing values, and the clinically meaningful criterion was modified to an improvement of at least 3 points in the remaining four categories.

Response rates on each outcome measure at each month of treatment and in follow-up are shown in Table 81. Analysis of the five signs and symptoms of endometriosis at month 6 as compared to baseline showed that DMPA-SC was statistically non-inferior to Lupron on all five of the outcome measures (dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness and induration). Although the response rate for DMPA-SC was less than that for Lupron on every outcome measure at month 6, the pre-specified criterion for statistical non-inferiority was met for each of the outcome measures.

Table 81 Study 270: Response of Signs and Symptoms of Endometriosis by Month and Treatment Group

Component Visit	DMPA-SC		Leuprolide			
	Total Reported	n (%)†	Total Reported	n (%)†	P-Value‡	96% CI
Dysmenorrhea						
Month 1	149	109 (73.2)	142	107 (75.4)	<0.001§	-12.73, 8.33
Month 2	147	124 (84.4)	139	136 (97.8)	0.022	-20.15, -6.83
Month 3	143	123 (86.0)	139	135 (97.1)	0.003§	-17.74, -4.47
Month 4	140	127 (90.7)	137	134 (97.8)	<0.001§	-12.75, -1.44
Month 5	138	127 (92.0)	136	133 (97.8)	<0.001§	-11.16, -0.37
Month 6 (EOT)	135	123 (91.1)	135	131 (97.0)	<0.001§	-11.79, -0.07
Month 12	118	101 (85.6)	118	89 (75.4)	<0.001§	-0.34, 20.68
Month 18	95	77 (81.1)	99	75 (75.8)	<0.001§	-6.81, 17.40
Dyspareunia						
Month 1	104	63 (60.6)	101	55 (54.5)	<0.001§	-8.04, 20.29
Month 2	103	79 (76.7)	101	82 (81.2)	0.003§	-16.20, 7.22
Month 3	101	78 (77.2)	101	81 (80.2)	0.002§	-14.80, 8.86
Month 4	99	71 (71.7)	95	79 (83.2)	0.075	-23.64, 0.76
Month 5	98	77 (78.6)	90	79 (87.8)	0.023	-20.29, 1.88
Month 6 (EOT)	88	73 (83.0)	88	78 (88.6)	0.003§	-16.46, 5.10
Month 12	81	64 (79.0)	79	66 (83.5)	0.006§	-17.18, 8.12
Month 18	63	51 (81.0)	66	60 (90.9)	0.049	-22.46, 2.54
Pelvic Pain						
Month 1	150	85 (56.7)	143	86 (60.1)	0.002§	-15.30, 8.36
Month 2	150	101 (67.3)	140	116 (82.9)	0.184	-25.76, -5.29
Month 3	146	115 (78.8)	140	121 (86.4)	0.003§	-16.81, 1.49
Month 4	141	111 (78.7)	138	118 (85.5)	0.002§	-16.17, 2.60
Month 5	141	112 (79.4)	137	121 (88.3)	0.006§	-17.87, 0.10
Month 6 (EOT)	136	111 (81.6)	136	124 (91.2)	0.006§	-18.02, -1.10
Month 12	120	102 (85.0)	117	93 (79.5)	<0.001§	-4.67, 15.70
Month 18	98	80 (81.6)	100	80 (80.0)	<0.001§	-9.86, 13.13
Pelvic Tenderness						
Month 1	145	61 (42.1)	137	53 (38.7)	<0.001§	-8.62, 15.39
Month 2						
Month 3	141	94 (66.7)	132	101 (76.5)	0.031	-20.99, 1.29
Month 4	138	104 (75.4)	131	107 (81.7)	0.003§	-16.57, 3.93
Month 5						
Month 6 (EOT)	133	108 (81.2)	128	109 (85.2)	<0.001§	-13.45, 5.54
Month 12	116	91 (78.4)	110	86 (78.2)	<0.001§	-11.01, 11.54
Month 18	93	74 (79.6)	94	76 (80.9)	<0.001§	-13.26, 10.69

Table is continued on next page

Component Visit	DMPA-SC		Leuprolide		P-Value‡	96% CI
	Total Reported	n (%)†	Total Reported	n (%)†		
Induration						
Month 1	126	37 (29.4)	124	47 (37.9)	0.027	-20.77, 3.70
Month 2						
Month 3	122	71 (58.2)	123	82 (66.7)	0.031	-21.14, 4.20
Month 4	120	80 (66.7)	122	90 (73.8)	0.014§	-19.15, 4.95
Month 5						
Month 6 (EOT)	117	84 (71.8)	119	95 (79.8)	0.016§	-19.45, 3.38
Month 12	100	80 (80.0)	104	82 (78.8)	<0.001§	-10.48, 12.79
Month 18	82	64 (78.0)	87	69 (79.3)	0.001§	-14.22, 11.70

* Response (ie, improvement) defined as a decrease of at least 1 point in the score relative to pretreatment (primary endpoint was the response at month 6).
† % = (n/total reported within period) x 100
‡ The p-value tests the null hypothesis DMPA-SC % improved - leuprolide % improved ≤-20%. Treatment equivalence was concluded when p<0.02.
§ Statistically equivalent between treatment groups (p<0.02).
At baseline, DMPA-SC N=153, Lupron N=146
Source: Table 11, *5.3.5.1.2, pp 76-7*

At month 12, six months after cessation of treatment, the statistical non-inferiority of DMPA-SC was maintained on all outcomes; in fact, at this time, a higher response rate for DMPA-SC than for Lupron was demonstrated on dysmenorrhea, pelvic pain, pelvic tenderness and induration.

At month 18, statistical non-inferiority of DMPA-SC persisted for dysmenorrhea, pelvic pain, pelvic tenderness and induration. At this time, a higher response rate for DMPA-SC than for Lupron was seen for dysmenorrhea and pelvic pain.

Results in the EP population were consistent, as was the ITT-LOCF analysis, which was carried out only at month 6.

Table 82 compares results reached by the ITT-OC analysis, which is the primary analysis reported by the applicant, with the ITT-LOCF and EP analyses. On the applicant's primary analysis, non-inferiority is demonstrated on all five endpoints, thus satisfying the pre-set criteria for overall DMPA-SC non-inferiority to Lupron. The ITT-LOCF and EP analyses were consistent with these results.

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Table 82 Study 270: Response at 6 Months: Comparison of Three Analyses

Component	Analysis	DMPA-SC		Lupron			
		N	%	N	%	p-value	96% CI
Dysmenorrhea	ITT-OC	135	91.1	135	97.0	<0.001	-11.79, -0.07
	ITT-LOCF	151	88.7	145	95.2	<0.001	-12.86, 0.00
	EP	103	91.3	99	98.0	<0.001	-13.13, -0.30
Dyspareunia	ITT-OC	88	83.0	88	88.6	0.003	-16.46, 5.10
	ITT-LOCF	101	81.2	95	83.2	<0.001	-13.20, 9.26
	EP	71	81.7	70	88.6	0.014	-19.13, 5.37
Pelvic Pain	ITT-OC	136	81.6	136	91.2	0.006	-18.02, -1.10
	ITT-LOCF	152	80.3	146	88.4	0.002	-16.68, 0.50
	EP	105	82.9	100	91.0	0.005	-17.72, 1.43
Pelvic Tenderness	ITT-OC	133	81.2	128	85.2	<0.001	-13.45, 5.54
	ITT-LOCF	148	78.4	140	80.7	<0.001	-12.10, 7.43
	EP	101	80.2	92	84.8	0.002	-15.79, 6.62
Induration	ITT-OC	117	71.8	119	79.8	0.016	-19.45, 3.38
	ITT-LOCF	128	70.3	127	77.2	0.008	-18.14, 4.44
	EP	93	72.0	87	78.2	0.015	-19.32, 7.09

N = Total reported; % = % improved (i.e., with >=1 point decrease in score relative to baseline)
p-value tests the H_0 that DMPA-SC % improved – Lupron % improved <= -20%. Statistical non-inferiority concluded if p <0.02.
CI = 96% confidence intervals around point estimate of difference in improvement rate between DMPA-SC and Lupron
Source: Based on Tables 10-12, *5.3.5.1.2, pp 76-79*

Medical Reviewer's Comments:

1) ***The FDA statistical review of the protocols for Studies 268 and 270 in January 2001 noted that the ITT-LOCF analysis would be considered the primary analysis. However, the reviewer also noted that the ICH E9 guidelines express concern about the role of ITT analyses in equivalence trials, as they may not be conservative. The FDA statistician recommended that a per protocol (PP) analysis also be performed, with a goal of demonstrating consistent results between the ITT-LOCF and PP analyses. In this study, the EP analysis would seem least useful, as it is overly restrictive and sacrifices data based on late administration of the study drugs. This is not warranted, since both study drugs are depot formulations that allow for "late" administration. The ITT-OC analysis would seem closest to the FDA-requested PP analysis, as it includes all subjects who have data at baseline and the 6 month primary outcome period.***
2) ***Although within the bounds accepted for concluding non-inferiority, in the ITT-OC analysis, the 96% confidence intervals around the difference in response rates for dysmenorrhea and pelvic pain indicate that DMPA-SC may be statistically inferior to Lupron.***

A composite score was also used to evaluate the clinical meaningfulness of the treatment results, with the criterion for meaningful change set at a mean decrease from baseline of at least 4 points. At the end of treatment, a statistically and clinically significant change from baseline was seen in each group: a mean decrease of 6.3 points in the DMPA-SC group, and a mean decrease of 7.3 points in the Lupron group. The improvement in the composite score remained statistically and clinically significant at 6 months of follow-up (month 12), with decreases of 6.5 points and 5.8 points in the DMPA-SC and Lupron groups, respectively. At 12 months of follow-up, the DMPA-SC group

continued to show a significant improvement with a decrease of 6.6 points, while the Lupron group's mean score decreased by 6.1 points. Results are displayed in Table 83. The confidence interval for the difference between treatment group mean changes indicates that the decrease in the Lupron group may have been statistically greater at months 3, 4 and 6. Results were similar when analyzed in the EP and ITT-LOCF populations (Table 84).

Table 83 Study 270: Mean Change in Composite Score by Time and Treatment Group

Visit		DMPA-SC	Leuprolide	95% CI†	
				Lower	Upper
Month 1	Total reported	109	105		
	Pretreatment mean (SD)‡	9.3 (2.4)	9.8 (1.9)		
	Mean change (SD)	-3.2 (2.9)	-3.5 (2.6)	-0.5	1.0
	Within group test§	<0.001	<0.001		
Month 3	Total reported	107	104		
	Pretreatment mean (SD)‡	9.3 (2.4)	9.9 (1.9)		
	Mean change (SD)	-5.0 (2.9)	-6.3 (2.4)	0.6	2.1
	Within group test§	<0.001	<0.001		
Month 4	Total reported	106	98		
	Pretreatment mean (SD)‡	9.4 (2.4)	9.8 (1.9)		
	Mean change (SD)	-5.6 (2.8)	-6.5 (2.4)	0.3	1.7
	Within group test§	<0.001	<0.001		
Month 6 (EOT)	Total reported	94	91		
	Pretreatment mean (SD)‡	9.3 (2.4)	9.7 (1.9)		
	Mean change (SD)	-6.3 (3.2)	-7.3 (2.4)	0.2	1.9
	Within group test§	<0.001	<0.001		
Month 12	Total reported	85	84		
	Pretreatment mean (SD)‡	9.3 (2.5)	9.7 (2.0)		
	Mean change (SD)	-6.5 (3.3)	-5.8 (3.3)	-1.7	0.3
	Within group test§	<0.001	<0.001		
Month 18	Total reported	66	72		
	Pretreatment mean (SD)‡	9.2 (2.5)	9.6 (1.9)		
	Mean change (SD)	-6.6 (3.6)	-6.1 (3.3)	-1.7	0.7
	Within group test§	<0.001	<0.001		

* The composite score includes dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and induration. The composite was not assessed at a visit if a component was not assessed at that visit (Primary efficacy timepoint was month 6).
† 95% CI for the difference between the treatment group mean changes.
‡ Based on patients who had non-missing values at both pretreatment and the change visit.
§ Wilcoxon signed rank test; significance defined at $p \leq 0.05$.
Source: Table 14, *5.3.5.1.2, p 80*

Table 84 Study 270: Change in Composite Score: Comparison of Three Analyses

Time Period	Analysis Population	DMPA-SC		Lupron		Threshold for Clinical Meaningfulness
		N	Change	N	Change	
Month 6 (End of Treatment)	ITT-OC	94	-6.3	91	-7.3	-4
	ITT-LOCF	108	-6.0	99	-6.9	-4
	EP	73	-6.2	72	-7.3	-4
Month 12 (6 mo F/U)	ITT-OC	85	-6.5	84	-5.8	-4
	EP	60	-6.5	67	-6.0	-4
Month 18 (12 mo F/U)	ITT-OC	66	-6.6	72	-6.1	-4
	EP	46	-6.8	58	-6.4	-4
Composite Score Excluding Dyspareunia						
Month 6 (End of Treatment	ITT-OC	135	-5.0	132	-6.0	-3
	ITT-LOCF	151	-4.8	143	-5.8	-3
	EP	104	-4.9	96	-5.9	-3
Month 12 (6 mo F/U)	ITT-OC	119	-5.1	113	-4.6	-3
	EP	88	-5.1	84	-4.6	-3
Month 18 (12 mo F/U)	ITT-OC	95	-5.0	96	-4.8	-3
	EP	68	-5.3	73	-4.8	-3

Source: Based on Tables 14-19, *5.3.5.1.2, pp 80-85*

Excluding dyspareunia from the composite score, the mean decrease in the composite score at the end of treatment was 5.0 points in the DMPA-SC group and 6.0 points in the Lupron group, surpassing the threshold for clinical significance that was set at decrease of 3 in the composite score excluding dyspareunia. These changes remained clinically significant at month 12, with mean changes of -5.1 and -4.6 in the DMPA-SC and Lupron groups, respectively, and at month 18, where the score decreases were 5.0 and 4.8, respectively. These results were upheld in analyses using EP and ITT-LOCF (Table 84).

There were no marked differences noted in subgroup analyses for BMI, age and race.

Medical Reviewer's Comment:

1) ***The composite score data was available on only 61% of the DMPA-SC subjects and 62% of Lupron subjects by the end of treatment; by 6 months of follow-up, it was calculated on 56% of DMPA-SC subjects and 58% of Lupron subjects, and by 12 months of follow-up on 43% of DMPA-SC subjects and 49% of Lupron subjects .***

10.2.8.4 Secondary Efficacy Endpoint Analysis

Secondary endpoints were:

- Time to recurrence of symptoms following treatment discontinuation
- The proportion of women in each treatment arm who experienced an improvement from baseline in each of the five categories, throughout treatment and the follow-up period

- Change from baseline in patient quality of life, compared between baseline and months 6, 12, 15 and 18

Time to symptom recurrence, defined as increase of at least one point in any of the five categories during the follow-up period was compared between treatment arms using a Kaplan-Meier survival analysis. Additional analyses of each of the five signs/symptoms of endometriosis were also done.

Overall, results on the secondary endpoints were similar between the DMPA-SC and Lupron groups, although no formal criteria for statistical non-inferiority were defined. There was an indication of longer effect duration after cessation of treatment in the DMPA-SC group for the symptoms of dysmenorrhea and pelvic pain.

Time to symptom recurrence/worsening (defined as an increase of at least one point from the value at the end of treatment on any of the five outcome categories) was evaluated during the follow-up period. The three patient-reported symptoms of dysmenorrhea, dyspareunia and pelvic pain were evaluated monthly in the follow-up period; the physician-assessed signs, pelvic tenderness and induration, were evaluated at 3-monthly intervals following treatment cessation (months 9, 12, 15 and 18). Results are displayed in Table 85. The three symptoms tended to recur or worsen, on average, six to seven months after discontinuation of DMPA-SC, while recurrence in the Lupron group was more variable, with dysmenorrhea returning approximately three months after the end of treatment; while the median times to resumption of pelvic pain and dyspareunia were about four and eight months, respectively. There appeared to be greater latency in the return of the two signs, although this may be due to longer ascertainment intervals. The median time to recurrence of induration was almost identical in each group, at over one year. Fewer than 50% of DMPA-SC subjects experienced recurrence of pelvic tenderness by the end of 12 months of follow-up, while those in the Lupron group took just over a year for recurrence. Although only those subjects who had experienced improvement during treatment were included in this analysis, over half of subjects in each group experienced exacerbation of their symptoms once treatment was stopped. Smaller proportions, on the order of 30-40%, had worsening of pelvic tenderness or induration. There were significant differences between the DMPA-SC and Lupron groups, with recurrence of dysmenorrhea and pelvic pain occurring with greater latency in the DMPA-SC group.

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Table 85 Study 270: Time to Recurrence Following Discontinuation of Treatment

Component	DMPA-SC	Leuprolide	P-value*
Dysmenorrhea			
Total reported†	123	131	
No. (%) of patients with event	81 (65.9)	109 (83.2)	
No. (%) of patients censored‡	42 (34.1)	22 (16.8)	
Median time (days)§	184	92	0.000
25th, 75th percentile (days)	99, --	64, 155	
Dyspareunia			
Total reported†	76	81	
No. (%) of patients with event	42 (55.3)	42 (51.9)	
No. (%) of patients censored‡	34 (44.7)	39 (48.1)	
Median time (days)§	217	246	0.502
25th, 75th percentile (days)	57, --	94, --	
Pelvic Pain			
Total reported†	111	124	
No. (%) of patients with event	63 (56.8)	90 (72.6)	
No. (%) of patients censored‡	48 (43.2)	34 (27.4)	
Median time (days)§	227	120	0.004
25th, 75th percentile (days)	88, --	61, 344	
Pelvic Tenderness			
Total reported†	108	109	
No. (%) of patients with event	34 (31.5)	46 (42.2)	
No. (%) of patients censored‡	74 (68.5)	63 (57.8)	
Median time (days)§	--	373	0.102
25th, 75th percentile (days)	228, --	169, 393	
Induration			
Total reported†	84	95	
No. (%) of patients with event	24 (28.6)	32 (33.7)	
No. (%) of patients censored‡	60 (71.4)	63 (66.3)	
Median time (days)§	392	393	0.566
25th, 75th percentile (days)	266, --	260, --	

p-value is based on log rank test; median time is Kaplan-Meier estimate
Source: Table 21, *5.3.5.1.2, p 88*

The mean change and the significance of the change in each sign/symptom from baseline at each month of treatment and follow-up was tested in each treatment group; the data are in Table 86. Each category showed significant decrease from pretreatment levels at each month assessed and in each treatment group.

Medical Reviewer's Comment:

1) ***It is not explicitly stated, but it appears that these analyses were only conducted using the ITT-OC population. No data are presented for EP or ITT-LOCF.***

2) ***Subjects who withdrew early from treatment generally had improvement scores about 50% less than completers in the DMPA-SC group. The difference between completers and early withdrawers was less in the Lupron group (see*** Table 27***).***

Table 86 Study 270: Mean Change from Baseline in Symptoms and Signs

	Dysmenorrhea		Dyspareunia		Pelvic Pain		Pelvic Tenderness		Induration	
Visit	DMPA -SC	Lupron	DMPA -SC	Lupron	DMPA -SC	Lupron	DMPA -SC	Lupron	DMPA -SC	Lupron
Pre-tx N, Mean (SD)	153 2.2 (0.7)	146 2.4 (0.6)	131 1.9 (0.8)	123 2.0 (0.8)	153 2.1 (0.6)	146 2.2 (0.5)	152 1.7 (0.7)	144 1.8 (0.6)	152 1.3 (0.9)	143 1.5 (0.8)
Month 1 (N, Mean change (SD); p value)	151 -1.2 (1.1) <0.001	143 -1.3 (1.1) <0.001	109 -0.7 (0.9) <0.001	105 -0.7 (0.9) <0.001	150 -0.7 (0.9) <0.001	143 -0.8 (0.8) <0.001	150 -0.5 (0.7) <0.001	141 -0.4 (0.7) <0.001	150 -0.2 (0.8) <0.001	140 -0.4 ((0.8) <0.001
Month 3 (N, Mean change (SD); p value)	146 -1.5 (1.0) <0.001	140 -2.2 (0.8) <0.001	107 -1.0 (1.1) <0.001	104 -1.2 (1.0) <0.001	146 -1.1 (0.8) <0.001	140 -1.3 (0.8) <0.001	145 -0.8 (0.8) <0.001	136 -1.0 (0.8) <0.001	145 -0.6 (0.9) <0.001	136 -0.8 (0.9) <0.001
Month 4 (N, Mean change (SD); p value)	142 -1.7 (0.9) <0.001	138 -2-2 (0.8) <0.001	106 -1.0 (1.1) <0.001	98 -1.2 (1.0) <0.001	141 -1.1 (0.9) <0.001	138 -1.3 (0.8) <0.001	141 -1.0 (0.8) <0.001	135 -1.1 (0.7) <0.001	141 -0.7 (0.9) <0.001	135 -0.9 (0.9) <0.001
Month 6 (N, Mean change (SD); p value)	137 -1.7 (1.0) <0.001	136 -2.2 (0.8) <0.001	94 -1.2 (1.0) <0.001	91 -1.4 (0.90) <0.001	136 -1.2 (0.9) <0.001	136 -1.5 (0.9) <0.001	136 -1.1 (0.9) <0.001	132 -1.3 (0.8) <0.001	136 -0.9 (1.0) <0.001	132 -1.1 (0.9) <0.001
Early tx W/D (N, Mean change (SD); p value)	5 -0.8 (1.3) NS	2 -1.5 (0.7) NS	4 -0.3 (0.5) NS	2 -0.5 (0.7) NS	5 -0.8 (0.4) NS	2 -1 0 (0) NS	5 -0.6 (0.9) NS	2 0 (1.4) NS	5 -0.4 (0.9) NS	2 1.0 (1.4) NS
Month 9 (N, Mean change (SD); p value)	129 -1.8 (1.0) <0.001	128 -1.4 (1.0) <0.001	90 -1.3 (1.1) <0.001	93 -1.5 (1.01) <0.001	129 -1.3 (1.1) <0.001	127 -1.4 (0.9) <0.001	128 -1.2 (0.9) <0.001	124 -1.2 (0.8) <0.001	128 -1.0 (1.0) <0.001	124 -1.1 (0.9) <0.001
Month 12 (N, Mean change (SD); p value)	120 -1.5 (1.0) <0.001	119 -1.2 (1.0) <0.001	85 -1.3 (1.3) <0.001	85 -1.4 (1.1) <0.001	120 -1.4 (0.9) <0.001	117 -1.3 (0.9) <0.001	119 -1.2 (0.9) <0.001	114 -1.1 (0.8) <0.001	119 -1.1 (1.0) <0.001	114 -1.0 (1.0) <0.001
Month 15 (N, Mean change (SD); p value)	102 -1.4 (1.0) <0.001	110 -1.3 (1.0) <0.001	75 -1.4 (1.1) <0.001	78 -1.5 (1.0) <0.001	103 -1.4 (1.0) <0.001	109 -1.4 (0.9) <0.001	102 -1.2 (0.8) <0.001	105 -1.2 (0.8) <0.001	102 -1.1 (1.0) <0.001	105 -1.0 (1.0) <0.001
Month 18 (N, Mean change (SD); p value)	97 -1.4 (1.1) <0.001	100 -1.2 (1.0) <0.001	67 -1.3 (1.2) <0.001	73 -1.4 (1.0) <0.001	98 -1.3 (1.0) <0.001	100 -1.3 (1.0) <0.001	96 -1.2 (0.9) <0.001	97 -1.2 (0.9) <0.001	96 -1.1 (1.0) <0.001	96 -1.0 (1.0) <0.001

* The p-value is based on the Wilcoxon Signed Rank test of **median change** from baseline within each treatment group
Note: Only data from those follow-up assessments at which all five signs/symptoms were scheduled to be assessed are shown. Changes in dysmenorrhea, dyspareunia and pelvic pain remained significant at all monthly intervals in the treatment and 12 month follow-up periods.
Source: Based on Tables T5.7-T5.8, *5.3.5.1.2, pp 410-441*

Quality of life was measured by outcomes research assessment measures, the EHP-30 and the SF-36, and by the Patient Satisfaction Questionnaire (PSQ) and the daily diary. Four scales of the EHP-30 were specified as endpoints and analyzed hierarchically (pain, sexual intercourse, emotional well-being and self-image). The SF-36 is a global quality of life measure, evaluating 36 items relative to

their status one year before. Three scales of this instrument were specified as endpoints and analyzed hierarchically (role-physical, social function and physical function). Subjects also completed the PSQ, rating response to and satisfaction with the assigned treatment. Finally, the daily diary was used to collect information relating to daily productivity as it was affected by endometriosis symptoms.

Data from the EHP-30 is in Table 87. The DMPA-SC group demonstrated decreases from baseline in the four pre-specified subscales at the end of treatment, and these changes were maintained at 12 months of follow-up. Similar results were seen in the Lupron group. The data remain significant when analyzed in the EP and ITT-LOCF populations.

Table 87 Study 270: EHP-30 Subscale Means (SD) and Change from Randomization

EHP-30 Scale		DMPA-SC		
		Randomization	Month 6	Month 18
Pain‡	Total reported	149	143	107
	Mean (SD)	43.08 (21.33)	17.53 (19.69)	21.04 (23.24)
	T-test of change from randomization		<0.001†	<0.001†
Sexual Intercourse‡	Total reported	118	95	83
	Mean (SD)	45.01 (26.81)	27.37 (26.98)	24.44 (28.42)
	T-test of change from randomization		<0.001†	<0.001†
Emotional Well-Being‡	Total reported	149	143	107
	Mean (SD)	45.11 (22.79)	28.96 (21.75)	24.33 (22.89)
	T-test of change from randomization		<0.001†	<0.001†
Self-Image‡	Total reported	149	143	107
	Mean (SD)	35.68 (26.93)	25.76 (24.46)	22.74 (25.76)
	T-test of change from randomization		<0.001†	<0.001†
Social Support	Total reported	149	143	107
	Mean (SD)	40.56 (26.36)	26.57 (24.70)	21.85 (25.90)
	T-test of change from randomization		<0.001†	<0.001†
Control and Powerlessness	Total reported	149	143	107
	Mean (SD)	45.82 (27.47)	24.18 (24.57)	24.30 (26.82)
	T-test of change from randomization		<0.001†	<0.001†

* Lower mean score indicates improvement.
† T-test significance defined as p≤0.05
‡ Prespecified scale
Source: Table 22, *5.3.5.1.2, p 90*

Medical Reviewer's Comments:

1) ***While the applicant indicates that both the EHP-30 and the SF-36 are validated measures, no details about the validation process, such as the population in which each questionnaire was validated, were provided. The applicant was advised during the clinical development program that quality of life measures are not generally accepted for labeling claims.***
2) ***Data at 12 months' follow-up which appears to show an ongoing decrease in symptomatology is likely to be biased by the withdrawal from follow-up of those subjects who failed to achieve or maintain symptom improvement.***

The SF-36 data for the DMPA-SC group is displayed in Table 88. The three pre-specified subscales all showed significant improvement from randomization to the end of treatment, which was maintained at 12 months' follow-up. Similar results were seen in the Lupron group. Again, the data remain significant when analyzed in the EP and ITT-LOCF populations.

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Table 88 Study 270: SF-36 Subscale Means and Change from Randomization

SF-36 Scale		DMPA-SC		
		Randomization	Month 6	Month 18
Role-Physical‡	Total reported	125	119	88
	Mean (SD)	36.80 (39.60)	68.49 (39.66)	68.18 (42.84)
	T-test of change from randomization		<0.001†	<0.001†
Social Function‡	Total reported	125	119	88
	Mean (SD)	58.30 (24.95)	72.27 (26.35)	74.29 (25.66)
	T-test of change from randomization		<0.001†	0.001†
Physical Function‡	Total reported	125	119	88
	Mean (SD)	69.14 (23.57)	81.58 (20.69)	80.87 (22.69)
	T-test of change from randomization		<0.001†	<0.001†
Bodily Pain	Total reported	125	119	88
	Mean (SD)	41.62 (19.39)	65.29 (24.80)	66.24 (27.15)
	T-test of change from randomization		<0.001†	<0.001†
General Health	Total reported	124	119	87
	Mean (SD)	50.10 (23.15)	59.97 (23.03)	63.82 (24.62)
	T-test of change from randomization		<0.001†	<0.001†
Vitality	Total reported	125	118	88
	Mean (SD)	45.96 (22.29)	54.07 (22.69)	60.63 (24.05)
	T-test of change from randomization		0.002†	<0.001†
Role Emotional	Total reported	125	119	88
	Mean (SD)	43.73 (42.63)	62.18 (42.94)	64.77 (42.69)
	T-test of change from randomization		0.001†	0.004†
Mental Health	Total reported	125	118	88
	Mean (SD)	55.48 (21.22)	62.47 (21.90)	69.82 (20.78)
	T-test of change from randomization		0.004†	<0.001†

* Higher mean score indicates improvement.
† T-test significance defined as p≤0.05
‡ Prespecified scale
Source: Table 23, *5.3.5.1.2, p 92*

The Patient Satisfaction Questionnaire evaluated patient-perceived improvements in status and satisfaction with the treatment at 3 month intervals during the treatment phase. Both groups indicated significant improvements in physical health and sexual relationship at both months 3 and 6, and the Lupron group in emotional health at months 3 and 6 (Table 89). The DMPA-SC group was less willing to recommend their treatment to a friend or to consider using it in the future (results based on a 10 point scale). Results analyzing the EP and ITT-LOCF populations were consistent in finding significant improvement in physical health in both treatment groups at 3 and 6 months. In the EP analysis, the DMPA-SC group showed improvement in emotional health and sexual relationships at both months, but in the ITT-LOCF analysis, improvement in sexual relationships was significant only at month 3, and emotional health only at month 6.

Table 89 Study 270: Patient Satisfaction Questionnaire Data

PSQ Item	Visit Mean (SD) N						T-Test of Change			
	Randomization		Month 3		Month 6		Randomization to Month 3		Randomization to Month 6	
	DMPA-SC	LPLD	DMPA-SC	LPLD	DMPA-SC	LPLD	DMPA-SC	LPLD	DMPA-SC	LPLD
Emotional Health	5.56 (2.30) 149	5.67 (2.03) 143	5.95 (2 23) 143	6.19 (2.24) 139	6.21 (2.29) 143	6.50 (2 12) 135	.061	.003*	.006*	< .001*
Physical Health	5.28 (2 21) 149	5.15 (2.16) 143	6 35 (2 07) 143	6.22 (2 08) 139	6.64 (2 09) 143	6.89 (1 98) 135	< 001*	< .001*	< .001*	< 001*
Sexual Relationship	5 39 (2 71) 109	5.48 (2 78) 103	5 97 (2.66) 100	6 08 (2.56) 102	6.08 (2.62) 101	6 30 (2 77) 100	049*	164	039*	318
Injection Anxiety	5 10 (2.95) 149	5.23 (3 11) 143	4 27 (2 95) 143	3 82 (2 84) 137			002*	< 001*		
Injection Pain	3.38 (2.74) 144	2.30 (1 86) 138	3.53 (2 52) 140	2.85 (2 08) 136			435	002*		
Recommend to a Friend			7 59 (2 60) 143	8.31 (2 07) 139	7.51 (2 61) 143	8 30 (2 24) 135				
Consider in the Future			7.38 (2.82) 143	8 01 (2.31) 139	7 31 (2.82) 143	7.93 (2 62) 135				

Source: Table T16.3.1, *5.3.5.1.2, p 1971*

Finally, the daily diary that subjects completed detailing the impact of endometriosis on their daily lives was evaluated. Both groups showed significant improvement at the end of treatment in:

1. Mean hours of work missed and mean % of work hours missed
2. Mean hours of housework missed and mean % of housework hours missed
3. Work productivity in work and housework

Medical Reviewer's Comment:

1) Although subjects in both groups showed significant improvements in amount of work/housework missed, they also had significantly decreased hours of work/housework scheduled; thus the improvement may result from lowering the demands upon them.

10.2.9 Safety

10.2.9.1 Safety Measurements

All participants who received at least one dose of study medication were included in the summaries and listings of safety data (N=299). Adverse events were monitored from the administration of the first dose of study medication until the final study visit with the exception of pregnancy, which was followed until conclusion. Adverse events were categorized according to the Medical Dictionary for Regulatory Action (MedDRA) and were summarized by organ system and preferred term. Safety analyses were conducted with no imputation of missing data.

The following safety measurements were evaluated:

- BMD assessments done at Visit 0 (baseline) and at months 6, 12 and 18 months. These measures were made from the spine (L1-4) and the proximal femur (femoral neck and total femur) using dual energy x-ray absorptiometry (DXA) scanners. To account for variations in repeated measurements, a 2% change in BMD over time was used as the criterion for true bone loss.
- The Kupperman Index evaluating hypoestrogenemic symptoms, reviewed by the same investigator with the subject at each visit during the treatment phase
- Occurrence of hot flushes as recorded in the daily diary. Subjects recorded the number of mild, moderate and severe hot flushes, or absence of this symptom, daily. Definitions were derived from the February 1997 FDA Guidance pertaining to vasomotor symptoms
- Changes in sex hormone binding globulin (SHBG), serum estradiol and progesterone, measured at visits 1, 4 and 7
- Reports of adverse events; not to include anticipated changes in subjects' menstrual cycles, although such changes were recorded in the subject diary
- Any pregnancy occurring or discovered during the treatment period or within 120 days after the last dose, with follow-up until the conclusion of the pregnancy
- Laboratory assessment (hematology, serum chemistries including hepatic panels, and urinalysis) done at baseline and at months 3 and 6. At selected sites in Poland and Sweden, coagulation and lipid panels were also obtained
- Blood pressure, assessed at each study visit
- Body weight and BMI
- Change in bleeding patterns, and other relevant data from the daily diaries, evaluated at each study visit during the treatment phase

10.2.9.1.1 Extent of exposure

Number of injections for the two groups is displayed in Table 90.

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Table 90 Study 270: Treatment Exposure by Group

Number of Injections*	DMPA-SC N=153		Leuprolide N=146	
	n	%	n	%
1	10	6.5	3	2.1
2	143	93.5	9†	6.2
4			2	1.4
5			1	0.7
6			131	89.7

* Patients in the DMPA-SC group were to receive 2 injections of study medication. At all study sites except the Netherlands, patients in the leuprolide group were to receive 6 injections of study medication. At the Netherlands' site, patients were to receive 2 injections of leuprolide.
† Includes the 6 patients at the Netherlands' site.

Source: Table 10, *5.3.5.1.2, p 74*

Medical Reviewer's Comment:

1) ***If the proportion of Lupron subjects receiving the expected number of injections is calculated including the six subjects in the Netherlands who received both of the two scheduled injections, the proportion of Lupron subjects who received the planned exposure is 93.8%, comparable to the DMPA-SC subjects.***

10.2.9.2 Adverse Events

10.2.9.2.1 Serious adverse events

Deaths: there were no deaths during treatment, nor through 12months of follow-up.

Premature termination due to adverse events: Three DMPA-SC subjects (2.0 %) and two Lupron subjects (1.4%) terminated prematurely from the study during the treatment phase because of adverse events. Vaginal hemorrhage, which occurred in two DMPA-SC subjects, was the only AE causing withdrawal of more than one subject. All adverse events leading to withdrawal in the treatment period are listed in Table 91.

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Table 91 Study 270: Treatment Withdrawals due to Adverse Events

Subject #	MedDRA Term	Treatment group	Drug-related	SAE
295	Insomnia	DMPA-SC	Yes	No
113	Vaginal hemorrhage	DMPA-SC	Yes	No
303	Breast tenderness	DMPA-SC	Yes	No
	Vaginal hemorrhage	DMPA-SC	Yes	No
044	Vulvovaginal dryness	Lupron	Yes	No
	Libido decreased	Lupron	Yes	No
315	Pelvic mass	Lupron	No	No

Source: Appendix 3.12.3, *5.3.5.1.2, pp 9638-40*

Serious adverse events: There were six DMPA-SC (3.9%) and three Lupron group subjects (2.1%) who experienced serious adverse events during treatment. An additional eight subjects (5.8%) in the DMPA-SC group experienced SAEs during the 12 months of follow-up, as did six in the Lupron group (4.4%). Overall, the rate of SAEs in the study was 8.6 % in the DMPA-SC group and 5.6% in the Lupron group. Individual SAEs are listed in Table 92. None of the SAEs in either group resulted in withdrawal. Only two SAEs, both in the DMPA-SC group, were considered to be treatment related: a case of breast neoplasia with no evidence of malignancy, and a severe case of endometriosis that developed coincident with the first dose of DMPA-SC.

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Table 92 Study 270: Listing of SAEs by Treatment Group and Study Phase

Investigator/ Patient No.	Age (yr)	Preferred Term*	Maximum Intensity	Drug-Related	Outcome	Action Taken
DMPA-SC (Treatment Period)						
,0105	26	Endometriosis	Severe	Yes	Recovered	None
.0043	26	Gastritis NOS	Severe	No	Recovered	None
/0129	33	Pulmonary embolism	Moderate	No	Recovered	None
,0051	23	Leiomyoma NOS	Severe	No	Recovered	None
.64	30	Abdominal pain NOS	Severe	No	Recovered	None
		Endometriosis	Severe	No	Recovered	None
		Abdominal pain lower	Severe	No	Recovered	None
		Muscle cramps	Moderate	No	Recovered	None
		Intermenstrual bleeding	Moderate	No	Recovered	None
		Vomiting NOS	Moderate	No	Recovered	None
		Vaginal hemorrhage	Moderate	No	Recovered	None
0227	38	Gastroenteritis NOS	Severe	No	Recovered	None
DMPA-SC (Follow-up Period)						
0052	34	Pelvic pain NOS	Severe	No	Recovered	None
/0189	33	Menorrhagia	Moderate	No	Recovered	None
,0098	30	Breast neoplasm NOS†	Moderate	Yes	Recovered	None
.0102	33	Vomiting NOS	Severe	No	Recovered	None
0249	26	Endometriosis	Severe	No	Recovered	None
		Dysmenorrhea	Severe	No	Recovered	None
0291	31	Endometriosis	Severe	No	Recovered	None
0227	38	Uterine hemorrhage	Severe	No	Recovered	None
0039	32	Menometrorrhagia	Moderate	No	Recovered	None
Leuprolide (Treatment Period)						
0193	33	Appendicitis	Severe	No	Recovered	None
.0041	37	Appendicitis	Severe	No	Recovered	None
0245	19	Concussion	Severe	No	Recovered	None
Leuprolide (Follow-up Period)						
0144	27	Pregnancy NOS	Severe	No	Recovered	None
0106	29	Pelvic pain NOS	Severe	No	Recovered	None
		Ovarian cyst	Moderate	No	Recovered	None
0041	37	Vaginal prolapse	Moderate	No	Recovered	None
		Complication of delivery NOS	Moderate	No	Recovered	None
0056	24	Abdominal pain NOS	Severe	No	Recovered with sequelae	None
0221	31	Pregnancy NOS	NA	No	Recovered	None
0017	29	Pregnancy NOS	NA	No	Recovered	None
		Gestational diabetes	Mild	No	Recovered	None

Source: Table 41, *5.3.5.1.2, p 128*

Medical Reviewer's Comments:

1) ***It is unclear why three of the 14 pregnancies occurring in the follow-up period were classified as SAEs.***
2) ***The classification of four subjects as having SAEs of endometriosis is unwarranted.***
3) ***The SAE of pulmonary embolism (PE) is a questionable diagnosis. Chest x-ray is not the standard diagnostic test for PE. The subject had a number of additional diagnoses that***

could have accounted for her symptoms. Without further diagnostic data, it is difficult to attribute her symptoms to PE.

4) ***Although not listed as SAEs leading to study withdrawal, two pregnancies in the Lupron group were considered to represent protocol violations, and these subjects were presumably withdrawn from the study.***

10.2.9.2.2 Frequent adverse events

At least one adverse event was reported during the treatment phase by 70% and 65% of the DMPA-SC and Lupron groups, respectively. The most frequent (>5%) adverse events in both groups were:

- Nausea
- Headache
- Hot flushes

Events occurring at >5% frequency only in the DMPA-SC group were:

- Intermenstrual bleeding
- Back pain
- Breast pain

Events occurring at >5% frequency only in the Lupron group were:

- Myalgia

Events occurring at significantly different rates (chi-square p<=0.05) in the two groups (DMPA vs. Lupron) were:

- Intermenstrual bleeding (13.2 vs. 1.4%)
- Uterine hemorrhage (4.6 vs. 0.7%)
- Vaginal hemorrhage (4.6 vs. 0%)
- Hot flushes (5.9 vs. 17.5%)
- Myalgia (1.3 vs. 5.6%)
- Vaginal discharge (0.7 vs. 4.2%)

Overall, adverse events occurring with frequency >3% in either group are reported in Table 93.

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Table 93 Study 270: Treatment-Emergent Adverse Events Occurring in >=3% of Subjects

Adverse Event	DMPA-SC		Lupron		Between-Treatment p-value
	N	%	N	%	
Intermenstrual bleeding	20	13.2	2	1.4	<0.001
Nausea	19	12.5	14	9.8	NS
Headache NOS	13	8.6	18	12.6	NS
Back pain	11	7.2	7	4.9	NS
Hot flushes	9	5.9	25	17.5	0.002
Breast pain	8	5.3	5	3.5	NS
Arthralgia	7	4.6	7	4.9	NS
Influenza	7	4.6	4	2.8	NS
Hypersomnia	7	4.6	3	2.1	NS
Uterine hemorrhage	7	4.6	1	0.7	0.039
Vaginal hemorrhage	7	4.6	0	0	0.009
Libido decreased	6	3.9	7	4.9	NS
Nasopharyngitis	6	3.9	7	4.9	NS
Vaginitis	6	3.9	7	4.9	NS
Depression NEC	6	3.9	6	4.2	NS
Gastritis NOS	6	3.9	4	2.8	NS
Abdominal pain NOS	6	3.9	1	0.7	NS
Constipation	5	3.3	4	2.8	NS
Diarrhea NOS	5	3.3	1	0.7	NS
Bronchitis NOS	3	2.0	5	3.5	NS
Myalgia	2	1.3	8	5.6	0.042
Insomnia NEC	2	1.3	7	4.9	NS
Dizziness	2	1.3	6	4.2	NS
Vulvovaginal dryness	2	1.3	5	3.5	NS
Vaginal discharge	1	0.7	6	4.2	0.046

Source: Based on Table T12.1.1, *5.3.5.1.2, pp 1885-1896*

The frequency of adverse events considered to be drug-related was statistically greater in the DMPA-SC group (51% vs. 39% , p=0.047); by system, there were significantly higher frequencies of reproductive system and breast disorders (primarily uterine and vaginal bleeding problems) (p<0.001) in the DMPA-SC group and vascular disorders (hot flushes) (p=0.003) in the Lupron group. Racial subgroups were evaluated for adverse events; however, small numbers of non-white subjects precluded statistical comparisons. Analysis by age or BMI category was not reported.

In the follow-up period, adverse events were reported by 55% of DMPA-SC subjects and 50% of Lupron subjects. The most frequent adverse event in both groups was breast pain; other adverse events occurring in >5% of subjects were:

- Nasopharyngitis
- Headache
- Nausea
- Arthralgia
- Intermenstrual bleeding
- Pregnancy

10.2.9.2.3 Injection site reactions

A single subject in each treatment group experienced an injection site reaction. The case occurring in the DMPA-SC subject was described as "cutaneous induration left thigh at the injection site." The case in the Lupron group was described as an injection site infection, and occurred in a subject who received monthly Lupron by the SC route. No subject withdrew from the study due to an injection site reaction.

10.2.9.3 Bone Mineral Density

Change from baseline in bone mineral density at the femur and lumbar spine was the primary safety measure in this study. The mean BMD measurements in each treatment group, at each skeletal site and each time period are shown in Table 94. By month 18, data were available for 62% of DMPA-SC subjects who had baseline measurements and for 63-65% of Lupron subjects. The baseline median total femur BMD was significantly higher in the Lupron group; there were no significant differences subsequently between the two groups in median total femur BMD. For spine BMD, the 6 month measurement was significantly higher in the DMPA-SC group than the Lupron group; differences at all other assessment times were not significant.

Table 94 Study 270: Mean (SD) BMD Scores at each Visit by Treatment Group

Visit	Femur BMD		Spine BMD	
	DMPA-SC	Lupron	DMPA-SC	Lupron
Baseline	1.06 (0.13)	1.09 (0.12)*	1.23 (0.12)	1.23 (0.12)
N	149	143	148	145
Month 6 (End of Treatment)	1.06 (0.12)	1.08 (0.12)	1.22 (0.12)	1.18 (0.12)*
N	131	130	134	132
Month 12 (6 month post-tx follow-up)	1.07 (0.13)	1.08 (0.12)	1.21 (0.12)	1.20 (0.12)
N	119	118	119	118
Month 18 (6 month post-tx follow-up)	1.07 (0.14)	1.10 (0.12)	1.23 (0.13)	1.22 (0.12)
N	93	93	93	91
Ss who discontinued tx early	1.02 (0.09)		1.20 (0.20)	
N	3	0	3	0

*Between-treatment Kruskal-Wallis p-value <=0.05
Source: based on Table T7.1.1., *5.3.5.1.2, pp 1150-1153*

Median percent changes at month 6 (end of treatment), month 12 (6 months off treatment) and month 18 (one year off treatment) are displayed in Table 95. The Lupron subjects showed a statistically significant decrease in BMD at both measurement sites after 6 months of treatment, while the DMPA-SC subjects showed a small, but statistically significant decrease only in lumbar spine BMD. The magnitude of the change from baseline was statistically significantly less at both sites in the DMPA-SC group as compared to the Lupron group. At 12 months, 6 months off study medication, the DMPA-SC subjects had nonsignificant decreases from baseline at the femur and a slightly greater decrease at the lumbar site than that seen at month 6. The Lupron subjects again showed statistically significant decreases from baseline at both sites; however, the magnitude of the decrease was less than it had been at month 6. Again, the difference between treatment groups was statistically significant at both sites, favoring DMPA-SC. By month 18, after a year off treatment, the DMPA-SC group showed small and nonsignificant decreases in BMD from baseline at both sites, while the Lupron group had continued statistically significant decreases from baseline, although of lower magnitude than seen at the two previous assessments in both sites. The difference between treatment

groups at month 18 was statistically significant only at the femur. These results suggest that recovery has begun by 6 months off treatment in both groups (except for the spine in the DMPA-SC group), but is essentially complete by one year only in the DMPA-SC group.

Table 95 Study 270: BMD Percent Change from Baseline Median by Treatment Group

Visit		DMPA-SC	Leuprolide	P-Value* Between Treatments
Baseline	**Femur Total BMD (g/cm^2)**			
	Total reported	149	143	
	Baseline median	1.06	1.09	0.026
	Spine Total BMD (g/cm^2)			
	Total reported	148	145	
	Baseline median	1.22	1.21	0.895
Month 6 (EOT)	**Femur Total BMD (g/cm^2)**			
	Total reported	130	129	
	Baseline median†	1.07	1.09	
	Median % change	-0.50	-2.10	<0.001
	Within group test‡	0.184	<0.001	
	Spine Total BMD (g/cm^2)			
	Total reported	131	131	
	Baseline median†	1.22	1.22	
	Median % change	-1.00	-4.00	<0.001
	Within group test‡	<0.001	<0.001	
Month 12	**Femur Total BMD (g/cm^2)**			
	Total reported	119	117	
	Baseline median†	1.07	1.09	
	Median % change	-0.40	-1.60	<0.001
	Within group test‡	0.261	<0.001	
	Spine Total BMD (g/cm^2)			
	Total reported	117	117	
	Baseline median†	1.22	1.22	
	Median % change	-1.30	-2.60	<0.001
	Within group test‡	<0.001	<0.001	
Month 18	**Femur Total BMD (g/cm^2)**			
	Total reported	93	92	
	Baseline median†	1.07	1.11	
	Median % change	-0.20	-1.05	0.006
	Within group test‡	0.908	0.002	
	Spine Total BMD (g/cm^2)			
	Total reported	93	91	
	Baseline median†	1.22	1.21	
	Median % change	-0.40	-1.30	0.080
	Within group test‡	0.059	<0.001	

* Kruskal-Wallis test; significance defined at p≤0.05
† Based on patients who had non-missing values at both baseline and the change visit.
‡ Wilcoxon signed rank test; significance defined at p≤0.05

Source: Table 27, *5.3.5.1.21, p 102*

Categorical analysis of the percent change showed similar trends, as displayed in Table 96. In general, at each evaluation time and each skeletal site surveyed, the proportion experiencing bone loss of >= 2.5% was two- to three-fold higher in the Lupron group, the exceptions being the spine at month 6, where the Lupron group exceeded the DMPA-SC by only about 1.5-fold and the spine at month 18, where the groups were about equivalent.

Table 96 Study 270: BMD Percent Change from Baseline Category by Treatment Group

Change from baseline to:	% change	Femur BMD		Spine BMD	
		DMPA-SC	Lupron	DMPA-SC	Lupron
Month 6 (End of Treatment)	>=+0.1%	42%	21%	32%	4%
	-2.4 to 0%	44%	33%	37%	21%
	<=-2.5 %	15%	47%	31%	76%
	N evaluated	130	129	131	131
Month 12 (6 month post-tx follow-up)	>=+0.1%	41%	26%	29%	11%
	-2.4 to 0%	40%	35%	38%	37%
	<=-2.5 %	19%	39%	33%	52%
	N evaluated	119	117	117	117
Month 18 (12 month post-tx follow-up)	>=+0.1%	43%	34%	42%	31%
	-2.4 to 0%	44%	36%	32%	40%
	<=-2.5 %	13%	31%	26%	30%
	N evaluated	93	92	93	91

Source: based on Tables 28 & 29, *5.3.5.1.2, pp 104-105*

Evaluation of bone effects by looking at the percent of subjects with for osteopenia (i.e., with a T-score <-1), showed relatively little change at the femur in either group at the end of treatment. At the spine, the DMPA-SC group showed an increase in the percent with osteopenia by six months, with a more pronounced (6-fold) increase seen in the Lupron group (Table 97). The shift in T-score category (defined in 0.5 increments) was also evaluated, with the finding that over both times and sites, the Lupron group had up to 2 times as many subjects dropping to a lower T-score category than did the DMPA-SC group.

Table 97 Study 270: BMD T-scores <-1 by Treatment Group

Visit	Femur T-Score < -1				Spine T-Score < -1			
	DMPA-SC		Lupron		DMPA-SC		Lupron	
	Total N	% < -1	Total N	% < -1	Total N	% < -1	Total N	% < -1
Baseline	149	7.4	143	4.2	148	4.1	145	3.4
Month 6	131	7.6	130	3.8	134	12.7	132	21.2
Month 12	119	6.7	118	5.1	119	10.1	118	17.8
Month 18	93	10.8	93	2.2	93	8.6	91	11.0

Source: Based on Table 30, *5.3.5.1.2, p 106*

No subject in either group experienced osteoporotic fractures, nor did any have T-scores meeting the definition of osteoporosis (T-score <2.5).

Subgroup analyses were conducted on age, BMI, race and country groups. No markedly different patterns were noted in any subgroup.

Medical Reviewer's Comments:

1) ***The categorical percent change analysis obscures the evaluation of subjects with neutral effects on BMD by collapsing subjects with no change in BMD into a category ranging down to a -2.4% change.***
2) ***On the primary endpoint, percent change in BMD, as well as the secondary BMD endpoints, the data clearly demonstrate the superiority of DMPA-SC over Lupron in minimizing the loss of BMD during the six month treatment course.***

10.2.9.4 Hypoestrogenic Symptoms

Symptoms of pharmaceutically lowered estrogen levels were assessed by three secondary safety endpoints: the Kupperman Index, a patient diary recording occurrence and severity of hot flushes, and reproductive hormone levels. The Kupperman Index, which measures 11 symptoms of decreased estrogen levels, was reviewed with subjects monthly throughout the treatment phase; median percent changes are displayed in Table 98. The Lupron group showed significant increases in symptoms of hypoestrogenemia from baseline at each month of treatment. The DMPA-SC group increased significantly from baseline at months 1 and 2, then decreased until showing a median change from baseline of 0 at months 5 and 6. DMPA-SC subjects had significantly lower symptomatology scores than the Lupron subjects at every time point.

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Table 98 Study 270: Median Percent Change in Kupperman Index by Treatment Group

Visit		DMPA-SC	Leuprolide	P-Value* Between Treatments
Pretreatment	Total reported	153	146	
	Pretreatment median	8.0	9.0	0.269
Month 1	Total reported	150	142	
	Pretreatment median†	8.0	9.0	
	Median change	1.0	5.0	<0.001
	Within group test‡	0.025	<0.001	
Month 2	Total reported	149	140	
	Pretreatment median†	9.0	9.0	
	Median change	0.0	7.0	<0.001
	Within group test‡	0.042	<0.001	
Month 3	Total reported	145	140	
	Pretreatment median†	8.0	9.0	
	Median change	1.0	8.0	<0.001
	Within group test‡	0.159	<0.001	
Month 4	Total reported	142	138	
	Pretreatment median†	8.5	9.0	
	Median change	0.5	8.0	<0.001
	Within group test‡	0.202	<0.001	
Month 5	Total reported	141	137	
	Pretreatment median†	9.0	9.0	
	Median change	0.0	6.0	<0.001
	Within group test‡	0.451	<0.001	
Month 6 (EOT)	Total reported	138	136	
	Pretreatment median†	9.0	9.0	
	Median change	0.0	6.0	<0.001
	Within group test‡	0.835	<0.001	

* Kruskal-Wallis test; significance defined at p≤0.05
† Based on patients who had non-missing values at both pretreatment and the change visit. Pretreatment values were the randomization visit values. If a randomization visit value was missing, then the baseline visit value was used.
‡ Wilcoxon signed rank test; significance defined at p≤0.05.
Note: Higher scores represent increased symptoms
Source: Table 32, *5.3.5.1.21, p 110*

Mean monthly scores on the Kupperman Index are shown in Table 99. The between group difference became significant at month 1 and persisted throughout the treatment period. After an initial small increase in the first two months of treatment, the DMPA-SC group then experienced a decrease in symptom scores, although not returning to baseline. The Lupron group reported an increase in symptom scores that peaked at month 3, then declined throughout the remainder of treatment, but never reached the baseline level and remained higher than those in the DMPA-SC subjects.

Table 99 Study 270: Mean (SD) Kupperman Index Scores by Month and Treatment Group

Visit	DMPA-SC	Lupron	Between-group p-value*
Baseline	9.1 (8.5)	10.3 (8.2)	0.11
Month 1	11.9 (9.7)	16.4 (9.3)	<0.001
Month 2	11.9 (9.6)	18.7 (9.7)	<0.001
Month 3	11.4 (9.3)	19.3 (9.7)	<0.001
Month 4	11.0 (8.8)	18.5 (9.9)	<0.001
Month 5	10.6 (8.5)	17.5 (10.3)	<0.001
Month 6	10.1 (8.3)	16.7 (10.1)	<0.001

* The p-value is based on the Kruskal-Wallis evaluation of medians
Source: Based on Table T9.1, *5.3.5.1.2, pp 1774-6*

Medical Reviewer's Comments:

1) ***The Kupperman Index has been criticized for unjustified weighting, overlapping criteria, and suboptimal patient understanding. The sponsor was clearly informed that outcomes based on the Kupperman Index were unlikely to be acceptable for labeling claims.***
2) ***The use of median change scores (the most prominent analysis reported) is less illuminating than comparison of means and medians across time periods and treatment groups. No statistical comparison of mean scores appears to have been done.***

Daily diaries were kept by subjects, recording frequency and severity of hot flushes. Median hot flush frequency data are presented in Table 100. The DMPA-SC subjects continued to report a median of 0 hot flushes in each month of treatment. The Lupron group experienced significantly more frequent hot flushes at each month of treatment, reaching a peak at month 3 that persisted through the remainder of treatment. In the worst month for each group, the median and range of daily hot flush frequency was 0 (0-33) in the DMPA-SC group (month 3) and 2.0 (0-60) in the Lupron group (month 5). Severity of hot flushes was also considered; summary data appear in Table 101. Beginning at month 2, at each month of treatment, average severity for the Lupron subjects was two- to three-fold higher.

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Table 100 Study 270: Median Hot Flush Frequency by Month and Treatment Group

Diary Reference Month*	Average Daily Number	DMPA-SC	Leuprolide	P-Value† Between Treatments
Pretreatment	Total reported	131	126	
	Median	0.0	0.0	0.463
	Range	0.0 – 9.0	0.0 – 6.5	
Month 1	Total reported	136	135	
	Median	0.0	0.5	<0.001
	Range	0.0 – 17.0	0.0 – 72.7	
Month 2	Total reported	137	127	
	Median	0.0	1.9	<0.001
	Range	0.0 – 32.2	0 – 29.9	
Month 3	Total reported	136	122	
	Median	0.0	2.0	<0.001
	Range	0.0 – 33.4	0.0 – 39.4	
Month 4	Total reported	134	125	
	Median	0.0	2.0	<0.001
	Range	0.0 – 9.2	0.0 – 59.1	
Month 5	Total reported	130	124	
	Median	0.0	2.0	<0.001
	Range	0.0 – 7.9	0.0 – 60.0	
Month 6 (EOT)	Total reported	125	116	
	Median	0.0	2.0	<0.001
	Range	0.0 – 7.0	0.0 – 48.6	

* 30-day intervals after the start of treatment. Pretreatment is the interval before the start of treatment.

† Kruskal-Wallis test; significance defined at $p \leq 0.05$

Source: Table 33, *5.3.5.1.2, p 112*

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Table 101 Study 270: Mean (SD) Average Daily Hot Flush Severity* by Month and Treatment Group

Visit	DMPA-SC	Lupron	Between-group p-value**
Baseline	0.21 (0.44)	0.24 (0.48)	0.45
Month 1	0.35 (0.56)	0.60 (0.68)	<0.001
Month 2	0.40 (0.61)	1.10 (0.85)	<0.001
Month 3	0.40 (0.62)	1.23 (0.87)	<0.001
Month 4	0.42 (0.64)	1.21 (0.83)	<0.001
Month 5	0.39 (0.57)	1.23 (0.85)	<0.001
Month 6	0.34 (0.57)	1.27 (0.86)	<0.001

*Average daily severity is calculated as the sum of daily [weighted severity (1x #mild, 2x #moderate, 3x #severe)/# hot flushes that day]/# days with data recorded. For example, a subject experiencing four mild hot flushes each day of the month would have a severity score of 1.
** The p-value is based on the Kruskal-Wallis evaluation of medians
Source: Based on Table T10.3, *5.3.5.1.2, pp 1825-7*

Medical Reviewer's Comment:

1) ***Both the mean values for daily hot flush severity and the median data for hot flush frequency demonstrate lower rates in the DMPA-SC group.***

Levels of estradiol, progesterone and sex hormone binding globulin (SHBG) were assessed at baseline and at months 3 and 6. Table 102 presents mean and median change in estradiol levels measured at baseline, and months 3 and 6 of the treatment phase. Compared to baseline, the DMPA-SC group showed a nonsignificant increase in mean (but not median) estradiol at month 3, while the Lupron group decreased significantly. By month 6, both groups showed significant decreases in estradiol. The Lupron group was significantly lower than the DMPA-SC group at both on-treatment assessment points.

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Table 102 Study 270: Change in Estradiol Levels by Treatment Group

Visit		DMPA-SC	Leuprolide	P-Value* Between Treatments
Estradiol, Unconjugated (pg/mL)				
Randomization	Total reported	143	131	
	Randomization mean (SD)	62.3 (49.2)	66.6 (64.1)	
	Randomization median	44.9	43.9	0.740
Month 3	Total reported	131	126	
	Randomization mean (SD)†	61.9 (50.7)	66.1 (64.7)	
	Randomization median†	43.0	43.9	
	Mean change (SD)	8.8 (81.3)	-26.9 (66.1)	
	Median change	0.0	-5.9	<0.001
	Within group test‡	0.115	<0.001	
Month 6 (EOT)	Total reported	127	123	
	Randomization mean (SD)†	62.7 (50.9)	66.9 (65.8)	
	Randomization median†	46.0	43.9	
	Mean change (SD)	-9.5 (57.8)	-26.5 (66.2)	
	Median change	0.0	-7.9	0.003
	Within group test‡	0.033	<0.001	

* Kruskal-Wallis test; significance defined at p≤0.05.
† Based on patients who had non-missing values at both randomization and the change visit.
‡ Wilcoxon signed rank test; significance defined at p≤0.05.
Source: Table 35, *5.3.5.1.2, p 114*

Estradiol levels below 41 pg/ml may be associated with increased incidence of bone loss[Error! Bookmark not defined.] and vasomotor symptoms. The proportion of subjects in each treatment group experiencing estradiol levels below this threshold are displayed in Table 103. In the DMPA-SC group, there was no increase in the frequency of the low estradiol category from baseline at month 3, and an increase from 47% to 62% at month 6; in contrast, in the Lupron group, there was an increase from 44% at baseline to 84% at month 3, and further increase to 90% at month 6. The Lupron group had a significantly higher proportion of hypoestrogenemic subjects than the DMPA-SC group at both treatment months that were assessed.

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Table 103 Study 270: Estradiol Levels <41 pg/ml by Treatment Group and Time

Visit ++	Estradiol Category	DMPA-SC N = 153		Leuprolide N = 146		Total N = 299		Between Treatment Test +	
		n	%	n	%	n	%	P-Value	*
Randomization	< 41 pg/mL	67	46.9	58	44.3	125	45.6	0.669	
	>= 41 pg/mL	76	53.1	73	55.7	149	54.4		
	Total Reported	143	100.0	131	100.0	274	100.0		
	Not Reported	2		6		8			
Month 3	< 41 pg/mL	56	40.0	114	83.8	170	61.6	<0.001	*
	>= 41 pg/mL	84	60.0	22	16.2	106	38.4		
	Total Reported	140	100.0	136	100.0	276	100.0		
	Not Reported	1		4		5			
Month 6 (EOT)	< 41 pg/mL	84	61.8	121	90.3	205	75.9	<0.001	*
	>= 41 pg/mL	52	38.2	13	9.7	65	24.1		
	Total Reported	136	100.0	134	100.0	270	100.0		
Early TRT Disc	< 41 pg/mL	4	66.7	1	50.0	5	62.5	0.673	
	>= 41 pg/mL	2	33.3	1	50.0	3	37.5		
	Total Reported	6	100.0	2	100.0	8	100.0		

Source: Table T8.3, *5.3.5.1.2, p 1773*

Mean progesterone and SHBG levels decreased significantly from baseline at months 3 and 6 in both groups; the groups did not differ significantly.

Medical Reviewer's Comment:

*1) **The sponsor has indicated that the sensitivity of the estradiol assay was only** ~~~~ **This greatly limits the utility of these measurements.***

10.2.9.5 Laboratory Values and Urinalysis

The serum chemistry, hematology, and urinalysis test results were reviewed. Mean values for selected laboratory parameters measured at intervals during the treatment period and at early withdrawal are presented in Table 104. Four subjects (three in the Lupron group) experienced elevated liver function values greater than 2.5 times the upper limit of normal during the treatment phase and after normal baseline values:

- one DMPA-SC subject (#305) had ALT values of 24 U/L at baseline, 114 U/L at month 3 and 80 U/L at month 6
- a Lupron subject (#49) had a baseline AST value of 25 U/L increase to 103 IU/L at month 3 and decrease to 38 IU/L at month 6; a baseline ALT value of 17 U/L increase to 196 IU/L at month 3 and decrease to 36 IU/L at month 6; and a baseline GGT value of 22 U/L increase to 149 IU/L at month 3 and decrease to 82 IU/L at month 6
- a Lupron subject (#209) had a baseline ALT value of 23 U/L increase to 116 IU/L at an unscheduled visit 11 days after what should have been the month 3 visit, and decrease to 72 IU/L at month 6

- a Lupron subject (#148) a baseline AST value of 19 U/L increase to 136 IU/L at month 3 and decrease to 42 IU/L at month 6

The laboratory changes in general were not deemed clinically significant, and no subject discontinued due to abnormal laboratory values.

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Table 104 Study 270: Mean (SD) Laboratory Safety Variables

Lab Test		DMPA-SC N=153		Lupron N=146	
		N	Mean (SD)	N	Mean (SD)
Hematocrit (fraction)	Baseline	135	0.40 (0.04)	133	0.40 (0.03)
	Month 3	128	0.40 (0.03)	113	0.40 (0.03)
	Month 6	117	0.40 (0.03)	115	0.40 (0.03)
	Early w/d	6	0.40 (0.01)	2	0.39 (0.04)
Hemoglobin (g/L)	Baseline	146	130.9 (14.0)	137	133.4 (11.7)
	Month 3	132	132.6 (12.4)	120	133.5 (9.0)
	Month 6	123	133.0 (12.1)	119	134.5 (9.1)
	Early w/d	6	129.3 (6.2)	2	132.5 (12.0)
AST (U/L)	Baseline	151	21.1 (7.2)	140	23.3 (10.5)
	Month 3	137	20.9 (7.4)	133	26.6 (14.3)
	Month 6	131	20.8 (8.6)	127	24.8 (9.9)
	Early w/d	6	19.7 (4.7)	2	29.0 (14.1)
ALT (U/L)	Baseline	151	19.2 (9.8)	140	22.2 (17.9)
	Month 3	137	19.4 (8.9)	133	26.7 (20.6)
	Month 6	131	19.0 (8.5)	127	24.6 (11.7)
	Early w/d	6	20.8 (10.3)	2	35.0 (19.8)
GGT (U/L)	Baseline	151	20.3 (20.9)	140	18.4 (9.8)
	Month 3	137	19.8 (15.9)	133	21.4 (16.9)
	Month 6	131	20.2 (19.5)	127	20.2 (12.4)
	Early w/d	6	18.7 (10.0)	2	18.5 (0.7)
Alk Phos (U/L)	Baseline	151	74.9 (23.2)	140	77.0 (22.8)
	Month 3	137	70.0 (21.7)	133	84.6 (27.1)
	Month 6	131	71.3 (21.9)	127	93.9 (28.3)
	Early w/d	6	61.2 (15.8)	2	88.0 (21.2)
Total Bili (µmol/L)	Baseline	151	9.0 (4.0)	139	9.2 (4.7)
	Month 3	137	9.9 (4.5)	132	9.6 (4.9)
	Month 6	131	10.2 (4.3)	127	8.5 (4.1)
	Early w/d	6	7.8 (1.3)	2	9.5 (0.7)
Creatinine (µmol/L)	Baseline	151	64.5 (12.5)	140	65.0 (13.3)
	Month 3	137	67.4 (13.5)	133	67.8 (12.4)
	Month 6	131	67.5 (13.4)	127	65.0 (13.3)
	Early w/d	6	60.5 (13.2)	2	75.5 (6.4)
Glucose (nmol/L)	Baseline	151	5.06 (1.05)	139	4.96 (1.07)
	Month 3	137	5.01 (0.64)	132	4.94 (0.70)
	Month 6	131	5.00 (0.72)	127	4.75 (0.07)
	Early w/d	6	5.13 (0.55)	2	4.75 (0.07)
Total Cholesterol (mmol/L)	Baseline	41	5.15 (1.20)	43	5.13 (1.04)
	Month 3	36	4.78 (0.92)	43	5.24 (1.08)
	Month 6	36	4.66 (0.85)	38	5.51 (1.17)
	Early w/d	3	4.28 (0.29)	1	5.08 (0)
Triglycerides (mmol/L)	Baseline	41	1.06 (0.50)	43	1.07 (0.54)
	Month 3	36	1.06 (0.55)	43	1.21 (0.73)
	Month 6	36	0.98 (0.52)	38	1.30 (0.74)
	Early w/d	3	1.25 (0.26)	1	0.80 (0)
HDL (mmol/L)	Baseline	41	1.54 (0.40)	43	1.57 (0.32)
	Month 3	36	1.49 (0.40)	43	1.67 (0.40)
	Month 6	36	1.46 (0.34)	38	1.60 (0.39)
	Early w/d	3	1.35 (0.09)	1	1.99 (0)
LDL (mmol/L)	Baseline	41	3.12 (1.05)	43	3.07 (0.96)
	Month 3	36	2.81 (0.69)	43	3.02 (1.07)
	Month 6	36	2. 75 (0.65)	38	3.32 (1.08)
	Early w/d	3	2.37 (0.28)	1	2.72 (0)

Source: Tables T13.1, T13.4, T13.7, *5.3.5.1.2, pp 2011-14 ,2065-2077, 2107-13*

Medical Reviewer's Comments:

1) ***Despite increased incidence of bleeding in the DMPA-SC group, there was no demonstrable impact on hemoglobin or hematocrit.***
2) ***Inspection of laboratory data for subjects who withdrew from treatment early does not reveal any clinically relevant discrepancies from that reported for completers.***

Urinalysis data showed that dipstick variables were rarely abnormal and changed little from baseline to the end of study.

Coagulation and fasting lipid panels were obtained as a planned substudy on all subjects enrolled in Sweden and Poland. Coagulation parameters assessed in this subset of subjects are displayed in Table 32; fasting lipid data are presented above in Table 104. At month 6, statistically significant differences between treatment groups were found for the median change from baseline for the following parameters:

- Platelet count (DMPA-SC decreased by 13 x 10^9/L, Lupron increased by 8 x 10^9/L, p=0.012)
- Factor VII (DMPA-SC increased by 0.085, Lupron by 0.3, p=0.011)
- Protein C (DMPA-SC increased by 0.06, Lupron by 0.225, p=0.002)
- Total cholesterol (DMPA-SC decreased by 0.415, Lupron increased by 0.025, p<0.001)
- Triglycerides (DMPA-SC decreased by 0.05, Lupron increased by 0.19, p=0.025)
- HDL-C (DMPA-SC decreased by 0.13, Lupron increased by 0.04, p=0.003)
- LDL-C (DMPA-SC decreased by 0.215, Lupron increased by 0.04, p=0.002)
- VLDL (DMPA-SC decreased by 30, Lupron increased by 100, p=0.02)

There were generally higher proportions of subjects in the Lupron group showing shifts from normal to high values on the clotting parameters between baseline and months 3 and 6 and the proportion shifting to high values generally increased over the two assessment intervals in both groups. Shifts from normal to high values on lipid parameters occurred for total cholesterol only at month 3 in the DMPA-SC group, with a low percent of subjects showing such shifts by month 6. Slightly greater proportions of Lupron subjects had shifts from normal to high at both months 3 and 6. In the DMPA-SC group, about 3% of subjects had shifts from normal to low values for HDL at both months 3 and 6, there were no such shifts in the Lupron group.

Medical Reviewer's Comments:

1) ***The clinical significance of changes and differences between groups in the coagulation parameters is uncertain. Most changes were more pronounced in the Lupron group.***

10.2.9.6 Pregnancies

No pregnancy occurred during the treatment phase of the study. During the follow-up period, six DMPA-SC subjects (4.3%) and eight Lupron subjects (5.9%) became pregnant. Details of three cases considered by the applicant to be SAEs are:

- #0144 – Lupron, last dose 4/1/02. Estimated date of conception — Normal full term live birth, date not given.
- #0221 – Lupron, last (monthly) dose 5/20/02. Positive urine pregnancy tes' — Normal full-term live birth
- #017 – Lupron, last dose 1/17/02. Ultrasound diagnosis of pregnancy on ,ith estimated date of conception — Pregnancy complicated by gestational diabetes, normal full-term live birth on

Medical Reviewer's Comments:

1) ***Although the applicant reports nine pregnancies in the Lupron group, one subject had two identical pregnancy reports; thus, was counted twice.***
2) ***No information is provided to explain why three pregnancies (almost half the total) in the Lupron group were considered SAEs, while none in the DMPA-SC group were so classified. It is also unclear why two pregnant Lupron subjects (both considered SAEs) were discontinued due to protocol violations, while none of the pregnancies occurring in the DMPA-SC group were treated as protocol violations.***

10.2.9.7 Vital Signs

Seated blood pressure was assessed at each study visit. There were no significant between-group differences and no changes over time that were felt to be clinically significant.

10.2.9.8 Weight and BMI

Weight was assessed at baseline, monthly during the treatment phase and at all follow-up visits. There were significant differences between groups in weight change from baseline at months 1, 2 and 5, with the DMPA-SC group showing a greater median change than the Lupron group at these three points. Table 105 presents weight data at major evaluation points. In the DMPA-SC group, significant weight gain from baseline was first demonstrated at month 2, and remained statistically heavier than baseline throughout treatment and during the follow-up period. and than month 6 at the follow-up visits. The Lupron subjects had a significant weight gain at month 1, and then showed a fairly steady, but not always statistically significant increase from baseline at all other measurement points. At the follow-up visits, these subjects also were heavier than they had been at baseline.

Table 105 Study 270: Mean (SD) Weight (kg) by Treatment Group and Time

Visit	DMPA-SC Mean (SD)	N	Within-group change from baseline p-value*	Lupron Mean (SD)	N	Within-group change from baseline p-value*	Between-group difference p-value
Baseline	61.3 (11.5)	153	--	62.4 (12.6)	146	--	NS
Treatment							
Month 1	61.7 (11.7)	151	NS	62.5 (12.7)	143	0.001	0.029
Month 2	62.0 (11.7)	150	0.003	62.5 (13.0)	140	0.015	<0.001
Month 3	61.9 (11.9)	146	0.027	62.7 (13.1)	140	NS	NS
Month 4	61.9 (11.9)	142	0.003	62.8 (13.3)	138	NS	NS
Month 5	62.4 (11.9)	141	<0.001	63.0 (13.3)	137	NS	0.02
Month 6	62.0 (11.8)	138	<0.001	63.3 (13.4)	136	0.048	NS
Post Treatment							
Month 9	62.7 (12.0)	129	<0.001	64.0 (13.4)	129	<0.001	NS
Month 12	62.4 (12.0)	120	<0.001	63.8 (13.6)	118	0.011	N
Month 15	62.2 (11.9)	103	0.007	64.3 (13.8)	110	0.043	NS
Month 18	62.4 (11.7)	99	0.021	64.3 (14.0)	100	NS	NS

* The p-value is based on the Kruskal-Wallis or Wilcoxon signed rank evaluation of medians
Source: Based on Tables T14.3 and T14.4, *5.3.5.1.2, pp 2211-19*

Medical Reviewer's Comment:

1) ***Absolute weight gain at the end of treatment was similar in the DMPA-SC (0.7 kg) and Lupron groups (0.9 kg). Interpretation of the persistent weight gain noted in both groups following completion of treatment is not possible in the absence of data on the natural history of weight gain over one year in women not using hormonal medications.***

10.2.9.9 Vaginal Bleeding

Bleeding data, derived from the patient diaries, was evaluated over 30 day intervals, beginning with receipt of the first injection of study drug. The initial interval contains the menstrual period during which the first injection was given; thus, virtually all subjects reported some bleeding. Table 106 presents data on the frequency of amenorrhea and categorical frequency of bleeding in those subjects who did not become amenorrheic. From month 2 on, the frequency of amenorrhea was much greater in the Lupron group. The proportion of subjects with frank bleeding (not spotting) was much greater in the DMPA-SC group than the Lupron group at all monthly intervals beyond the first. In those subjects who did not experience amenorrhea, the duration of bleeding or spotting at the last monthly interval during treatment tended to be longer in the DMPA-SC group, with over half the women experiencing bleeding that lasted longer than a typical menstrual period; the comparative proportion in the Lupron group was only 2%.

The applicant also reported subjects' characterization of their bleeding patterns during two 90-day intervals during the treatment phase. The most common categorizations of bleeding pattern in the DMPA-SC group were "prolonged and irregular" over the first interval and "prolonged" over the second interval. In the Lupron group, the most frequent categorizations were "irregular" and "amenorrhea," respectively, at the first and second intervals.

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Table 106 Study 270: Bleeding Patterns by Treatment Group

Outcome	30 Day Interval	DMPA-SC N=153		Lupron N=146	
		N	%	N	%
Percent of subjects with bleeding	1	131	82.5	132	88.7
	2	135	55.6	128	7.8
	3	133	51.9	129	10.1
	4	130	41.6	130	7.7
	5	127	48.1	126	4.8
	6	104	49.0	99	5.0
Percent of subjects with spotting only	1	131	13.7	132	9.8
	2	135	25.9	128	12.5
	3	133	28.6	129	6.2
	4	130	30.8	130	3.8
	5	127	25.2	126	5.6
	6	104	26.9	99	5.1
Percent of subjects with amenorrhea	1	131	3.8	132	1.5
	2	135	18.5	128	79.7
	3	133	19.5	129	83.7
	4	130	27.7	130	88.5
	5	127	26.8	126	89.7
	6	104	24.0	99	89.9
Bleeding or spotting duration at end of treatment	# days/mo	104		99	
	0		24.0		89.9
	1-7		18.3		7.1
	8-10		5.8		1.0
	11-30		51.9		2.0

Source: Based on Tables 270.0 & 270.1, pp 94-5, 102-3, September 15, 2004 communication from applicant

Medical Reviewer's Comment:

1) ***The bleeding seen in DMPA-SC subjects may impact the acceptability of the treatment; however, data from contraceptive trials and from the existing IM formulation suggest that most women will become amenorrheic on DMPA with longer duration of use.***

10.2.10 Reviewer's assessment of efficacy and safety

Efficacy:

In the primary efficacy analysis, non-inferiority of DMPA-SC compared to Lupron in reduction of signs and symptoms of endometriosis from baseline to the end of treatment at month 6 was evaluated using a responder analysis on each of the 5 variables on the Biberoglu and Behrman scale. Response was defined as the proportion of subjects in each treatment arm who improved at least one point from baseline in each of the five categories. Non-inferiority was defined where the lower bound of the 96% two-sided confidence interval for the difference between the two drugs' improvement rates exceeded -20%. In order for DMPA-SC to be considered clinically non-inferior, statistical non-inferiority was required on at least four of the five signs/symptoms evaluated.

Three populations were analyzed; the ITT-OC analysis was considered primary by the applicant, but ITT-LOCF and EP analyses were also presented. The results in this study were concordant in all three populations. At the end of treatment, the criteria for statistical non-inferiority were met on all five outcome measures.

In addition, an overall clinically meaningful improvement over baseline was required, as demonstrated by an improvement of at least 4 points over baseline in the total composite score. In those subjects who were sexually inactive for reasons unrelated to endometriosis, dyspareunia scores were missing values, and the clinically meaningful criterion was modified to an improvement of at least 3 points in the remaining four categories. At the end of treatment, all three analysis populations demonstrated clinically meaningful change in the composite score, both with and without dyspareunia included, exceeding the specified thresholds for change.

Evaluated individually as secondary endpoints, each symptom/sign of endometriosis showed significant improvement in each treatment group from baseline to each assessment period.

There was significantly greater latency in recurrence of dysmenorrhea and pelvic pain in the DMPA-SC group, following cessation of treatment, when only those subjects who had improved during treatment were analyzed. The median time to recurrence of these symptoms was about six months in the DMPA-SC group, as compared to about three months in the Lupron group. These secondary endpoints, however, were not used to formally evaluate non-inferiority of DMPA-SC to Lupron.

In summary, this study met all of the pre-specified criteria for demonstrating non-inferiority to Lupron in reducing the signs and symptoms associated with endometriosis, and these findings were robust whether an ITT-OC or ITT-LOCF population was analyzed.

Safety:

There were no deaths and relatively few serious adverse events in this study; the rate of SAEs was higher in the DMPA-SC group (3.0% vs. 2.1% in the Lupron group), with increased rates of bleeding in the DMPA-SC group accounting for much of the difference. Discontinuations due to AEs during the treatment period were similar (3 and 2 subjects in the DMPA-SC and Lupron groups, respectively). The overall frequency of adverse events was similar between the treatment groups, with bleeding events in the DMPA-SC group and hot flushes in the Lupron group showing significant between-group differences in frequency. Laboratory and vital signs data showed no worrisome trends.

The primary safety endpoint was change in BMD measurement with six months of treatment, with a goal of demonstrating superiority of DMPA-SC over Lupron in minimizing bone loss. This goal was achieved on the primary safety endpoint of percent change in BMD at six months of treatment. Results of two supportive and less meaningful methods used to evaluate bone loss (mean BMD scores and BMD T-scores) were inconsistent.

Percent decrease in BMD was significantly less in the DMPA-SC group at both the femur and spine sites, and at all assessment periods (except the month 18 visit for the spine only). Comparative median percent changes in BMD at the end of treatment were -0.5% and -2.1% at the femur in the DMPA-SC and Lupron groups, respectively, and -1.0% and -4.0% at the spine in the respective groups. Once treatment was discontinued, the both groups showed recovery at the femur beginning at 6 months off treatment. Although neither group returned to baseline status at either site by the end of one-year follow-up, the DMPA-SC group was closer to full recovery.

Secondary safety endpoints included the experience of hypoestrogenic symptoms, as measured by the Kupperman Index, frequency and severity of hot flushes and levels of estradiol, progesterone and SHBG. Bleeding patterns and the prevalence of amenorrhea were also assessed. These various measures support the proposition that DMPA-SC confers less suppression of estrogen (and therefore fewer hypoestrogenemic side effects) than does Lupron. The frequency and severity of recorded hot flushes was significantly lower in the DMPA-SC group at each month of treatment. Regarding bleeding, the Lupron group had a significantly higher rate of amenorrhea by the second treatment

interval, while the frequency of bleeding was significantly greater at both intervals in the DMPA-SC group.

Overall Risk-Benefit Assessment:

The efficacy results clearly demonstrate non-inferiority of DMPA-SC relative to Lupron in management of painful symptoms of endometriosis. The safety profile of DMPA-SC was reassuring, with few serious adverse events and no worrisome signals in laboratory or vital signs values. DMPA-SC offers benefits over the current approved treatment in reducing bone mineral density loss over the course of treatment, and in minimizing bothersome symptoms of hypoestrogenemia. Side effects more common to DMPA-SC include injection site reactions and vaginal bleeding; these may affect tolerability of the treatment, but do not represent serious safety concerns.

11 LINE-BY-LINE LABELING REVIEW

At the time of this review, the applicant had not yet submitted revised proposed labeling for the endometriosis indication.

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12 REFERENCES

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[7] The hot flush average daily severity index is derived as follows:
- 1x #mild hot flushes +
- 2x #moderate hot flushes +
- 3x # severe hot flushes

[8] http://csi.micromedex.com/DATA/RX/RX2087.htm?top=yes

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[12] Dahlberg K Some effects of depot-medroxyprogesterone acetate (DMPA): Observations in the nursing infant and in the long-term user. Int J Gynaecol Obstet 20:43-8, 1982

[13] The weighted Kupperman Index is derived as follows:
- 4x Hot flushes
- 2x Abnormal sensations, Insomnia, and Nervousness
- 1x Depression, Vertigo, Fatigue, Pain in joints/muscles, headache, palpitations, and formication

Thus, the maximum score is 17.

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/s/

Lisa Soule
10/15/04 11:56:13 AM
MEDICAL OFFICER

Scott Monroe
10/18/04 03:19:41 PM
MEDICAL OFFICER
I concur with Dr. Soule's recommendation regarding approvability.