CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-584

STATISTICAL REVIEW(S)

Memorandum of Statistical Review
Recommendations for Labeling

NDA: 21-584 (SN 000; BZ)

Name of Drug: depo-subQ provera 104 (medroxyprogesterone acetate injectable suspension 104 mg/0.65 mL)

Indication: management of endometriosis-associated pain

Applicant: Pfizer, Inc.

Documents: \\Cdsesub1\N21584\N_000\2005-01-27

Clinical Reviewer: Lisa Soule, M.D. (HFD-580)

Clinical team Leader: Scott Monroe, M.D. (HFD-580)

Project Manager: Nenita Crisostomo, (HFD-580)

Dates: Received 1/27/05; User Fee 23/28/05

Reviewer: Kate Meaker, M.S. (HFD-715)

Biometrics Team Leader: Mike Welch, Ph.D. (HFD-715)

Background

Depot Medroxyprogesterone Acetate Subcutaneous Injection currently has an indication for the prevention of pregnancy. On December 17, 2003, Pfizer, Inc. submitted NDA 21-584 requesting an additional indication for the management of endometriosis-associated pain The sponsor received an Approvable letter on October 18, 2004. On January 27, 2005, the sponsor submitted revised labeling with the addition of information regarding the endometriosis indication. The review of this label is due by March 28, 2005.

Review of Label

In the Endometriosis Studies section, the two endometriosis studies are described accurately. The sponsor's provides the efficacy endpoints, which are the percent of patients improved for the 5 signs/symptoms, by groups within each study. The confidence intervals on the between-group differences are not given, although those were the basis for the efficacy (non-inferiority) assessment.

The Medical Officers want to replace with a bar graph. For each time point and each sign/symptom endpoint, there will be two bars, one for Depot MPA and the other for the active-comparator Lupron. The vertical axis will be the percent who improve on treatment.

The Medical Officers propose to show the results for the two clinical trials separately in the bar graph. No between-group comparisons are being made, and they plan to only report the point estimates (percent who improved) without confidence intervals. The two clinical studies are very similar in design and patient population, and sample size. The main difference is that one was conducted in the U.S. and the other was conducted in Europe, Asia, and Latin America. This is explained in the study description.

In the NDA, both a Last Observation Carried Forward (LOCF) analysis and an Observed Cases (OC) analysis were done. In the non-US study, the results of the two analyses both met the non-inferiority criteria. In the US study, the results of the OC analysis met the non-inferiority criteria, but the results of the LOCF analysis did not. Based on previous advice to the sponsor (Feb. 2001), the Medical Officers relied on the OC analysis to make the clinical decision. It is believed that discontinuations prior to completion of treatment may contribute to the discrepancy between the analyses.

I have the following comments regarding the proposed label:

1. I support replacing — with a bar graph. — A bar graph will provide easier assessment and summary of the efficacy outcomes.

2. I support showing the results from the two clinical studies separately in the bar graph. The results were similar across the two studies, but there was generally a higher response rate in the non-US study.

3. Because the Last Observation Carried Forward (LOCF) analysis reflects the discontinuations prior to completing treatment, it is preferable to present the LOCF results in the bar graph.

4.

5. The second paragraph — , should be removed. —

6. The third paragraph — should also be removed. —

Katherine B. Meaker, M.S.
Mathematical Statistician

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/s/

Katherine Meaker
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Mike Welch
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Concur with comments.

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-584 / 000
Drug Name:	Depot Medroxyprogesterone Acetate Subcutaneous Injection
Indication(s):	management of endometriosis-associated pain
Applicant:	Pfizer, Inc.
Date(s):	Submitted: 12/18/03
	PDUFA User Fee Date: 10/18/04
Review Priority:	Std.
Biometrics Division:	Biometric II
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Mike Welch, Ph.D.
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Keywords: clinical studies; NDA review

Table of Contents

1. EXECUTIVE SUMMARY

This application includes two Phase 3 clinical studies to support Depot Medroxyprogesterone Acetate Subcutaneous Injection (DMPA-SC) for the indication of the management of endometriosis-associated pain [redacted]. Both studies are active-control studies, with Lupron Intramuscular Injection (IM) as the active control treatment. Evaluating efficacy for this indication involves 5 signs and symptoms of endometriosis. For each item, the percent of women who improve during treatment is compared for the treatment groups using two-sided confidence intervals. The focus is on the lower bound of each confidence interval to determine non-inferiority.

1.1 Conclusions and Recommendations

Study 270 meets the planned efficacy requirements to support efficacy. Specifically, for all of the five signs/symptoms, the percent of women in the DMPA-SC treatment group who improved was no worse than 20% lower than for the Lupron treatment group. This comparison is based on the lower bound of the 96% confidence intervals. This is true for the results of both the Intent-to-treat end-of-treatment (ITT-OC) and the last observation carried forward (ITT-LOCF) analyses. The OC analysis is also referred to as an Observed Cases (OC) analysis.

In Study 268, the ITT-OC analyses did meet the efficacy requirements. For 4 of the 5 sign/symptom endpoints, the percent of women in the DMPA-SC treatment group who improved was no worse than 20% lower than for the Lupron treatment group. For the induration symptom endpoint, the lower bound is -26.1%, below the non-inferiority criteria. However, overall, the study still meets the planned efficacy criteria of 4 out of 5 of the signs/symptoms meeting the non-inferiority cutoff.

In Study 268, the ITT-LOCF analysis did not meet the efficacy criteria. Only one of the 5 endpoints (pelvic tenderness) had a lower bound of the 96% confidence interval greater than -20% different than Lupron. In the protocol, the sponsor planned, at the advice of the Agency (DMEDP), to do both the ITT-OC and ITT-LOCF analyses, and to investigate any discrepancies between the analyses if necessary.

My assessment of the discrepancies is that a combination of factors contributes to the difference in the results of the two analyses. These factors include a higher discontinuation rate in study 268 than in study 270 (but within the anticipated rate when the study was planned), and a moderately higher difference in the discontinuation rate for the DMPA-SC treatment group than the Lupron group. The "consent withdrawn" category was the source of the difference in reasons across the groups, but it was difficult to determine any specific or driving cause for patients withdrawing consent. Otherwise, the reasons for discontinuation were balanced across the groups. There is a delay in onset for the treatment of signs and symptoms, so women who dropped early were less likely to have improved at the time of

discontinuation. Women who remained on treatment through the 6-month timepoint were more likely to experience improvement, as seen in the OC analysis.

The sponsor was advised (Feb. 5, 2001 statistical comments) that both the ITT-OC and ITT-LOCF analyses would be considered together, and neither would be considered as primary. This approach is supported by the ICH E9 document titled Statistical Principles for Clinical Trials (sections 3.3.2 and 5.2.3 regarding equivalence or non-inferiority trials). Given the earlier agreements, and the reasonable explanations for the discrepancies, my conclusion is that the results of Study 268 provide support for the efficacy of DMPA-SC as non-inferior to Lupron.

The Medical Officers requested an additional analysis to assess the strength of evidence from study 268. They wanted to consider what percentage of Lupron's treatment effect versus placebo is preserved by DMPA. A small study (Dlugi; n=49) from the Summary of Approval for Lupron presented results of Lupron versus placebo. Using this placebo group as the reference, for each component, I calculated the percentage of Lupron's treatment effect preserved by DMPA as:

$$\frac{(\%\text{ of responders in DMPA current study} - \%\text{ of responders in placebo in Dlugi study})}{(\%\text{ of responders in Lupron current study} - \%\text{ of responders in placebo in Dlugi study})}$$

The results are presented in Table 6. For each of the components, DMPA preserved a minimum of 65% of the treatment effect of Lupron versus placebo.

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. The results of study 268 provide supportive efficacy evidence for non-inferiority of DMPA-SC. My conclusion is that these studies together provide sufficient evidence to support the efficacy of DMPA-SC for the signs and symptoms of endometriosis.

1.2 Brief Overview of Clinical Studies

There are two studies to support the efficacy of DMPA-SC as non-inferior to Lupron IM. Both studies are Phase 3, multicenter, evaluator-blind, parallel-arm, active-control studies with Lupron IM as the active comparator. The studies are evaluator-blind, rather than double-blind, because the method of injection (SC versus IM) could not be blinded. Both treatments were given every three months, for a total of 6 months on treatment. There was a 12-month follow-up period after treatment. The studies enrolled women, ages 18 and over, who had endometriosis confirmed by laparoscopy. The main difference in the studies is that study 268 was conducted in the United States and Canada, and study 270 was conducted in twelve countries in Europe, Asia, and Latin America.

In both studies, the efficacy assessment is based on the percent of women who improve on each of 5 signs/symptoms measured using the Biberoglu and Behrman scale. These are

dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and induration. Each item is measured on a 4-point scale (absent=0; mild=1; moderate=2; severe=3). Improvement is considered to be any reduction by at least one category from baseline to end of 6 months on treatment.

In both studies, efficacy was assessed by comparing the DMPA-SC group to the active-control group, Lupron. For each of the 5 symptoms/signs, a 96% two-sided confidence interval was calculated. The efficacy criterion was defined as the lower bound of the confidence interval would not be lower than -20% for at least 4 of the 5 symptoms/signs.

1.3 Statistical Issues and Findings

The sponsor originally planned to do an Intent-to-Treat (ITT) analysis with Last Observation Carried Forward (LOCF) as the primary efficacy analysis. However, based on advise from an Agency statistical review (February 5, 2001 statistical comments), the sponsor amended the statistical analysis plan in the protocol. The revised protocol specified that "efficacy analyses for the primary endpoint will be done for both the ITT and evaluable patient populations. The LOCF analysis will be done for the ITT population. An observed case (OC) analysis will be performed for both the ITT and evaluable patient population. In the LOCF analysis, for cases where there is no information after the baseline visit, the baseline information will be used for all subsequent time periods. In the OC analysis, only data that is collected will be used for analysis. Consistency between these analyses will be explored." This approach is supported by the ICH E9 document, Statistical Principles for Clinical Trials, in Sections 3.3.2 and 5.203 regarding equivalence or non-inferiority trials.

In the protocols, the sponsor planned to use 96% two-sided confidence intervals constructed on the difference in the percent of patients who improved for each of the symptoms/signs endpoints. The decision to use a 96% confidence level was based on the Hailperin-Ruger method for adjusting for multiple endpoints. This method addresses the situation where groups are compared on *r out of c* endpoints. The adjusted alpha level for each comparison is $r\alpha/c$. In this case, 4 out of 5 of the symptoms/signs endpoints had to meet the non-inferiority criteria that the lower bound of the confidence interval could not exceed -20%. The overall Type I error rate was 0.05. The adjusted alpha level for each confidence interval is $4(0.05)/5 = 0.04$.

2. INTRODUCTION

2.1 Overview

The desired indication is the management of endometriosis-associated pain [redacted]. Efficacy for this indication is measured using the Biberoglu and Behrman scale, which includes 5 symptoms/signs of endometriosis. The 5 items are dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and induration. Each item is

measured on a 4-point scale (absent=0; mild=1; moderate=2; severe=3). Improvement is considered to be any reduction by at least one category from baseline to end of 6 months on treatment.

The sponsor carried out two Phase 3 active-control studies to support the efficacy of DMPA-SC for this indication. These studies are referred to as Study 268, conducted in the US and Canada, and Study 270, conducted in 12 countries in Europe, Asia, and Latin America. In both studies the active-comparator was Lupron-IM. The studies were planned as equivalence studies using two-sided confidence intervals to compare DMPA-SC to Lupron. The efficacy criterion only involved the lower bound of the confidence interval, making this a non-inferiority assessment. The criterion for non-inferiority was that the lower bound of the confidence interval on the difference in the percentage of women who improved from baseline to end of 6 months on treatment could not be lower than -20%. At least 4 of the 5 symptoms/signs have to meet this criterion to support efficacy for this indication.

2.2 Data Sources

The electronic submission included all study reports, protocols and amendments, and literature references. The sponsor provided SAS datasets for studies 268 and 270. These included all necessary demographic, disposition, and efficacy information needed to perform this review.

Also mention august submission with explanation of ITT vs. OC and explanation of impact of dropouts and extra info they provided on reasons where they could find them

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study 268

Study 268 was conducted in 50 centers in the United States and Canada. It is a randomized, multicenter, evaluator-blind, two group parallel arm study. The active-comparator is Lupron IM. It was not possible to make this double-blind study because the two treatment arms were administered differently. DMPA-SC is a subcutaneous injection, and Lupron IM is an intramuscular injection. Women received 6 months of treatment (two injections, each 3 months in duration) with a 12 month follow-up period.

Enrolled patients were premenopausal women, ages 18-49, with endometriosis confirmed by laparoscopy, with a total score on the 5 symptoms/signs of at least 6 at baseline. A total of 274 women were randomized, 136 to receive DMPA-SC, and 138 to receive Lupron-IM. Patients received an injection of the assigned treatment at time of randomization and again at

the 3 month visit, for a total of 6 months on treatment. Efficacy and safety assessments were collected at monthly visits during the on-treatment period.

Overall, 84 patients (31%) discontinued from the study prior to completing the 6 months assessments. This was less than the overall rate planned in the protocol of 35%. However, the actual rate was somewhat uneven across the two treatment groups. As shown in Table 1, the discontinuation rate was 35% in the DMPA-SC group and 26% in the Lupron group.

Table 1: Study 268 On-Treatment Discontinuations

Reason for Discontinuation	DMPA-SC N = 136 n (%)	Lupron-IM N = 138 n (%)
Total Discontinued Patients	48 (35.3)	36 (26.1)
Adverse Event	9 (6.6)	10 (7.2)
Protocol Violation	4 (2.9)	7 (5.1)
Consent Withdrawn	21 (15.4)	8 (5.8)
Lost to Follow-up	14 (10.3)	11 (8.0)

Source: Study Report Table 4

The difference between the groups is in the Consent Withdrawn category. It is hard to determine why this difference occurred based only on the discontinuation information. The sponsor and Medical Officer investigated the reasons further, and there may be a perceived lack of efficacy in the DMPA-SC group, as some of the women who discontinued only received 1 dose of treatment. The Medical Officer's report discusses this issue in more detail.

In the protocol, the sponsor planned to perform two efficacy analyses. Both would include the ITT population of all randomized. One analysis would use LOCF to impute data for patients who discontinued prior to completing the 6 months on treatment or who missed visits. The second analysis is an Observed Case (OC) analysis which will only include data recorded by visit and will not impute values for missing data. Neither would be predetermined as the primary analysis, and any discrepancies between the results would be explored and discussed. This analysis plan was developed based on advice in statistical comments from the Agency (Feb. 21, 2001).

The results of these two analyses are shown in Tables 2 and 3. The pre-specified efficacy criterion is that, for at least 4 of 5 items, the lower bound of the confidence interval could not be lower than -20%. For the ITT-LOCF analysis, only one of the items (pelvic tenderness) meets the lower bound limit. However, in the ITT-OC analysis, 4 of the 5 items (all but induration) do meet the lower bound limit. Therefore, the ITT-LOCF analysis does not meet the efficacy criterion, but the ITT-OC analysis does.

The discrepancy between the two analyses can be trace to the imputation of values in the LOCF analysis for women who discontinued. There is an expected delay of onset for relief of symptoms/signs of endometriosis after the treatment injection is received. Women who

discontinued early were less likely to have perceived improvement in symptoms/signs, so that lack of improvement would be carried forward to missed visits. It is unknown what improvement in symptoms/signs would have been experienced for those women if they had stayed on treatment. The percent of women who discontinued early was uneven across the two treatment groups, which would impact the LOCF analysis.

Table 2: Study 268 Efficacy Results (ITT-LOCF)

Component	DMPA-SC N=136	Lupron-IM N=137	96% Confidence Interval
Dysmenorrhea	102/135 75.6%	126/137 92.0%	-25.4%, -7.4%
Dyspareunia	66/100 66.0%	87/108 80.6%	-27.1%, -2.1%
Pelvic Pain	90/134 67.2%	109/136 80.1%	-23.9%, -2.1%
Pelvic Tenderness	90/134 67.2%	97/133 72.9%	-17.3%, 5.7%
Induration	67/105 63.8%	83/101 82.2%	-30.8%, -6.0%

Source: Study Report Table 12 and SAS datasets

Table 3: Study 268 Efficacy Results (ITT-OC)

Component	DMPA-SC N=136	Lupron-IM N=137	96% Confidence Interval
Dysmenorrhea	80/88 90.9%	97/100 97.0%	-13.3%, 1.1%
Dyspareunia	51/65 78.5%	67/79 84.8%	-19.7%, 7.0%
Pelvic Pain	71/86 82.6%	88/101 87.1%	-15.4%, 6.3%
Pelvic Tenderness	65/85 76.5%	79/98 80.6%	-16.7%, 8.4%
Induration	49/66 74.2%	65/75 86.7%	-26.1%, 1.3%

Source: Study Report Table 10 and SAS datasets

According to the pre-specified analysis plan in the protocol, which was developed based on advice from the Agency, the ITT-OC analysis results are sufficient to support efficacy from this study. The efficacy criterion that the lower bound of the confidence interval was not lower than -20% for at least 4 of the 5 symptoms/signs is met in that analysis. In addition, the discrepancies between the ITT-OC and ITT-LOCF analyses are explainable based on the subjects who discontinued prior to completing the 6 months on treatment. Considering this,

my conclusion is that the results of Study 268 provide support for the efficacy of DMPA-SC as non-inferior to Lupron.

Study 270

Study 270 was conducted in 37 centers in 12 countries in Europe, Asia, and Latin America. The study design was the same as Study 268. It is a randomized, multicenter, evaluator-blind, two group parallel arm study. The active-comparator is Lupron IM. It was not possible to make this double-blind study because the two treatment arms were administered differently. DMPA-SC is a subcutaneous injection, and Lupron IM is an intramuscular injection. Women received 6 months of treatment (two injections, each 3 months in duration) with a 12 month follow-up period.

Enrolled patients were premenopausal women, ages 18-49, with endometriosis confirmed by laparoscopy, with a total score on the 5 symptoms/signs of at least 6 at baseline. A total of 299 women were randomized, 153 to receive DMPA-SC, and 146 to receive Lupron-IM. Patients received an injection of the assigned treatment at time of randomization and again at the 3 month visit, for a total of 6 months on treatment. Efficacy and safety assessments were collected at monthly visits during the on-treatment period.

Overall, 25 patients (8%) discontinued from the study prior to completing the 6 months assessments. This was less than the overall rate planned in the protocol of 35%. The rates were similar across the two treatment groups (10% in DMPA-SC; 7% in Lupron-IM) and across reasons for discontinuations.

In the protocol, the sponsor planned to perform two efficacy analyses. Both would include the ITT population of all randomized patients. One analysis would use LOCF to impute data for patients who discontinued prior to completing the 6 months on treatment or who missed visits. The second analysis is an Observed Case (OC) analysis which will only include data recorded by visit and will not impute values for missing data. For Study 270, the protocol specified that the ITT-LOCF analysis would be the primary analysis for assessing efficacy (Section 10.1.3 of protocol).

The results of these two analyses are shown in Tables 4 and 5. The pre-specified efficacy criterion is that, for at least 4 of 5 items, the lower bound of the confidence interval could not be lower than -20%. In both analyses, all 5 items meet the lower bound limit. Therefore, both the ITT-LOCF and the ITT-OC analyses meet the pre-specified efficacy criterion. These results support the efficacy conclusion that DMPA-SC is non-inferior to Lupron-IM.

Table 4: Study 270 Efficacy Results (ITT-LOCF)

Component	DMPA-SC N=153	Lupron-IM N=146	96% Confidence Interval
Dysmenorrhea	134/151 88.7%	138/145 95.2%	-12.9%, -0.0%
Dyspareunia	82/101 81.2%	79/95 83.2%	-13.2%, 9.3%
Pelvic Pain	122/152 80.3%	129/146 88.4%	-16.7%, 0.5%
Pelvic Tenderness	116/148 78.4%	113/140 80.7%	-12.1%, 7.4%
Induration	90/128 70.3%	98/127 77.2%	-18.1%, 4.4%

Source: Study Report Table 13 and SAS datasets

Table 5: Study 270 Efficacy Results (ITT-OC)

Component	DMPA-SC N=153	Lupron-IM N=146	96% Confidence Interval
Dysmenorrhea	123/135 91.1%	131/135 97.0%	-11.8%, -0.1%
Dyspareunia	73/88 83.0%	78/88 88.6%	-16.5%, 5.1%
Pelvic Pain	111/136 81.6%	124/136 91.2%	-18.0%, -1.1%
Pelvic Tenderness	108/133 81.2%	109/128 85.2%	-13.4%, 5.5%
Induration	84/117 71.8%	95/119 79.8%	-19.4%, 3.4%

Source: Study Report Table 11 and SAS datasets

Additional Efficacy Considerations

In comparing the results from Studies 268 and 270, there are two differences. The first concerns discontinuation of patients prior to completing the 6 months on treatment. The discontinuation rate in Study 268 was higher than in Study 270 (31% vs. 8%) and was the rates were somewhat uneven across the two groups in 268. The second difference between the two studies is that in Study 268 the ITT-LOCF and ITT-OC analyses gave difference conclusions regarding the efficacy criterion, while in Study 270 the analyses reached the same conclusion for the efficacy criterion. However, overall the results of the two studies are similar in terms of the treatment effect observed for DMPA-SC and Lupron-IM.

The Medical Officers requested an additional analysis to determine what percentage of Lupron's treatment effect versus placebo is preserved by DMPA-SC. The intent is to add clarity to the strength of the efficacy results from Study 268. The only comparison of Lupron to placebo which the Medical Officers could provide was from a small study (n=49 total) reported in the Summary for approval for Lupron. This study is referred to as the Dlugi study, and only measured 4 of the 5 component of the endometriosis scale. Induration was not recorded.

For each component, I calculated the percentage of Lupron's treatment effect preserved by DMPA as:

$$\frac{(\%\text{ of responders in DMPA current study} - \%\text{ of responders in placebo in Dlugi study})}{(\%\text{ of responders in Lupron current study} - \%\text{ of responders in placebo in Dlugi study})}$$

The results are presented in Table 6. For each of the components, DMPA preserved a minimum of 65% of the treatment effect of Lupron versus placebo. It is important to note that these point estimates are based on a small sample for the placebo group (n=21). The variance on such estimates may be large.

Table 6: Preservation of Effect Compared to Lupron

	Dlugi Study		**Study 268 (LOCF-ITT)**			**Study 270 (LOCF-ITT)**		
	Placebo n=21	Lupron n=28	DMPA n=136	Lupron n=137	% of Lupron effect preserved	DMPA n=153	Lupron n=146	% of Lupron effect preserved
Component								
Dysmenorrhea	8/21 38.1%	26/27 96.3%	102/135 75.6%	126/137 92.0%	69.6%	134/151 88.7%	138/145 95.2%	88.6%
Dyspareunia	3/10 30.0%	7/15 46.7%	66/100 66.0%	87/108 80.6%	71.1%	82/101 81.2%	79/95 83.2%	96.2%
Pelvic Pain	9/21 42.9%	22/26 84.6%	90/134 67.2%	109/136 80.1%	65.4%	122/152 80.3%	129/146 88.4%	82.2%
Pelvic Tenderness	7/21 33.3%	19/26 73.1%	90/134 67.2%	97/133 72.9%	85.6%	116/148 78.4%	113/140 80.7%	95.1%
Induration	na	na	67/105 63.8%	83/101 82.2%	na	90/128 70.3%	98/127 77.2%	na

Sources: *Dlugi Study* - Summary of approval for Lupron;
Study 268 - Table 12; Study 270 - Table 13

3.2 Evaluation of Safety

I discussed the safety outcomes with the Medical Officers. No further analyses were requested.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Analyses by gender or age are not applicable for this indication. The subjects in each study were predominantly white (86% in study 268, 60% in study 270). In both studies, efficacy outcomes were similar across race subgroups.

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There are 5 symptoms/signs of endometriosis which are used to assess efficacy for this indication. For each item, the percent of patients who improve by at least one category (on a 0-3 scale) from baseline to the end of 6 months on treatment is calculated. The efficacy decision is based on non-inferiority comparisons of DMPA-SC to an active-comparator, Lupron-IM. The comparisons are based on two-sided 96% confidence intervals on the difference between the two groups for the percent who improve. The pre-specified efficacy criterion is that, for at least 4 of the 5 items, the lower bound of the confidence interval would not be lower than -20%.

For Study 268, the protocol specified that two analyses would be performed, with neither considered as primary. These are an ITT-LOCF analysis with values carried forward for missing visits, and an ITT-OC analysis without any imputed values. The results of the two analyses are not consistent. The ITT-LOCF analysis does not meet the pre-specified efficacy criterion, with only one of the 5 confidence intervals having a lower limit above -20%. However, the results of the ITT-OC analysis did meet the efficacy criterion, with 4 of the 5 confidence intervals having lower bounds greater than -20%. Investigation of the discrepancy indicates that the difference in the discontinuation rates across the two groups, with "consent withdrawn" as the primary reason, appears to account for the difference in the results.

The sponsor amended the protocol to include both analyses based on advice from the Agency (February 5, 2001; statistical comments). This approach is also supported by the ICH E-9 document, Statistical Principles for Clinical Trials. Therefore, my conclusion is that the results of this study provide sufficient evidence to support the efficacy of DMPA-SC.

The results of study 270 meet the efficacy criterion for both the ITT-LOCF and ITT-OC analyses. The lower bounds of the confidence intervals for all 5 items are greater than -20% in both analyses. These results support the conclusion that DMPA-SC is non-inferior to Lupron-IM for this indication.

5.2 Conclusions and Recommendations

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. The results of study 268 provide supportive efficacy evidence for non-inferiority of DMPA-SC. My conclusion is that these studies together provide sufficient evidence to support the efficacy of DMPA-SC for the signs and symptoms of endometriosis.

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/s/

Mike Welch
10/18/04 05:46:31 PM
BIOMETRICS
Concur with review.
Submitted for Kate Meaker

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BIOMETRICS
Concur with review.