CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-583

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA:	21-583
Name of Drug:	Depot Medroxyprogesterone Acetate (DMPA) Injectable Suspension, 104 mg/0.65 mL
Indication:	Subcutaneous Formulation Contraceptive for the Prevention of Pregnancy
Sponsor:	Pfizer Inc. (Previously, Pharmacia & Upjohn Company)
Documents Reviewed:	Study Reports and the data submitted to Electronic Document Room \\CDSESUB1\N21583\N_000\2003-06-30
Dates:	July 15, 2003 (Received), August 02, 2004 (PDUFA)
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Key Words:	Clinical studies, NDA review

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1 EXECUTIVE SUMMARY

The sponsor has submitted results of two 1-year open-label, non-comparative multinational studies, and one controlled, 2-year, randomized, evaluator-blinded parallel-group (an extension of study 267) to evaluate the safety and efficacy of a new subcutaneous (SC) formulation of Medroxyprogesterone Acetate (DMPA-SC) for preventing pregnancy in sexually active women aged 18 to 49 years of childbearing potential. Medroxyprogesterone Acetate is an extended regimen injectable contraceptive therapy (four 91-day cycles per year).

Efficacy assessment is based on the Pearl Index (PI) using pregnancy rates and the associated two-sided 95% Confidence Intervals (CI).

The sponsor reported no pregnancies in all of the clinical trials. Therefore, the pregnancy rate and the Pearl Index are zero. The confidence intervals for the pregnancy rates and the PI's are shown below:

Upper Bounds of 95% Confidence Intervals for Pregnancy Rates and Pearl Indices for All Studies (Reviewer Analysis)

Study		Upper Bound 95% CI***	
		Pregnancy Rate	Pearl Index
Study 267			
Whole Group	(N=722)	0.0051	0.61
≤ 35 Yrs.	(n=610)	0.0060	0.73
≤ 35 Yrs. With No Other Form of Contraception	(n=508)	0.0072	0.84
Study 267BMD*			
Whole Group	(N=193)	0.0189	2.27
≤ 35 Yrs. **		**	**
≤ 35 Yrs. With No Other Form of Contraception	(n= 173)	0.0211	2.44
Study 269			
Whole Group	(N=1,065)	0.0035	0.39
≤ 35 Yrs.	(n=739)	0.0050	0.56
≤ 35 Yrs. With No Other Form of Contraception	(n=708)	0.0052	0.57

*All subjects in Study 267 BMD were 35 years or younger
** Reported only for SC arm
***Confidence intervals are two-sided

Since there were no pregnancies in the studies, the Life Table assessment was not required.

From a statistical standpoint, the sponsor has provided three studies that are adequate for demonstrating the effectiveness of Medroxyprogesterone Acetate SC in the prevention of pregnancy. No pregnancies occurred, and the upper bounds of 95% CI for the Pearl Index ranged from 0.39 to 2.44.

2 BACKGROUND

Medroxyprogesterone Acetate (DMPA) has been marketed previously in oral (Provera Tablets) and intramuscular (IM) injection (Depo-Provera, DMPA-IM) forms for prevention of pregnancy. This submission is for a new subcutaneous (SC) formulation of DMPA (DMPA-SC), (104 mg DMPA/0.65 mL injection volume per dose) every 3 months (13 weeks).

3 STUDY DESIGN

3.1 Study Description

The sponsor has submitted three Phase 3 studies. The three studies enrolled non-pregnant, sexually active women of childbearing potential aged 18 to 49 years for studies 267 and 269 and 18 to 35 for study 267BMD who desired long term contraception. Subjects in studies 267 and 269 were to receive a 104-mg dose of DMPA-SC every 3 months (at 0, 13, 26 and 39 weeks) for a total of 4 doses during the 1-year study.

Study 267BMD, an extension of study 267, is an evaluator-blinded, randomized, 2-year study to compare the effects of DMPA_SC on bone mineral density (BMD) with those of DMPA_IM. Subjects in study 267BMD were to receive a 104-mg dose of DMPA-SC or a 150-mg dose of DMPA-IM every 3 months (at 0, 13, 26, 39, 52, 65, 78 and 91 weeks) for a total of 8 doses during the 2-year study.

Table 1 summarizes the three studies.

Table 1: Brief Summary of Studies

Study #	# of Centers (Location)	Sample Size	Duration of Treatment	Design
839-FEH-0012-267	(US, Canada, Mexico, Chile, Peru and Brazil)	722	1 Year	Open Label, Noncomparative, Multinational (US, Canada, Mexico, Chile, Peru and Brazil
839-FEH-0012-267BMD		386*	2 Years	(Sub-study of 267) Evaluator-blinded, Randomized
839-FEH-0012-269	(Europe & Asia)	1065	1 Year	Open Label, Noncomparative, Multinational (Europe and Asia)

Source: Sponsor's submission
* This study was randomized 1:1 between DMPA-SC (n=193) or DMPA-IM (n=193)

For brevity, throughout this review, these studies will be referred to as Study 267, 267BMD and 269 respectively.

3.2 Primary Objective and Efficacy Variable

The primary efficacy variable in studies 267 and 269 was the treatment failure or cumulative pregnancy rate at 1 year, which was defined as a positive pregnancy test prior to the next scheduled dose.

The secondary objective was to assess the safety of DMPA_SC contraceptive injection administered every 3 months. In addition, subject satisfaction with the treatment results and treatment processes of self injection at home.

The study 267BMD was to compare the effects of DMPA_SC on bone mineral density (BMD) with those of DMPA_IM.

However, in agreement with the reviewing Medical Officer, I will only report the DMPA_SC treatment failure or cumulative pregnancy rate at 1 year and the 95% CI for Pregnancy Rates and the Pearl Indices for all subjects, subject 35 years and younger, and subject 35 and younger who did not use any other method of contraception at each cycle.

3.3 Statistical and Analytical Plans

The primary efficacy analysis consists of the calculation of two-sided 95% Confidence Interval (CI) of Pearl Index, where the Pearl Index was defined as the pregnancy rates in woman 18 to 35 years of age who were sexually active and did not use any other barrier contraception in the cycles under the study.
The Pearl Index is defined as follows:

Pearl Index = [(number of pregnancies) / (total number of months completed)] × (100 × 12)

The Pearl Index was to be calculated as the number of pregnancies per 100 women-years of exposure, where the numerator is the number of failures and the denominator is a function of each woman's total months of exposure.

Total Woman-Cycle of exposure was calculated by multiplying the number of injections received by 3 (since the injections were received every 3 months).

This review will focus only on the results of the primary efficacy objective, contraception, in woman 18 to 35 years of age who did not use any other method of contraception in the cycles under the study. For these analyses, the specific cycles when subjects had missed an injection or had used another method of contraception, were deleted. The data for the rest of the cycles for that subject was used.

4 STUDY RESULTS

4.1 Subject Enrollment, Randomization, Disposition, and Demographics

In Study 267, a total of 233 (233/722=32.3%) subjects did not finish the study treatment, of which 13.6% were due to Adverse Events (AE). For Study 267 BMD this number was 84 (84/193=43.5%) in the SC arm, where 16.6% were due to AE. And a total of 209 (209/1065=19.6%) subjects did not complete the treatment in Study 269, with only 5.3% because of AE. The AE's were not considered clinically significant by the reviewing Medical Officer (MO). See the MO's review for further details.

The majority of subjects were White, 67% in Study 267, 60% in Study 267BMD and 98% in Study 269. Almost 85% of the women is Study 267 were 35 years or younger (with the mean age ± sd of 28 ± 7). All (100%) of the subjects in Study 267BMD were 35 or younger and (with the mean age ± sd of 26 ± 5). In Study 269, 69% were in that age category (with the mean age ± sd of 32 ± 7).

The mean ± sd for pre-treatment weight for Study 267 was 66 ± 17, for Study 267BMD was 71 ± 19 and for Study 269 was 63 ± 11.

See Appendix for the sponsors' tables on "Randomization, Disposition, and Demographics.

4.2 Efficacy Results

No pregnancies occurred in any of the three studies. Hence, based on the Pearl Index formula stated above, this rate would be 0. In addition, no Life Tables were constructed for the reason of zero pregnancies.

The sponsor had not provided the upper limit of the 95% CI for the pregnancy rates and Pearl Indices. The upper limits of the 95% CI for the Pregnancy Rates and the Pearl Indices, for different sub-populations, were calculated by this reviewer and they are presented in this report.

4.2A Reviewer's Efficacy Analyses

Table 2 presents the total number of subjects who received 1, 2, 3 or 4 injections in each study. For sponsor's results regarding "Number of Injections by Study, Number of pregnancies & Total Woman Cycles of Exposure, and Number Of Pregnancies & Total Woman Cycles Of Exposure, Months With Other Form of Contraception Excluded", please refer to the Section Six- Appendix, of this review.

Table 2: Reviewer's Analyses: The Number of Subjects with Their Number of Injections

Study	Study 267			Study 267BMD		Study 269		
# Injections	All (N=722)	≤ 35 * (n=610)	≤ 35 NC** (n= 507)	All (N=193)	≤ 35 NC (n=173)	All (N=1065)	≤ 35 (n=739)	≤ 35 NC (n=708)
1	86 (12%)	76 (12%)	41 (8%)	17 99%)	10 (6%)	70 (7%)	57 (8%)	36 (5%)
2	86 (12%)	76 (12%)	62 (12%)	30 (16%)	25 (14%)	90 (8%)	55 (7%)	47 (7%)
3	53 (7%)	45 (7%)	40 (8%)	18 (9%)	14 (8%)	40 (4%)	28 (4%)	26 (4%)
4	497 (69%)	413 (68%)	364 (72%)	128 (66%)	124 (72%)	865 (81%)	599 (81%)	599 (85%)

* Subjects 35 years old or younger

** Subjects 35 years old or younger with no other form of Contraception

Table 3 presents the Number of subjects in each selected group, then Pearl Index for all treated subjects, subjects18-35 years of age and subjects 35 and younger with no other form of contraception.

Table 3: Reviewer's Analyses: The Upper Bound for the Two-Sided 95% Confidence Interval for Pregnancy Rate and for the Pearl Index for All the Studies

Study	Number of Subjects	Number of Months of Exposure	Upper Bound 95% CI	
			Pregnancy Rate	Pearl Index
Study 267				
Whole Group	722	7,215	0.0051	0.61
≤ 35 Yrs.	610	6,045	0.0060	0.73
≤ 35 Yrs. With No Other Form of Contraception	508	5,223	0.0072	0.84
Study 267BMD*				
Whole Group	193**	1,929	0.0189	2.27
≤ 35 Yrs.	-	-	-	-
≤ 35 Yrs. With No Other Form of Contraception	173	1,794	0.0211	2.44
Study 269				
Whole Group	1,065	11,490	0.0035	0.39
≤ 35 Yrs.	739	7,941	0.0050	0.56
≤ 35 Yrs. With No Other Form of Contraception	708	7,812	0.0052	0.57

*All the subjects in this study were 35 years old or younger.

** The numbers reported for Study 267BMD are all for the SC group only

As shown in Table 3, the upper bounds of the two-sided 95% CI for Studies 267 and 269 are below 1. Study 267BMD had upper bounds exceeding 2, which might have resulted from lower sample size and lower women-months of exposure.

Since there were no pregnancies in the studies, the Life Table assessment was not required.

5 CONCLUSIONS

From a statistical standpoint, the sponsor has provided studies that are adequate for demonstrating the effectiveness of Medroxyprogesterone Acetate SC in the prevention of pregnancy. No pregnancies occurred, and the upper bounds of the two-sided 95% CI for the Pearl Index ranged from 0.39 to 2.44.

6 APPENDIX

The following tables have all been extracted from the sponsor's submission; "Summary of Clinical Efficacy" section.

Table 6.1: Number and Percent of Randomized Subjects and the Disposition of Treated Subjects

Patient Disposition +	267 Non-BMD DMPA-SC N = 722		267 BMD DMPA-SC N = 193		269 DMPA-SC N = 1065		Combined DMPA-SC N = 1980		267 BMD DMPA-IM N = 193	
	n	%	n	%	n	%	n	%	n	%
Treatment/Study Medication Completion										
Study Ongoing			109	56.5			109	5.5	108	56.0
Completed Treatment/Study Medication Period	489	67.7			856	80.4	1345	67.9		
Did Not Complete Treatment/Study Medication Period	233	32.3	84	43.5	209	19.6	526	26.6	85	44.0
Total Reported	722	100.0	193	100.0	1065	100.0	1980	100.0	193	100.0

Source: Sponsor's Summary of Clinical Efficacy Section, Page 4 of 2312 – Table T1

Table 6.2: Reasons for Withdrawal

Reason for Withdrawal from Treatment	267 Non-BMD DMPA-SC N = 722		267 BMD DMPA-SC N = 193		269 DMPA-SC N = 1065		Combined DMPA-SC N = 1980		267 BMD DMPA-IM N = 193	
	n	%	n	%	n	%	n	%	n	%
Adverse Event	98	13.6	32	16.6	56	5.3	186	9.4	33	17.1
Protocol Violation	8	1.1	5	2.6	5	0.5	18	0.9	2	1.0
Consent Withdrawn	78	10.8	26	13.5	116	10.9	220	11.1	20	10.4
Lost to Follow-up	49	6.8	21	10.9	32	3.0	102	5.2	30	15.5
Total Withdrawn	233	32.3	84	43.5	209	19.6	526	26.6	85	44.0

Source: Sponsor's Summary of Clinical Efficacy Section, Page 6 of 2312 – Table T2

Table 6.3: Demographic and Baseline Characteristics

Demographic/Baseline Variables	267 Non-BMD DMPA-SC N = 722		267 BMD DMPA-SC N = 193		269 DMPA-SC N = 1065		Combined DMPA-SC N = 1980		267 BMD DMPA-IM N = 193	
Race										
White (n,%)	485	(67.2)	115	(59.6)	1043	(97.9)	1643	(83.0)	125	(64.8)
Black (n,%)	61	(8.4)	31	(16.1)	1	(0.1)	93	(4.7)	31	(16.1)
Asian or Pacific Islander (n,%)	22	(3.0)	8	(4.1)	20	(1.9)	50	(2.5)	6	(3.1)
Mixed/Multiracial (n,%)	154	(21.3)	39	(20.2)	1	(0.1)	194	(9.8)	31	(16.1)
Total Reported	722		193		1065		1980		193	
Age (yrs)										
<= 35 (n,%)	610	(84.5)	193	(100.0)	739	(69.4)	1542	(77.9)	193	(100.0)
> 35 (n,%)	112	(15.5)			326	(30.6)	438	(22.1)		
Mean (SD)	28.17	(6.95)	26.13	(4.90)	32.20	(7.20)	30.14	(7.29)	26.21	(4.76)
Median	26.95		26.00		31.70		29.40		26.00	
Min-Max	18.0 - 49.9		18.0 - 35.7		18.0 - 49.6		18.0 - 49.9		18.0 - 35.7	
Total Reported	722		193		1065		1980		193	
Pretreatment Weight (kg) +										
Mean (SD)	66.48	(16.68)	70.57	(18.56)	62.60	(11.29)	64.79	(14.50)	74.18	(19.91)
Median	62.90		66.80		61.00		62.00		69.00	
Min-Max	38.8 - 164.9		40.0 - 142.9		35.0 - 113.2		35.0 - 164.9		46.3 - 140.6	
Total Reported	720		193		1065		1978		193	
Not Reported	2						2			

Source: Sponsor's Summary of Clinical Efficacy Section, Page 7 of 2312 – Table T3

Table 6.4: Number of Injections by Study - ITT

Number of Injections	267 Non-BMD DMPA-SC N = 722		267 BMD DMPA-SC N = 193		269 DMPA-SC N = 1065		Combined DMPA-SC N = 1980		267 BMD DMPA-IM N = 193	
	n	%	n	%	n	%	n	%	n	%
1	86	11.9	17	8.8	70	6.6	173	8.7	28	14.5
2	86	11.9	30	15.5	90	8.5	206	10.4	17	8.8
3	53	7.3	18	9.3	40	3.8	111	5.6	18	9.3
4	497	68.8	128	66.3	865	81.2	1490	75.3	130	67.4
Total Reported	722	100.0	193	100.0	1065	100.0	1980	100.0	193	100.0

Source: Sponsor's Summary of Clinical Efficacy Section, Page 9 of 2312 – Table T4

Table 6.5: Number of Pregnancies and Total Woman Cycles of Exposure

Protocol/Treatment	Number of Pregnancies	Total Woman Cycles of Exposure	Pearl Index +	Pearl Index 95% Confidence Interval	Life Table Rate ++ (%)	Life Table 95% Confidence Interval
267 Non-BMD DMPA-SC	0	7209	0		0	
267 BMD DMPA-SC	0	1926	0		0	
269 DMPA-SC	0	11472	0		0	
Combined DMPA-SC	0	20607	0		0	
267 BMD DMPA-IM	0	1899	0		0	

Source: Sponsor's Summary of Clinical Efficacy Section, Page 14 of 2312 – Table T9

Table 6.6: Number of Pregnancies and Total Woman Cycles of Exposure, Months with Other Form of Contraception Excluded

Protocol/Treatment	Number of Pregnancies	Total Woman Cycles of Exposure +++	Pearl Index +	Pearl Index 95% Confidence Interval	Life Table Rate ++ (%)	Life Table 95% Confidence Interval
267 Non-BMD DMPA-SC	0	6605	0		0	
267 BMD DMPA-SC	0	1738	0		0	
269 DMPA-SC	0	10699	0		0	
Combined DMPA-SC	0	19042	0		0	
267 BMD DMPA-IM	0	1674	0		0	

Source: Sponsor's Summary of Clinical Efficacy Section, Page 15 of 2312 – Table T10.1

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