

9 Integrated Review of Safety

9.1 Brief Statement of Conclusions

Although DMPA-SC users are exposed to less MPA than DMPA-IM users, the safety profiles of the 2 products were similar. In particular, endogenous hormone suppression, weight gain and bone mineral density loss were not different for either formulation. The only notable difference in safety were injection site reactions that were reported in 5% of the DMPA-SC users and in none of the DMPA-IM users. The reactions were usually rated as mild and not serious by investigators.

9.2 Description of Patient Exposure

The integrated review of safety used all 1,980 subjects from the Phase 3 contraception trials who received at least 1 injection of DMPA-SC. The number of subjects used in the ITT safety population differed slightly from that in the ITT efficacy group (1,980 women versus 1,971 women treated with DMPA-SC) because there was no efficacy data for 9 subjects.

The data in the Applicant's Integrated Assessment of Safety (IAS) database (SAS files submitted as part of the NDA) includes data from 193 women treated with DMPA-IM. The datasets sent to the FDA as part of the IAS were blinded, but the Applicant prepared text and tables using unblinded data. After some negotiation, the Applicant agreed to supply the FDA with unblinded data for Study 267BMD. However, the IAS datasets remained blinded. Therefore, the few tables in this review created by the reviewer from the IAS dataset include data from 193 women treated with DMPA-IM, and data from 1,980 women treated with DMPA-SC.

The sponsor used the Phase 1/2 trials and the 6-month endometriosis trial as supportive trials, reasoning that

- the Phase 1/2 trials would be difficult to integrate because they were 1- month trials and doses varied
- the 6-month endometriosis trials would be difficult to integrate because they were of shorter duration and involved a different population than the contraception trials

However, the 6-month endometrial safety trial provided data on fasting lipid and coagulation profiles, and these data are reviewed below.

9.3 Methods and Specific Findings of Safety Review

9.3.1 Deaths

One death was reported in the original NDA submission. (Study 267, Case ID 47037-0479). A 32-year-old woman received her first injection on June 22, 2001. The adverse event forms note mild headaches from June 25 through June 28, August 15, August 30 and September 15. On August 1, she had a urinary tract infection. She was seen for her second injection on _____ and died in a car accident 5 days later, on _____.

A second death was reported in the four-month safety update. A 27-year-old subject in Study — died suddenly after 16 months of therapy with DMPA-SC. Autopsy led to the diagnosis of myocarditis, and cause of death was listed as arrhythmia due to myocarditis. (—)

Comment: Treatment does not appear to have contributed to either death.

9.3.2 Serious Adverse Events

Thirty of 1,980 subjects had serious adverse events (SAEs): 28 in the DMPA-SC treatment group and 2 in the DMPA-IM treatment group. Table 13 shows SAEs organized by organ class and treatment group.

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Table 13 Treatment-Emergent SAEs by MedDRA Preferred Terms

	All DMPA-SC N = 1,980		DMPA-IM N = 193	
	n	%	n	%
Total subjects reported	1,971	100.0	187	100.0
Subjects with at least 1 serious adverse event	28	1.4	2	1.1
Eye disorders				
▪ Retinal edema§	1	0.1	0	0.0
Gastrointestinal disorders				
▪ Abdominal pain NOS	2	0.1	0	0.0
▪ Appendicitis	0	0.0	1	0.5
▪ Appendix disorder NOS	1	0.1	0	0.0
▪ Diverticulitis NOS	1	0.1	0	0.0
▪ Gastric ulcer	1	0.1	0	0.0
▪ Hematemesis	1	0.1	0	0.0
General disorders and administration site conditions				
▪ Difficulty in walking	1	0.1	0	0.0
▪ Swelling NOS	1	0.1	0	0.0
Hepato-biliary disorders				
▪ Cholelithiasis	0	0.0	1	0.5
Infections and infestations				
▪ Hepatitis A	1	0.1	0	0.0
▪ Pyelonephritis NOS	1	0.1	0	0.0
▪ Pyelonephritis chronic NOS	1	0.1	0	0.0
▪ Tonsillitis NOS	1	0.1	0	0.0
▪ Typhoid fever	1	0.1	0	0.0
Injury and poisoning				
▪ Arthropod bite	1	0.1	0	0.0
▪ Patella fracture	1	0.1	0	0.0
▪ Road traffic accident	1	0.1	0	0.0
Investigations				
▪ Weight increased	1	0.1	0	0.0
Musculoskeletal, connective tissue, and bone disorders				
▪ Back pain	1	0.1	0	0.0
▪ Intervertebral disc prolapse	1	0.1	0	0.0
▪ Pain in limb	1	0.1	0	0.0
▪ Breast cancer stage II	1	0.1	0	0.0
▪ Breast lump NOS	1	0.1	0	0.0
▪ Gastric cancer NOS	1	0.1	0	0.0
Nervous system disorders				
▪ Cerebrovascular accident NOS	0	0.0	1	0.5
▪ Syncope	1	0.1	0	0.0
Pregnancy, puerperium, and perinatal conditions				
▪ Abortion spontaneous NOS	1	0.1	0	0.0
Psychiatric disorders				
▪ Depression aggravated	1	0.1	0	0.0
Renal and urinary disorders				
▪ Calculus ureteric	2	0.1	0	0.0
Reproductive system and breast disorders				
▪ Menometrorrhagia	2	0.1	0	0.0
▪ Uterine hemorrhage	2	0.1	0	0.0
Surgical and medical procedures				
▪ Nephrectomy	1	0.1	0	0.0
▪ Operation NOS	1	0.1	0	0.0
Vascular disorders				
▪ Venous thrombosis deep limb	0	0.0	1	0.5

Source: Modified from Applicant's Table 9 in Summary of Clinical Safety, NDA Module 2.7.4

From the list of SAEs, I chose those in Table 14 for scrutiny as possibly treatment-related.

Table 14. Brief Narratives of Selected SAEs

Study	Investigator ID	Subject ID	Event	Days from start of treatment
267	48961	0022	Breast lump (fibroadenomas), noted at time of first injection., excised on day 106.	106 days
	51205	0197	Depression and suicide attempt in a woman with a history of depression and substance abuse.	327
	48961	558	Spontaneous abortion (reviewed in efficacy section)	22
269	51744	644	Retinal edema.. Sudden blindness in left eye diagnosed as chorioretinopathy. Not recovered.	353
	51857	613	Menometrorrhagia in a 38-year-old resulting in a D&C that showed a polyp. Recovered.	27
	51751	28	Menometrorrhagia, hospitalized for intravenous oxytocin 3 months after initial diagnosis. Recovered.	77
	43372	401	Weight gain of 16 kg, pain in left leg diagnosed as spondylosis.	211
	50899	172	Prolonged uterine bleeding, in a 42-year-old woman resulting in a D&C which showed chronic endocervicitis. Recovered.	277
	50899	423	Prolonged uterine bleeding in a 46-year-old who had a D&C showing pseudodecidual endometrium. Treated with hormones and tranexamic acid.	52
267BMD	48961*	2311	35-year-old woman who weighed 52 kg at baseline had gallstone surgery, followed 1 week later by a stroke, and 2 months later, a DVT.	280
	33430	2116	Breast cancer stage 2, invasive ductal carcinoma in a 33-year-old who did not have a baseline mammogram.	320

Source: Modified from listing L9.1, Summary of Clinical Safety - Data Source Displays

*Patient in DMPA-IM treatment group

Comments:

Uterine bleeding is the most common SAE with 4 cases.

Usually single cases of these SAEs are not enough to allow conclusions about drug risks, especially when other risk factors are present. For example, the thrombotic events in one subject followed surgery, a risk factor for thrombosis.

9.3.3 Adverse Events Associated with Dropouts

Among all subjects treated with DMPA-SC, 9.5% dropped out for adverse events. In Study 267BMD, there were no important differences between the dropouts in the DMPA-SC group (16.8%) and the dropouts in the DMPA-IM group (18.2%). Table 15 lists AEs associated with dropouts in order of decreasing frequency.

The most frequently reported AEs leading to dropout were weight gain, bleeding problems, decreased libido, mood disorders, and acne.

Table 15. Adverse Events for Studies 267, 267BMD, and 269 Associated with Dropouts by Organ Class and Preferred Term

MedDRA System Organ Class	MedDRA Preferred Term	Number of Subjects
Cardiac disorders	Oedema lower limb	1
	Tachycardia NOS	1
Ear and labyrinth disorders	Vestibular disorder NOS	1
Gastrointestinal disorders	Nausea	10
	Abdominal distension	5
	Abdominal pain NOS	2
	Dyspepsia	2
	Vomiting NOS	2
	Abdominal pain upper	1
	Dyspepsia aggravated	1
	Haematemesis	1
General disorders and administration site conditions	Fatigue	8
	Injection site atrophy	6
	Haemorrhage NOS	5
	Injection site granuloma	2
	Chronic fatigue syndrome	1
	Difficulty in walking	1
	Discomfort NOS	1
	Injection site induration	1
	Injection site pain	1
Infections and infestations	Hepatitis C	2
	Cervicitis NEC	1
	Hepatitis B	1
Injury and poisoning	Road traffic accident	1
Investigations	Weight increased	40
	Liver function tests NOS abnormal	2
	Bleeding time prolonged	1
	Smear cervix abnormal	1
Metabolism and nutrition disorders	Appetite increased NOS	1
	Diabetes mellitus NOS	1
Musculoskeletal, connective tissue and bone disorders	Muscle cramps	3
	Pain in limb	2
Neoplasms benign and malignant (including cysts and polyps)	Cervical carcinoma NOS	1
	Gastric cancer NOS	1
	Vaginal intraepithelial neoplasm	1
Nervous system disorders	Headache NOS	10
	Insomnia NEC	4
	Dizziness (exc vertigo)	3
	Migraine NOS	3
	Cerebrovascular accident NOS	1
	Headache NOS aggravated	1
	Loss of consciousness NEC	1
	Middle insomnia	1
	Migraine aggravated	1
Syncope	1	
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous NOS	1
Psychiatric disorders	Libido decreased	23
	Irritability	8
	Depression NEC	7
	Mood swings	7
	Anxiety NEC	4
	Depressed mood	4
	Depression aggravated	4
	Mood alteration NOS	4
	Loss of libido	3
	Major depressive disorder NOS	2
	Anger	1
	Anorgasmia	1
	Bipolar disorder NEC	1

MedDRA System Organ Class	MedDRA Preferred Term	Number of Subjects
	Obsessive-compulsive disorder	1
Renal and urinary disorders	Fluid retention	3
Reproductive system and breast disorders	Intermenstrual bleeding	25
	Vaginal haemorrhage	20
	Menometrorrhagia	10
	Uterine haemorrhage	6
	Breast pain	5
	Amenorrhoea NOS	4
	Dyspareunia NEC	3
	Dysfunctional uterine bleeding	2
	Menstruation irregular	2
	Dysmenorrhoea	1
	Genital haemorrhage NOS	1
	Menorrhagia	1
	Menstrual disorder NOS	1
	Oligomenorrhoea NOS	1
	Ovarian cyst	1
	Pelvic pain NOS	1
	Premenstrual syndrome	1
	Uterine disorder NOS	1
	Vaginal discharge	1
	Vulvovaginal dryness	1
Skin & subcutaneous tissue disorders	Acne NOS	24
	Hair growth abnormal	2
	Rash papular	2
	Alopecia	1
	Night sweats	1
	Sweating increased	1
	Urticaria NOS	1
Surgical and medical procedures	Tubal ligation	1
Vascular disorders	Hot flushes NOS	4
	Venous thrombosis deep limb	1

Source: Created by reviewer from dataset labeled AEMD.xpt in folder called ias. Contains AEs from DMPA-SC (N=1980) and DMPA-IM groups (N=193).

Table 16 presents the dropouts for the SC and IM subgroups for adverse events that occurred in $\geq 1\%$ of subjects. No clinically significant differences were detected between treatment groups.

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Table 16. Adverse Events Leading to Discontinuation of $\geq 1\%$ of Subjects (ITT)

System/Organ Class Preferred Term	All DMPA-SC N = 1980		267BMD			
			DMPA-SC N = 193		DMPA-IM N = 193	
	n	%	n	%	n	%
Total subjects reported	1971§	100.0	191§	100.0	187§	100.0
Subjects with at least 1 adverse event leading to discontinuation	188	9.5	32	16.8	34	18.2
Gastrointestinal disorders						
Nausea	7	0.4	1	0.5	3	1.6
Vomiting NOS	0	0.0	0	0.0	2	1.1
General disorders and administration site conditions						
Fatigue	6	0.3	0	0.0	2	1.1
Investigations						
Weight increased	33	1.7	8	4.2	7	3.7
Nervous system disorders						
Insomnia NEC	2	0.1	1	0.5	2	1.1
Psychiatric disorders						
Depression**	13	0.7	4	2.1	2	1.1
Irritability	6	0.3	2	1.0	2	1.1
Libido decreased**	22	1.1	1	0.5	4	2.1
Major depressive disorder NOS	0	0.0	0	0.0	2	1.1
Mood disorder**	8	0.4	3	1.6	3	1.6
Reproductive system and breast disorders						
Breast pain	3	0.2	0	0.0	2	1.1
Intermenstrual bleeding	22	1.1	2	1.0	3	1.6
Vaginal hemorrhage	18	0.9	2	1.0	2	1.1
Skin and subcutaneous tissue Disorders						
Acne**	19	1.0	3	1.6	5	2.7
Vascular disorders						
Hot flushes NOS	2	0.1	0	0.0	2	1.1

The 1% cut-point was based on all DMPA-SC-treated subjects and all DMPA-IM-treated subjects. Both treatment groups in study 267BMD are included as a comparison.

§ Data were not available for 9 DMPA-SC-treated subjects (including 2 in study 267BMD) and 6 DMPA-IM-treated subjects.

**Includes more than one MedDRA preferred term

Abbreviations: ITT = intent-to-treat, NEC = not elsewhere classified, NOS = not otherwise specified

Source: Applicant's Table 10, NDA Module 2.7.4

Selected dropouts were reviewed in more detail:

A single subject dropped out because of elevated liver enzymes (ID 46120-350). This 37-year-old white woman complained of decreased energy, decreased sexual drive, and irritability about 2 weeks after her second injection. Then, about 2 months and 2 weeks after her second injection, she had abnormally high liver enzymes. Her AST was 386 U/L and ALT was 640 U/L. (GGT normal and bilirubin were normal). Data indicate the liver function abnormalities resolved on follow-up and the elevated liver enzymes lasted 43 days.

(An investigator listed a second subject as dropping out for liver function abnormalities. However, the investigator term was "abnormal low liver enzymes", and the laboratory dataset failed to confirm an abnormality.)

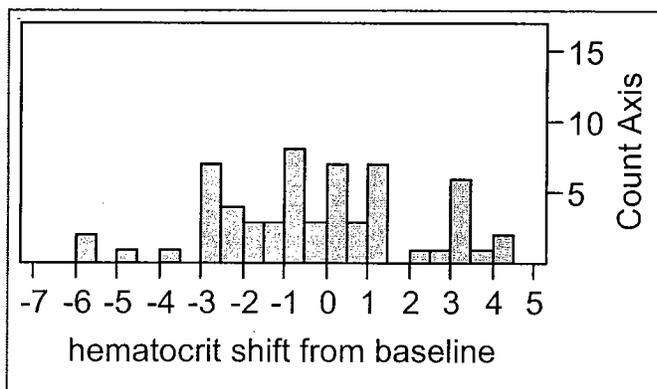
Comment: The subject with abnormally high liver function tests recovered during a time when she was likely to have had continued exposure to MPA from this depot medication.

To see if women who dropped out of the study for heavy bleeding had clinically significant decreases in hematocrit, I looked at the 67 women who dropped out for the following reasons (see Table 15):

- Intermenstrual bleeding
- Vaginal haemorrhage
- Menometrorrhagia
- Uterine haemorrhage
- Dysfunctional uterine bleeding
- Menstruation irregular
- Genital haemorrhage NOS
- Menorrhagia
- Menstrual disorder NOS
- Uterine disorder NOS

Investigator terms for these 67 women confirmed that 65 of them had excessive bleeding and 2 did not. Among the 65 women who had excessive bleeding, most did not have clinically significant drops in hematocrit from baseline. The mean hematocrit shift was a drop of 0.4%. These data appear below. The largest negative shift was a drop of 6% for 2 women. One of these women dropped her hematocrit from 43% to 37% on treatment. The second woman dropped her hematocrit from 35% to 29%, followed by an increase to 38% four months later.

Figure 5. Hematocrit Shifts from Baseline for Women Who Dropped Out of the Study for Excess Bleeding



Source: Created by reviewer from datasets AEMD.xpt and LBRSLBAS.xpt in Applicant's ias datasets.

Comment: In general, clinically significant hematocrit changes were not detected for women who dropped out of the studies for excessive vaginal bleeding.

A flaw in study design was that the case report forms allowed investigators to check off "consent withdrawn" as a reason for study termination, without prompting for a reason consent was withdrawn. This might have caused underestimation of adverse events causing dropout. To evaluate this possibility, I joined the data sets for adverse events and study termination.

All 240 women who withdrew consent also complained of adverse events. Although some of these adverse events were routine events such as pharyngitis, others were the same as reasons listed for dropping out of the study. For example, there were injection site complaints (12), weight gain (4), vaginal bleeding complaints (8), and acne (8) suggesting that some of the women who withdrew consent may have done so because of adverse events.

9.3.4 Common Adverse Events

Table 17 shows all adverse events reported by 1% or more of the 2173 women in the ITT safety database.

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Table 17. Adverse Events Reported by 1% or More of Women in the Phase 3 Contraception Trials (Studies 267, 267BMD[both treatment groups], and 269)

MedDRA Preferred Term	Number of Subjects	% of Subjects
Headache NOS	177	8
Intermenstrual bleeding	149	7
Weight increased	145	7
Amenorrhoea NOS	134	6
Nasopharyngitis	88	4
Acne NOS	80	4
Vaginal haemorrhage	72	3
Libido decreased	69	3
Nausea	66	3
Upper respiratory tract infection NOS	55	3
Back pain	51	2
Abdominal pain NOS	49	2
Fatigue	47	2
Urinary tract infection NOS	47	2
Menometrorrhagia	45	2
Depression NEC	44	2
Influenza	44	2
Sinusitis NOS	38	2
Smear cervix abnormal	37	2
Menorrhagia	36	2
Insomnia NEC	31	1
Breast pain	28	1
Dizziness (except vertigo)	28	1
Pain in limb	28	1
Menstruation irregular	27	1
Injection site pain	26	1
Vaginal candidiasis	26	1
Pharyngitis NOS	25	1
Vaginitis bacterial NOS	25	1
Bronchitis NOS	24	1
Irritability	24	1
Abdominal pain lower	23	1
Dysmenorrhoea	22	1

Source: Created by reviewer from Applicant's dataset labeled AEMD.xpt in the folder ias.

Study 267BMD provided an opportunity to look at how adverse event reporting related to MPA trough concentrations. Trough MPA concentrations were drawn at 6 and 12 months. I arbitrarily chose MPA concentrations less than 400 pg/ml and greater than 1200 pg/ml as the subgroups to explore. Adverse events that occurred only once in either subgroup were excluded. Table 18 shows the results.

Table 18. Adverse Events by Trough Concentration of MPA, Study 267BMD (SC and IM Groups Combined)

MedDRA Preferred Term	% of Subjects with MPA Trough Concentration >1200 pg/ml N=48	% of Subjects with MPA Trough Concentration <400 pg/ml N=70
Headache NOS	13	3
Nasopharyngitis	13	13
Intermenstrual bleeding	8	11
Nausea	8	3
Dysmenorrhoea	6	4
Abdominal pain NOS	4	6
Acne NOS	4	11
Amenorrhoea NOS	4	3
Depression NEC	4	4
Sinusitis NOS	4	11
Urinary tract infection NOS	4	6
Vaginitis bacterial NOS	4	3
Weight increased	4	17

Source: Created by reviewer from unblinded datasets labeled pkdata.xpt and aemd.xpt, Study 267BMD

Comment: No relationship between MPA trough concentrations and adverse event reporting was detected, but numbers were small.

9.3.5 Adverse Events Following Self-Injection

A total of 741 women elected to self-inject for their 3rd or 4th injections. No SAEs were reported after self-injection. Table 19 shows adverse events that occurred in more than 1 subject after self-injection.

Table 19. Adverse Events Reported after Self-injection

Adverse Event by MedDRA Preferred Term	Number of Subjects
Headache NOS	10
Vaginal candidiasis	8
Smear cervix abnormal	6
Depression NEC	3
Laboratory test abnormal NOS	2
Nasopharyngitis	2
Toothache	2
Urinary tract infection NOS	2
Vaginitis	2

Source: Created by reviewer from Applicant's dataset labeled AEMD.xpt in the folder ias.

Comment: No unexpected adverse events were reported after self-injection.

9.3.6 Routine Laboratory Tests

The following tables summarize changes from baseline in routine laboratory tests selected by the reviewer. No worrisome trends were detected in these labs or the labs not shown (e.g. eosinophils, GGT, etc.)

Table 20. Hematocrit Change from Baseline Visit (ITT)

Hematocrit Fraction			
Visit	Results	DMPA-SC N = 1980	DMPA-IM N = 193
Month 12	Total Reported	1187	107
	Baseline Mean	.403	.396
	Mean change from baseline	.000	.000
	Min to Max change	-0.28 to 0.15	-0.06 to 0.06

Source: Table 22.3.1, NDA Module 2, Section 2.7.4, Summary of Clinical Safety

Table 21. AST/SGOT Change from Baseline (ITT)

Analysis Variable: AST/SGOT (U/L)			
Visit	Results	DMPA-SC N = 1980	DMPA-IM N = 193
Month 12	Total Reported	1324	110
	Baseline Mean	20.9	22.6
	Mean change from baseline	0.4	0.0
	Min to Max change	-119 to 177	-22 to 114

Source: Table 22.5, NDA Module 2, Section 2.7.4, Summary of Clinical Safety

Table 22. ALT/SGPT Change from Baseline (ITT)

Analysis Variable: ALT/SGPT (U/L)			
Visit	Results	DMPA-SC N = 1980	DMPA-IM N = 193
Month 12	Total Reported	1325	110
	Baseline Mean	19.1	20.1
	Mean change from baseline	1.6	1.7
	Min to Max	-63 to 146	-50 to 93

Source: Table 22.5, NDA Module 2, Section 2.7.4, Summary of Clinical Safety

Table 23. Bilirubin Change from Baseline (ITT)

Analysis Variable: Bilirubin, Total (umol/L)			
Visit	Results	DMPA-SC N = 1980	DMPA-IM N = 193
Month 12	Total Reported	1323	110
	Baseline Mean	8.78	8.47
	Mean change from baseline	0.52	-0.10
	Min to Max	-21.0 to 26.0	-8.6 to 10.3

Source: Table 22.5, NDA Module 2, Section 2.7.4, Summary of Clinical Safety

Table 24. Creatinine Change from Baseline (ITT)

Analysis Variable: Creatinine (umol/L)			
Visit	Results	DMPA-SC N = 1980	DMPA-IM N = 193
Month 12	Total Reported	1326	110
	Baseline Mean	65.1	67.7
	Mean	2.9	7.4
	Min to Max	-36 to 70	-18 to 35

Source: Table 22.5, NDA Module 2, Section 2.7.4, Summary of Clinical Safety

Table 25. Glucose Change from Baseline

Analysis Variable: Glucose (mmol/L)			
Visit	Results	DMPA-SC N = 1980	DMPA-IM N = 193
Month 12	Total Reported	1312	110
	Baseline Mean	4.92	4.79
	Mean	0.13	0.09
	Min to Max	-3.3 to 11.3	-3.1 to 7.9

Source: Table 22.5, NDA Module 2, Section 2.7.4, Summary of Clinical Safety

Selected Outliers

A single subject had a hematocrit less than 25%. She had an unscheduled hematocrit on day 274 that was 25% and another on day 365 that was 19%. Her bleeding diary was incomplete, noting only amenorrhea between days 194 and 274. She was taking ibuprofen for arthritis, but there was not record of gastrointestinal bleeding. She had no risk factors or explanation for her anemia. No follow-up was available.

No safety issues were detected on review of summary statistics hematology data. Table 26 shows the data for hematocrit changes.

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Table 26. Hematocrit: Summary of Shifts from Baseline (ITT)

Treatment: DMPA-SC (N = 1980)										
Visit	Results	Results at Baseline								
		Low		Normal		High		Total Reported		Not Reported
		n	%	n	%	n	%	n	%	n
Month 6	Low	10		29	2.4			39	3.2	4
	Normal	34	2.8	1129	92.8	12	1.0	1175	96.5	64
	High			3	0.2			3	0.2	1
	Total Reported	44	3.6	1161	95.4	12	1.0	1217	100.0	69
	Not Reported	11		212				223		20
Month 12	Low	10	0.8	18	1.5			28	2.4	5
	Normal	36	3.0	1103	92.9	11	0.9	1150	96.9	52
	High			8	0.7	1	0.1	9	0.8	
	Total Reported	46	3.9	1129	95.1	12	1.0	1187	100.0	57
	Not Reported	6		142		2		150		22

Source: Applicant's Table T21.1, NDA Module 2, Section 2.7.4, Summary of Clinical Safety

No safety issues were detected on review of the liver function test data. The single SAE related to liver disease was a case of hepatitis A. Only one subject dropped out of the study because of unexplained elevations in liver function tests, and her liver function test abnormalities resolved despite continued exposure to DMPA.

A single subject had a serum creatinine greater than 2 mg/dl (2.6 mg/dl) at 6 months. She continued treatment and her serum creatinine was normal at 12 months.

Comment: There was no evidence of treatment-related liver or kidney toxicity.

Data on coagulation tests and fasting lipid profiles came from a substudy of Study 270, a 6-month study of DMPA-SC in women with endometriosis. Table 27 and Table 28 summarize these data.

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Table 27. Change of Fasting Lipid Profile from Baseline in Women Using DMPA-SC, Study 270

	Baseline	Month 3 Change	Month 6 Change
Cholesterol, Total (mmol/L) Normal Range (3.37 - 5.18)			
N	41	32	35
Median/Median Change	4.97	-0.34	-0.41
Range	--	-6.11 to 1.09	-6.32 to 1.27
Triglycerides (mmol/L) Normal Range (0.51 - 2.83)			
N	41	32	35
Median/Median Change	0.93	0.02	-0.03
Range	--	-1.36 to 1.32	-1.43 to 2.15
HDL Cholesterol (mmol/L) Normal Range (0.91 - 2.20)			
N	41	32	35
Median/Median Change	1.50	-0.12	-0.13
Range	--	-0.52 to 0.39	-0.78 to 0.34
LDL Cholesterol (mmol/L) Normal Range (0.00 - 3.37)			
N	41	32	35
Median/Median Change	2.93	-0.30	-0.23
Range	--	-5.75 to 1.33	-5.99 to 0.70
VLDL (μmol/L) Normal Range (260 - 1300)			
N	41	32	35
Median/Median Change	410	10	-20
Range	--	-620 to 590	-670 to 980

Source: Modified from Applicant's Table 11, Page 27, in Safety Summary Report for Studies 268 and 270.

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Table 28. Change of Coagulation Profiles from Baseline in Women Using DMPA-SC, Study 270*

	Baseline	Month 3 Change	Month 6 Change
Platelet Count (109/L) Normal Range (140 - 450)			
N	167	118	111
Median/Median Change	266.0	-7.0 (-3%)	-5.5 (-2%)
Range	--	-425 to 99	-275 to 80
Prothrombin Time (sec) Normal Range (10.0 - 14.5)			
N	35	25	26
Median/Median Change	10.90	0.00 (0%)	-0.05 (-0.4%)
Range	--	-2.5 to 3.5	-2.7 to 3.0
AP Thromboplastin Time (sec) Normal Range (20.0 - 33.0)			
N	35	25	26
Median/Median Change	25.6	-0.8 (-3%)	0.1 (+0.4%)
Range	--	-28 to 5	-10 to 10
Fibrinogen (g/L) Normal Range (2.0 - 4.0)			
N	35	25	26
Median/Median Change	3.73	0.17 (+5%)	0.38 (+10%)
Range	--	-2.1 to 4.1	-2.0 to 2.8
Factor VII (fraction) Normal Range (0.65 - 1.20)			
N	40	30	35
Median/Median Change	1.180	0.005 (+0.4%)	0.080 (+7%)
Range	--	-0.43 to 0.56	-0.30 to 0.50
Factor X (fraction) Normal Range (0.65 - 1.20)			
N	40	30	35
Median/Median Change	1.160	0.045 (+4%)	0.160 (+14%)
Range	--	-0.22 to 0.38	-0.13 to 0.71
Antithrombin III (mg/L) Normal Range (0.70 - 1.30)			
N	40	30	35
Median/Median Change	1.130	-0.010 (-0.8%)	0.020 (+2%)
Range	--	-0.64 to 0.65	-0.94 to 0.51
Protein C (nmol/L) Normal Range (0.70 - 1.30)			
N	40	30	35
Median/Median Change	0.910	-0.015 (+2%)	0.050 (+5%)
Range	--	-0.51 to 0.74	-0.38 to 0.48
Free Protein S (fraction) Normal Range (0.57 - 1.20)			
N	40	30	35
Median/Median Change	0.920	0.015 (+2%)	0.070 (+8%)
Range	--	-0.30 to 0.35	-0.36 to 0.44

*The table includes platelet counts from women in Study 268.

Source: Modified from Applicant's Table 11, Page 25, in Safety Summary Report for Studies 268 and 270.

Comment: The clinical significance of these small changes in lipid levels and coagulation factors from baseline is unclear. For example, while a decrease in HDL is undesirable, decreases in VLDL, triglycerides, and total cholesterol are desirable changes. And whether or not small increases in clotting factors might increase the risk of thrombosis is unknown. It is interesting to note that there were small increases in factor VII, Factor X, and fibrinogen, all factors that increase in estrogen-treated subjects.

9.3.7 Hormone Profiles

Hormone profiles came from Study 267BMD and Study 269. Results were consistent between studies, and between time points. The data do *not* suggest less hormone suppression for the DMPA-SC compared with the DMPA-IM.

There was a trend toward decreases in serum levels of progesterone, estradiol, and SHBG compared with pretreatment levels. The changes were small and usually not statistically significant. Baseline levels were measured during the first 5 days of menses, a natural nadir for serum levels of progesterone and estrogen, and treatment levels were measured at 6 and 12 months. Table 29 and Table 30 show mean changes in hormone levels after 12 months of treatment.

Table 29. Hormone Profile from Subjects in Studies 269 and 267BMD

Visit		All DMPA-SC N = 1251	267BMD	
			DMPA-SC N = 193	DMPA-IM N = 193
Estradiol (pg/mL)				
Enrollment	Total reported	1215	168	159
	Visit median	46.0	52.0	50.0
6-month	Total reported	1030	132	134
	Visit median	40.0	49.5	50.0
12-month	Total reported	871	106	104
	Visit median	40.0	40.0	40.0
Progesterone (ng/mL)				
Enrollment	Total reported	1215	168	159
	Visit median	1.0	0.9	0.9
6-month	Total reported	1030	132	134
	Visit median	1.0	0.7	0.8
12-month	Total reported	871	106	104
	Visit median	1.0	0.6	0.6
SHBG (ug/dL)				
Enrollment	Total reported	1205	168	159
	Visit median	7.6	5.2	4.6
6-month	Total reported	1013	132	134
	Visit median	5.6	3.9	3.9
12-month	Total reported	849	106	104
	Visit median	5.6	3.4	3.9

Source: Table 21, NDA Module 2.7.4. Summary of Clinical Safety

Table 30. Mean (SE)Change in Hormone Levels from Baseline to 12 Months by Study

Treatment	Study 267 BMD		Study 269
	DMPA-SC	DMPA-IM	DMPA-SC
Progesterone (ng/ml)	-0.36 (0.50) N=88	-0.16 (0.10) N=81	-0.23 (0.11) N=868
Estradiol (pg/ml)	-15.2 (3.9) N=88	-5.5 (5.3) N=81	-4.8 (6.1) N=868
SHBG (nmol/L)	-1.5 (0.2) N=88	-1.4 (0.3) N=81	-1.9 (0.1) N=841

Source: Created by reviewer from data sets labeled lbslbas.xpt in Study 267BMD, Study 269

I evaluated progesterone data in more detail to see if there was evidence of ovulation. In Study 267 BMD, no progesterone values >4 ng/ml were detected on treatment. In Study 269, 24 of 1,797 on-treatment progesterone levels were greater than 4 ng/ml. None of the women were taking CYP 3A4 inducers, their mean baseline BMI was 23 kg/m², and their mean progesterone was 26 ng/ml. In 8 subjects, estradiol levels >400 pg/ml suggested lab errors (7 out of 8 abnormal estradiol levels came from the same site). However, in 9 of the remaining cases estradiol levels were greater than 100 pg/ml and consistent with possible ovulation.

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Table 31. On-treatment Progesterone Levels >4ng/ml in Study 269

Patient ID	Progesterone ng/ml	Estradiol pg/ml
50901-00048		
50901-00051		
43351-00154		
50901-00163		
43351-00200		
51751-00309		
51767-00377		
51767-00382		
51767-00389		
50901-00396		
43372-00418		
51788-00562		
51788-00563		
51788-00563		
51763-00635		
51763-00638		
51785-00643		
51802-00656		
51788-00698		
51788-00699		
51800-00724		
51767-00749		
51788-00852		
51788-01040		

Source: Created by reviewer from data sets labeled lbrslbas.xpt in Study 269

Comments:

Ovulation may occur occasionally in women using DMPA-SC. Intravascular injection and rapid clearance of DMPA-SC might allow ovulation. However, there was no evidence that contraceptive efficacy was compromised. Possibly another contraceptive effect of progestin, such as thickening of cervical mucus, was maintained.

Women using DMPA have serum progesterone, estradiol, and SHBG levels that are less than or comparable to the levels that occur naturally during menses, which is a hormonal nadir of the menstrual cycle. Low overall exposure to estradiol may explain the loss in BMD experienced by DMPA users.

9.3.8 Vital Signs

There were no clinically significant changes in mean blood pressure over 1 year of treatment. (See Table 32.)

Table 32. Blood Pressure: Change from Pretreatment at Month 12 (ITT)

Results	DMPA-SC N = 1458	DMPA-IM N = 112
Diastolic Blood Pressure (mmHg):		
Mean (SD)	0.8 (8.9)	0.4 (10.3)
Median	0.0	0.0
Min-Max	-30 to 32	-20 to 24
Systolic Blood Pressure (mmHg):		
Mean (SD)	1.1 (10.5)	1.9 (12.4)
Median	0.0	0.0
Min-Max	-70 to 42	-36 to 30

Source: Modified from Table T25.1, NDA Section 5.3.5.3.2,
Summary of Clinical Safety Tables

9.3.9 Safety Issues of Special Concern

Injection Site Reactions

Injection site reactions were reported as an adverse event for 101 of 1,980 women (5.1%) treated with DMPA-SC. In contrast, there were no reports of injections site reactions among 193 women treated with DMPA-IM. Two injections site reactions were reported after home self-injection.

Among women with injection site reactions, 28 were listed as "not recovered", and 5 were listed as "recovered with sequelae". The five women who "recovered with sequelae" had a mean BMI of 20 kg/m², and the 28 who were listed as "not recovered" had a mean BMI of 21 kg/m². In contrast, women listed as "recovered" from their injections site reactions had a mean BMI of 25 k/m².

Comment: Thin women may be more likely to have chronic injection site reactions.

Ten women stopped treatment because of injection site reactions. Table 33 summarizes these cases. Investigators described the typical reaction as chronic induration at the injection site. The investigators rated the reactions as mild and not serious. Women were not asked to rate the reactions. However, when asked to rate the likelihood that they would use DMPA-SC in the future, 9 of 10 women who stopped treatment for injection site reactions chose #1 (= "extremely unlikely"), and the remaining woman chose #2 (adjacent to "extremely unlikely"). The scale was a 1 to 10 scale, where #1 was "extremely unlikely and # 10 was "extremely likely".

Comment: Affected women appeared to view chronic skin reactions as a significant problem.

Table 33. Listing of Subjects Who Withdrew from Studies because of Injection Site Reactions (Studies 267 BMD, 267, and 269)

PID	Reaction in Investigator's Words	Investigator Rating Intensity/Seriousness	Time on Treatment to Start Date of Reaction	Race	Outcome	Baseline Weight (kg)
2247	Indentation at injection site	Mild/not serious	5 months	White	Not recovered, chronic or stable	51.4
2342	Indentation at injection site	Mild/ not serious	5 months	White	Not recovered, chronic or stable	51.8
292	Indentation right anterior thigh (Same subject complained of hypopigmented nodularity of abdomen at 5 months)	Severe/ not serious	Started at first injection	Black	Unknown	60
696	Injection site nodule-left anterior thigh	Mild/not serious	4 months	White	Not recovered, chronic or stable	65
729	Nodule injection site. Area over nodule appears concave.	Mild/not serious	3 months	White	Not recovered, chronic or stable	60
500	Dimpling at injection site right thigh. Dimpling at injection site abdomen.	Mild/not serious (both)	Started at 1 st injection, second site started after 2 nd injection	White	Not recovered, stable (both)	58
693	Induration of muscle on rt upper thigh-injection site. Subject has induration at injection site, right upper thigh about the size of a nickel, since last injection. Dr. Salmon believes this may be muscle wasting.	Moderate/not serious	4 months	White	Not recovered, chronic or stable	56.7
435	Pain at injection site. Patient decided to end study on 2/18/2001 due to pain at site after first injection	Moderate/not serious	Started at 1 st injection	White	Recovered	42
615	Atrophy, injection site	Mild/ not serious	9 months	White	With sequelae	39.9
848	Lipoatrophy injection site	Mild/ not serious	3 months	White	Not recovered, then lost to follow-up	55.5

Source: Created by reviewer from case report forms submitted to NDA on October 30, 2003, in response to FDA request.

Comments:

A few DMPA-SC users may develop persistent induration at the injection site. Although this is a cosmetic issue rather than a public health issue, it is adverse event that will be important to users. For at least 10 women, injection site reactions caused them to drop out of the study. For at least 7 of these 10 women, the injection site reactions persisted at follow-up.

Weight Gain

Weight gain is a common complaint in DMPA users and a reason for discontinuation of therapy. Table 34 shows that women had mean weight gain of 1.5 kg after 1 year of treatment, and weight gain was similar for users of either formulation.

Table 34. Mean Change in Weight (kg) from Pretreatment at 12 Months (ITT)

Visit	Results	All DMPA-SC N = 1980	267 BMD	
			DMPA-SC N = 193	DMPA-IM N = 193
Pretreatment	Pretreatment mean (kg) ± SD	64.8 ± 14.5*	70.6 ± 18.6	74.2 ± 19.9
Month 12	Mean change (kg) ± SD	1.6 ± 4.1**	2.6 ± 5.2***	1.9 ± 5.7****
	Range (kg)	-31.3 to 20.1	-31.3 to 15.0	-16.4 to 20.1

*Based on data from 1978 subjects.

**Based on 1458 subjects at month 12.

***Based on 115 subjects at month 12.

****Based on 113 subjects at month 12.

Source: Applicant's Table 12, NDA Module 2.7.4, Summary of Clinical Safety

The mean weight change from baseline for women who discontinued treatment early was 1.8 kg. Women who reported weight increase as an adverse event had a mean weight gain of 6.7 kg (15 lbs) at month 12.

Comment: The lower dose of MPA in DMPA-SC compared with DMPA-IM did not affect weight gain.

Table 35 shows that there was considerable variability in weight changes.

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Table 35. Overall Body Weight Changes by Weight Categories for Subjects Administered DMPA-SC (ITT)

Weight Change (kg) from Pretreatment	Month 12	
	n	%
>9.1	45	3.1
7.0 to 9.1	69	4.7
4.7 to 6.9	145	9.9
2.4 to 4.6	286	19.6
0.1 to 2.3	424	29.0
-2.2 to 0	310	21.2
-4.5 to -2.3	107	7.3
-6.8 to -4.6	38	2.6
-9.1 to -6.9	17	1.2
<-9.1	17	1.2
Total reported	1458	

Source: Modified from Applicant's Table 13, NDA Module 2.7.4, Summary of Clinical Safety

Table 36 shows weight changes in selected subgroups. Black women had a greater mean weight gain than white women and Asian or Pacific Islanders.

Table 36. Weight Changes in Selected Subgroups, Studies 267, 267BMD*, and 269

	Mean Weight Change from Baseline at 12 Months in kg (95% CI)	Mean Baseline Weight in kg
Race:		
• Black	3.0 (2.1, 3.9)	70
• Mixed/Multiracial	1.9 (1.3, 2.5)	60
• White	1.5 (1.3, 1.7)	66
• Asian or Pacific Islander	0.5 (-0.9, 1.9)	56
U.S. vs. Non-U.S.		
• U.S.	2.0 (1.4, 2.6)	73
• Non-U.S.	1.5 (1.3, 1.7)	66

*Includes IM and SC groups

Source: Created by reviewer from dataset labeled VS.xpt in Integrated Assessment of Safety, folder named 267-269ias

Comment: The significance of the apparent greater weight gain in black women is unclear. The subgroup analysis was exploratory. Of note, 8% of women in the studies were Black, 8% of women who reported weight gain as an adverse event were Black, and 8% of women who withdrew from the study as a result of weight gain were Black, suggesting that Black women perceived no greater problem with weight gain compared with other racial groups.

The weight gain was similar to the weight gain described on the DMPA-IM label. According to the label, average weight gain in clinical trials at 1 year was 5.4 lb. In this NDA, average weight gain at 1 year was 3.3 lb for all subjects, 4.4 lb for US subjects, and 6.6 lb for Black subjects.

Bone Mineral Density

The current label for DMPA-IM states, "Use of Depo-Provera Contraceptive Injection may be considered among the risk factors for development of osteoporosis. The rate of bone loss is greatest in the early years of use and then subsequently approaches the normal rate of age related fall." However, the Applicant's data indicate that bone loss continues at least over a 5-year period of observation.

The medical literature suggests that DMPA-IM use is associated with a loss of bone mineral density.^{3,4,5,6,7,8} The loss of BMD is

- greater with longer use
- greater in younger users
- largely reversible in older users when treatment stops

The loss of BMD is thought to be related to the low estrogen levels in women using DMPA. The reversibility of BMD loss in adolescents has not yet been determined, although the Applicant is doing a study to address this issue.

The clinical significance of the loss of BMD in DMPA-IM users is unknown. There have been no reports of an increase in fracture risk among users of DMPA-IM. For perspective, pregnancy and lactation, conditions prevented by DMPA-IM, also decrease BMD.⁹ The bone mineral density loss from lactation is 3-7%, which is similar to the bone loss experienced by users of DMPA-IM. Lactation is not a risk factor for osteoporosis in observational studies, suggesting that BMD loss from lactation is reversible.

Women recover from the BMD losses related to pregnancy and lactation, but whether they recover completely from the BMD losses related to DMPA is unknown. Pregnancy and lactation are intermittent, and are followed naturally by recovery of ovulation, estrogen production, and

³ Petitti DB, et al. Steroid Hormone Contraception and Bone Mineral Density: A Cross-Sectional Study in an International Population. 2000 *Obstet & Gynecol* 95:736-744

⁴ Cundy T, et al. Recovery of bone density in women who stop using medroxyprogesterone acetate. 1994 *BMJ*;308:247-248

⁵ Cromer BA et al. A prospective comparison of bone density in adolescent girls receiving depot medroxyprogesterone acetate, levonorgestrel or oral contraceptives. 1996 *J Pediatr* 129:671-676

⁶ Cundy T, et al. Menopausal bone loss in long-term users of depot medroxyprogesterone acetate contraception. *Am J Obstet Gynecol* 186:978-983

⁷ Cundy T, et al. Spinal bone density in women using depot medroxyprogesterone contraception. 1998. *Obstet & Gynecol* 92:569-573

⁸ Scholes D, et al. Bone mineral density in women using depot medroxyprogesterone acetate for contraception. 1999. *Obstet and Gynecol* 93:233-238

⁹ Kalkwarf HJ, Specker BL. Bone mineral changes during pregnancy and lactation. 2002 *Endocrine* 17:49-53

BMD. Women who use DMPA for years will not ovulate for years, and may continue to lose bone mass during that time. It is conceivable there may be too much bone loss for complete recovery in some DMPA users.

In this NDA, the Applicant provided the following data regarding BMD:

- Interim study report for Study 267BMD, in which BMD in women using DMPA-IM was compared with BMD in women using DMPA-SC during 2 years of treatment
- Final Study report for Study 234, a 7-year observational study of BMD in adult women using DMPA-IM for up to 5 years, with a 2-year follow-up period
- An short interim report for Study 261, a 7-year observational study of BMD in adolescent women using DMPA. The treatment phase of this study was stopped early by a data safety monitoring board to start the follow-up phase.

All 3 studies showed progressive bone loss with increasing duration of treatment. Study 234 provided support for partial recovery of BMD when treatment stopped. Summaries of the findings from each study follow. In addition, consultation with internal experts and an external expert was requested during the course of the review, and a short summary of their opinions follows the study summaries.

Study 267 BMD

Women using DMPA for up to 2 years experienced progressive loss of BMD, and there was no significant difference between the IM and SC groups for median percent change in BMD from baseline, except for less BMD loss in the spine at 12 months in the DMPA-SC group. (See Table 37.) Women with pretreatment T-scores less than -1 were not eligible for the study. BMD was measured by dual energy X-ray absorptiometry (DEXA) at baseline, 1 year, and 2 years.

Subgroup analyses done by the Applicant showed no trends with regard to age, race, or geographical location. There were 5 subjects who had bone fractures while on treatment: 4 in the DMPA-SC group and 1 in the DMPA-IM group. None of these women had T-scores less than -1. Less than 4% of subjects took calcium-containing medications in either group.

Table 37. BMD Median at Baseline and Percent Change from Baseline (ITT Population)

Visit		DMPA-SC	DMPA-IM	p-value Between Treatments
Baseline	Femur			
	N	264	267	
	Baseline Median(g/cm ²)	1.03	1.03	0.922
	Spine			
	N	264	268	
	Baseline Median(g/cm ²)	1.16	1.15	0.840
Month 12	Femur			
	N	166	162	
	Median Percent Change from Baseline	-1.4%	-2.0%	0.165
	Range	-19.9 to 4.9	-18.0 to 4.3	
	Within-Group Test†	<0.001	<0.001	
	Spine			
	N	166	162	
	Median Percent Change from Baseline	-2.4%	-3.4%	0.021
	Range	-9.9 to 4.2	-10.7 to 3.5	
Within-Group Test†	<0.001	<0.001		
Month 24	Femur			
	N	106	101	
	Median Percent Change from Baseline	-3.3%	-3.6%	0.724
	Range	-22.7 to 8.1	-18.3 to 6.6	
	Within-Group Test†	<0.001	<0.001	
	Spine			
	N	106	102	
	Median Percent Change from Baseline	-4.3%	-5.0%	0.191
	Range	-10.8 to 3.4	-11.8 to 4.8	
Within-Group Test†	<0.001	<0.001		

Kruskal-Wallis test, significance defined at $p \leq 0.049$

† Wilcoxon signed rank test, significance defined at $p \leq 0.050$

Source: Applicant's Table 7, Revision 2 Study Report for Study 267 BMD

T-scores less than -1 were considered osteopenic. Most women did not become osteopenic. Table 38 shows that the percentage of women who had T-scores less than -1 was similar in both treatment groups.

Table 38. Femur Total and Lumbar Spine Total BMD T-Scores less than -1.0 (ITT Population)

Visit	Femur				Spine			
	DMPA-SC		DMPA-IM		DMPA-SC		DMPA-IM	
	n/N	%	n/N	%	n/N	%	n/N	%
Baseline	1/264	0.4	2/267	0.7	2/264	0.8	5/268	1.9
Month 12	1/166	0.6	5/162	3.1	14/166	8.4	18/162	11.1
Month 24	5/106	4.7	6/101	5.9	13/106	12.3	12/102	11.8

Source: Applicant's Table 10, Revision 2 Study Report for Study 267 BMD

To assess whether women who started with a low BMD were at the same risk of BMD loss as women who started with a high BMD, I did a subgroup analysis by baseline spinal T-Score. I arbitrarily grouped women into 3 groups by baseline spinal T-score: <0, 0 to 1, and >1. Table 39 shows that the mean percent change in BMD did not differ significantly among the 3 subgroups.

Table 39. BMD Change by Baseline T-Score (ITT Population, SC plus IM)

Baseline Spinal T-Score	N	Mean Percent Change in BMD at 24 Months (95% CI)
<0	201	-3.7 (-2.9 to -4.5)
0 to 1	195	-4.6 (-5.2 to -4.0)
>1	137	-4.8 (-5.6 to -4.0)

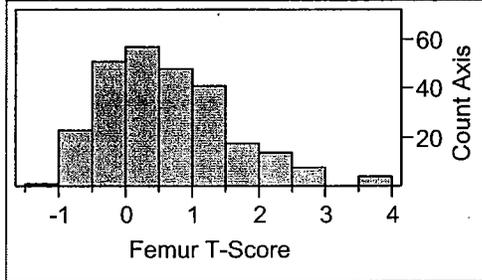
Source: Prepared by reviewer using JMP software from Applicant's dataset labeled BMD.xpt, Revision 2: Study Report for Study 267BMD

The following figures show the distribution of T-scores at different times during the study.

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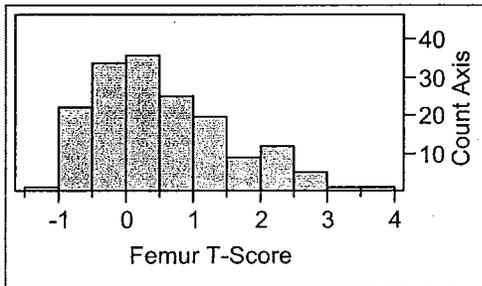
Figure 6. Distribution of Femur T-Scores in DMPA-SC Group, Study 267BMD

At Baseline:



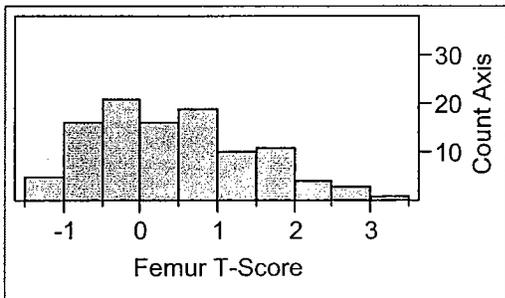
N = 265
Mean = 0.64

At Month 12:



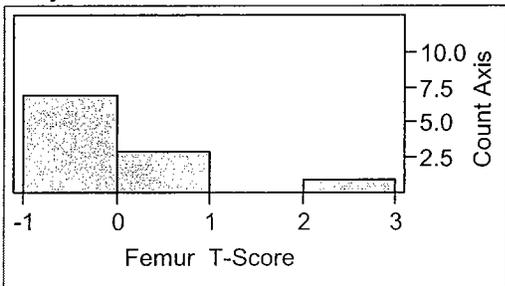
N = 166
Mean = 0.53

At Month 24:



N=106
Mean =0.47

Early Treatment Discontinuations:

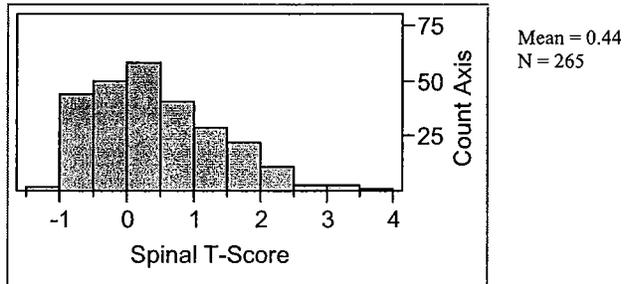


N= 11
Mean = 0.01

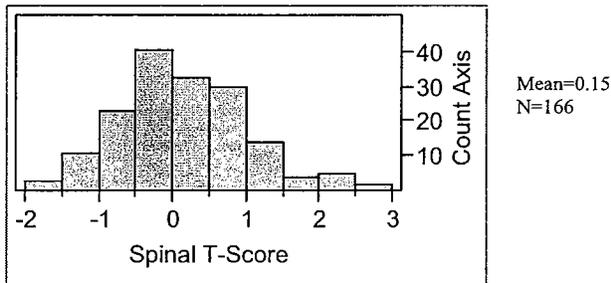
Source: Prepared by reviewer using JMP software from Applicant's dataset labeled BMD.xpt, Revision 2: Study Report for Study 267BMD

Figure 7. Distribution of Spinal T-Scores in DMPA-SC Group, Study 267BMD

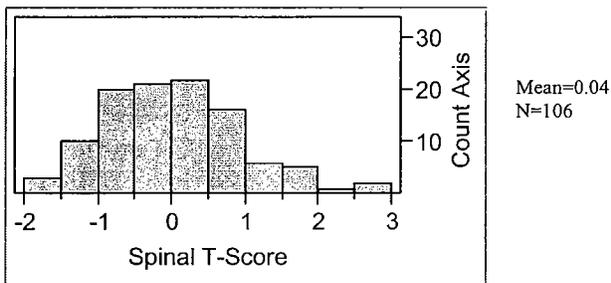
At Baseline:



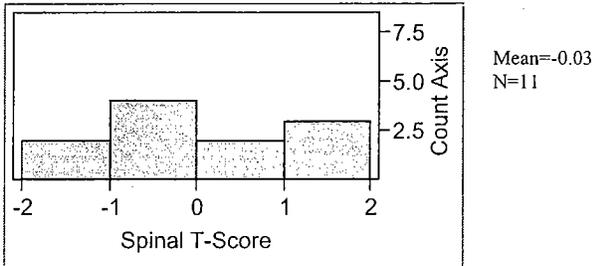
At 12 Months:



At 24 Months:



Early Treatment Discontinuations:



Source: Prepared by reviewer using JMP software from Applicant's dataset labeled BMD.xpt, Revision 2: Study Report for Study 267BMD

Comments: BMD losses were similar and progressive in both groups through 2 years.

Although there was no control group, historically, women of reproductive age with a mean age of 26 years at baseline should have little or no loss in BMD.

Study 234 - Phase 4 BMD Study of DMPA-IM in Adult Women

Study 234 satisfied the only clinical postmarketing commitment for DMPA-IM. The Appendix contains a detailed review of the study. In summary, the study showed that BMD was progressive for the five years of treatment, and that there was partial and progressive recovery during the 2 years of follow-up. At 5 years, the difference between the control group and the DMPA-IM treatment group in percentage change from baseline in BMD ranged from -5.47% (femur total) to -6.55% (femoral trochanter). (See Tables 5 through 10 in detailed Review of Study 234, Appendix)

The current label for DMPA-IM states, "Use of Depo-Provera Contraceptive Injection may be considered among the risk factors for development of osteoporosis. The rate of bone loss is greatest in the early years of use and then subsequently approaches the normal rate of age related fall." Results of Study 234 do not support the second statement.

Study 261 - Phase 4 BMD Study of DMPA-IM in Adolescents

To evaluate bone loss in adolescent users of DMPA-IM, the Applicant undertook a study of bone density in 12-18 year old adolescents. The study was a non-randomized, prospective cohort study in which the bone density of girls using DMPA-IM was compared with the bone density of girls not using hormonal contraception. The treatment phase of the study ended on February 25, 2003, on the advice of the Data Safety Monitoring Board, "upon review of individual participant records of those subjects falling into various safety categories". Follow-up will continue for at least another 2 years.

The Applicant submitted an updated interim report in May 2004. As in the adult study (Study 234), subjects in the DMPA group lost BMD. In general, the BMD loss was greater with greater duration of exposure to DMPA, although the number of subjects in the longer exposure groups was small. There was also partial recovery during the follow-up period, although data are limited (and still accruing.)

Table 40 provides a summary of BMD % change from baseline. The control group consists of subjects who did not receive any Depo-Provera injections before the indicated time point. The Depo-Provera group consists of subjects who had uninterrupted therapy with Depo-Provera up to the indicated time point. At 5 years, the difference between the control group and the DMPA-IM treatment group in percentage change from baseline in BMD ranged from -4.17% (spine) to -6.92% (total hip).

Table 40. Percent Change from Baseline in BMD (g/cm²), Study 261

Visit	n	DMPA-IM Mean (SD)	n	Control Mean (SD)	Difference [DMPA-IM – Control] *Adjusted Mean Change (95% CI)	P-Value
Total Hip BMD						
Week 24	148	-1.47 (2.14)	205	0.76 (2.38)	-2.20 (-2.74 - -1.65)	<0.001
Week 60	103	-2.82 (3.18)	171	1.32 (2.80)	-4.19 (-5.03 - -3.34)	<0.001
Week 84	78	-4.45 (2.97)	155	1.69 (3.57)	-5.76 (-6.83 - -4.70)	<0.001
Week 120	58	-5.26 (3.42)	110	2.09 (4.44)	-6.97 (-8.58 - -5.37)	<0.001
Week 144	45	-6.16 (3.15)	111	1.74 (4.47)	-7.29 (-9.16 - -5.43)	<0.001
Week 180	30	-7.06 (3.07)	77	2.25 (5.78)	-8.28 (-10.89 - -5.68)	<0.001
Week 204	22	-5.35 (4.62)	90	1.76 (5.27)	-4.95 (-7.97 - -1.93)	0.002
Week 240	9	-6.92 (4.27)	69	1.12 (5.14)	-8.05 (-13.12 - -2.97)	0.002
Femoral Neck BMD						
Week 24	148	-1.68 (3.17)	205	0.99 (2.95)	-2.70 (-3.43 - -1.98)	<0.001
Week 60	103	-3.05 (4.17)	171	1.87 (3.65)	-4.31 (-5.41 - -3.21)	<0.001
Week 84	78	-4.21 (4.37)	155	2.39 (4.11)	-5.77 (-7.11 - -4.44)	<0.001
Week 120	58	-5.76 (4.48)	110	2.76 (5.44)	-8.37 (-10.33 - -6.41)	<0.001
Week 144	45	-6.01 (4.61)	111	2.54 (5.95)	-7.15 (-9.62 - -4.69)	<0.001
Week 180	30	-6.87 (4.40)	77	2.60 (6.78)	-8.74 (-11.94 - -5.55)	<0.001
Week 204	22	-5.94 (4.69)	91	2.15 (6.68)	-5.90 (-9.60 - -2.20)	0.002
Week 240	9	-6.06 (5.14)	69	1.45 (6.21)	-6.83 (-12.80 - -0.85)	0.026
Spine BMD						
Week 24	149	-1.23 (2.01)	207	1.66 (2.26)	-2.57 (-3.06 - -2.08)	<0.001
Week 60	104	-2.42 (2.79)	171	3.47 (3.31)	-5.33 (-6.18 - -4.49)	<0.001
Week 84	80	-3.02 (3.27)	154	4.26 (4.06)	-6.39 (-7.48 - -5.30)	<0.001
Week 120	58	-2.62 (3.81)	110	5.23 (5.60)	-6.07 (-7.78 - -4.35)	<0.001
Week 144	46	-2.78 (4.03)	111	5.41 (5.49)	-7.01 (-8.98 - -5.04)	<0.001
Week 180	29	-2.43 (4.48)	77	6.77 (6.92)	-6.61 (-9.55 - -3.67)	<0.001
Week 204	23	-1.90 (4.76)	91	6.64 (6.90)	-5.69 (-8.88 - -2.51)	<0.001
Week 240	9	-4.17 (5.39)	70	5.12 (6.14)	-9.72 (-15.22 - -4.21)	<0.001

*Analyzed by analysis of covariance with smoking status at baseline, race, and treatment as factors and BMD at baseline, BMI, and age at baseline as covariates

Source: Modified from Table 1, Appendix A, Applicant's May 2004 Interim Analysis of Study 261

Table 41 and Table 42 allow the reader to view the same time points for the adult and the adolescent study. As expected, the control group in the adolescent study gained bone mass while the control group in the adult study showed little change. Adolescents appear to have a greater mean loss in BMD than adults; however, confidence intervals overlap.

Table 41. Percentage Change from Baseline in BMD, Study 234 (Adults)

Visit	DMPA-IM		Control		Difference [DMPA-IM – Control] adjusted mean change (95% CI)
	n	Mean (SD)	n	Mean (SD)	
Spine Total BMD					
Week 24	178	-1.41 (2.37)	291	0.19 (2.75)	-1.87 (-2.37 - -1.36)
Week 144	71	-4.89 (3.16)	159	0.31 (2.75)	-5.21 (-6.06 - -4.35)
Week 240	33	-5.38 (3.57)	105	0.43 (3.27)	-5.65 (-7.06 - -4.23)
Femur Total BMD					
Week 24	108	-0.72 (2.07)	144	0.57 (2.32)	-1.34 (-1.93 - -0.76)
Week 144	42	-3.89(3.37)	77	-0.02 (2.76)	-3.66(-4.80 - -2.53)
Week 240	21	-5.16 (3.60)	65	0.19 (3.18)	-5.47 (-7.10 - -3.84)
Femoral Neck BMD					
Week 24	179	-1.24 (3.29)	289	0.22 (4.61)	-1.60 (-2.42 - -0.78)
Week 144	72	-4.80 (4.39)	159	-0.23 (3.87)	-4.45 (-5.63 - -3.27)
Week 240	34	-6.12 (4.68)	106	-0.27 (5.22)	-5.75 (-7.86 - -3.64)

Source: Modified from Applicant's table on p. 44 of Study Report for Study 234

Table 42. Percentage Change from Baseline in BMD, Study 261 (Adolescents)

Visit	DMPA-IM		Control		Difference [DMPA-IM – Control] Adjusted Mean Change (95% CI)
	n	Mean (SD)	n	Mean (SD)	
Spine BMD					
Week 24	149	-1.23 (2.01)	207	1.66 (2.26)	-2.57 (-3.06 - -2.08)
Week 144	46	-2.78 (4.03)	111	5.41 (5.49)	-7.01 (-8.98 - -5.04)
Week 240	9	-4.17 (5.39)	70	5.12 (6.14)	-9.72 (-15.22 - -4.21)
Total Hip BMD					
Week 24	148	-1.47 (2.14)	205	0.76 (2.38)	-2.20 (-2.74 - -1.65)
Week 144	45	-6.16 (3.15)	111	1.74 (4.47)	-7.29 (-9.16 - -5.43)
Week 240	9	-6.92 (4.27)	69	1.12 (5.14)	-8.05 (-13.12 - -2.97)
Femoral Neck BMD					
Week 24	148	-1.68 (3.17)	205	0.99 (2.95)	-2.70 (-3.43 - -1.98)
Week 144	45	-6.01 (4.61)	111	2.54 (5.95)	-7.15 (-9.62 - -4.69)
Week 240	9	-6.06 (5.14)	69	1.45 (6.21)	-6.83 (-12.80 - -0.85)

Source: Modified from Table 1, Appendix A, Applicant's May 2004 Interim Analysis of Study 261

Comment: When available, the final results of this study may (or may not) lead to further labeling for the adolescent user.

Summary of Consultations with Endocrinologists

FDA's Division of Metabolic and Endocrine Drug Products (DEM DP) and an academic endocrinologist with expertise in bone disease were consulted regarding BMD data. Consultants were provided with data from Studies 267BMD, 234, and 261. Their recommendations regarding labeling changes are summarized in the following section. All consultants agreed that labeling regarding BMD needed to change. Otherwise, there were differences of opinion based on uncertainty about

- how to measure and interpret BMD changes in young women
- the extent of recovery of BMD after discontinuing therapy

Questions of the consult and a summary of the answers from the consultants follow.

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 Trade Secret / Confidential

 Draft Labeling

✓ Deliberative Process

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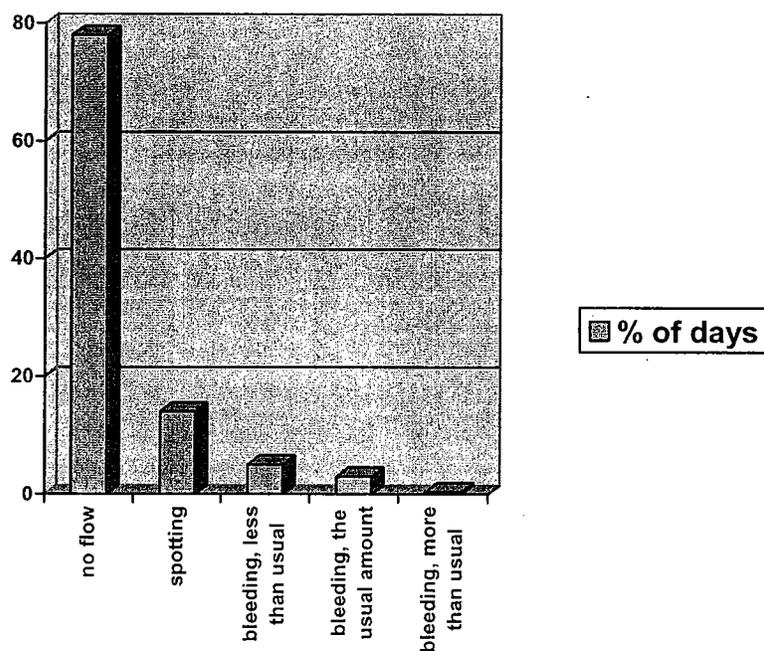
Bleeding Analysis

Four women had SAEs related to bleeding. A brief summary of these cases is provided above.

Thirty women dropped out of the contraception studies because of vaginal bleeding problems. These cases are listed in the Applicant's Listing 10.1 and 10.2, Module 5, Section 5.3.5.3.2. All were rated by investigators as not serious, and all but 3 were listed as "recovered." I did not detect any age, racial, BMI, or CYP3A4 patterns on scanning this data listing.

Bleeding diaries were provided by 2124 patients (including women treated with DMPA-IM). Of 695,041 days recorded, there were 541,903 days of "no flow", 97,774 days of "spotting", 34,071 days of "bleeding, but less than usual", 18,211 days of "bleeding, the usual amount", and 2,831 days of "bleeding, more than usual". Figure 8 shows these data in percent of total days recorded.

Figure 8. Percent of Days with Each Bleeding Pattern



Source: Reviewer analysis of dataset MNDEMNDE (Menses Diary Evaluation) provided in Applicant's Integrated Assessment of Safety (includes SC and IM groups)

Table 43 shows that the percentage of days with no flow increased with duration of treatment, and there were no important differences between the DMPA-SC and DMPA-IM groups in Study 267BMD.

Table 43. Bleeding Status as Percentage of Recorded Days by 3-Month Treatment Interval, Study 267 BMD

Treatment		1 st Interval	2 nd Interval	3 rd Interval	4 th Interval
DMPA-IM	Days recorded	15,812	15,750	13,262	7,837
	Bleeding more than usual	0.5	0.4	0.6	0.3
	Bleeding, the usual amount	2.9	1.2	1.0	1.0
	Bleeding, but less than usual	6.2	4.3	3.4	2.4
	Spotting	17.5	15.3	10.0	9.1
	No flow	73.0	78.8	85.0	87.2
DMPA-SC	Days recorded	15,750	13,510	11,522	8,046
	Bleeding more than usual	0.8	0.3	0.3	0.2
	Bleeding, the usual amount	3.8	1.8	0.6	0.5
	Bleeding, but less than usual	6.7	5.8	2.6	1.5
	Spotting	21.1	15.4	9.7	9.2
	No flow	67.7	76.6	86.8	88.5

Source: Created by reviewer using JMP software and Applicant's data set called MNDEMNDE.xpt in unblinded data sets for Study BMD267

Comment: In a theoretical average cycle of 28 days with 6 days of bleeding¹⁰, about 78% of days are "no flow" days. In comparison, users of DMPA experienced fewer "no flow" days than average in the 1st treatment cycle, and more "no flow" days than average by the 3rd and 4th treatment cycles.

For women who remained in the study, diaries show more amenorrhea and fewer prolonged bleeding/spotting episodes with each treatment cycle. Table 44 and Figure 9 show these data.

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¹⁰ Belsey EM, Pinol APY, et al. Menstrual bleeding patterns in untreated women. Contraception 1997;55:57-65

Table 44. Bleeding Pattern by 90-Day Treatment Interval in Studies 267, 267BMD and 269

	1 st Interval	2 nd Interval	3 rd Interval	4 th Interval	Total
N cycles	1949	1786	1600	1379	6730**
Amenorrhea	37	366	529	544	1487
Prolonged bleeding*	1174	778	486	339	2778
Mean Number of Bleeding/spotting days in 90-day interval (all patients)	28	21	15	12	20

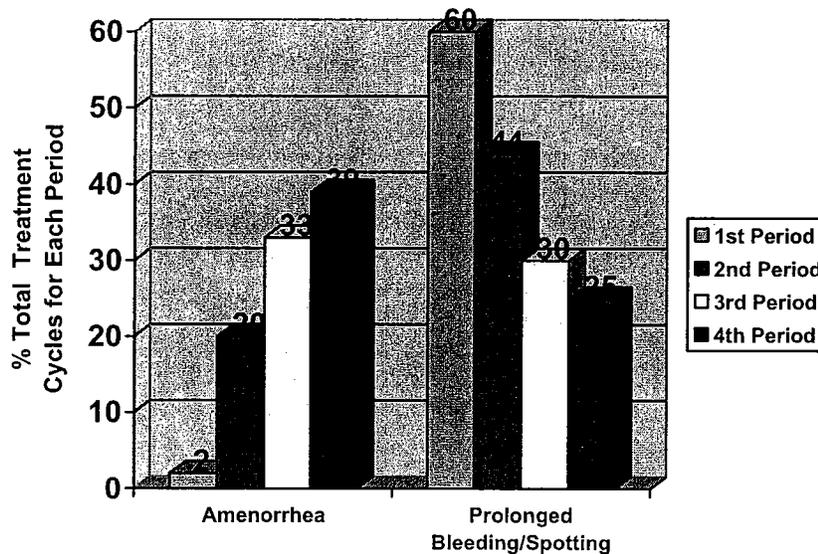
Source: Reviewer analysis of dataset EPISODE (Diary Summary - Bleeding Patterns) provided in Applicant's Integrated Assessment of Safety (SC and IM groups)

*Prolonged bleeding was defined as a bleeding/spotting episode lasting 10 days or more starting in a 90-day reference period.

**Total does not equal the sum of 4 treatment cycles because 16 women had a 5th treatment cycle. 11 of these 16 women had amenorrhea in the 5th treatment cycle.

Figure 9 presents the data from Table 44 as % of total treatment cycles for each of 4 treatment periods. With each treatment cycle, the percentage of treatment cycles with amenorrhea increases, and the percentage of cycles with prolonged bleeding and spotting decreases.

Figure 9. Bleeding Trends by 3-Month Treatment Period



Source: Graphic display of data in Table 44

Table 45 shows that an analysis of bleeding patterns for selected subgroups did not reveal any clinically important differences.

Table 45. Bleeding Patterns for Selected Subgroups in Studies 267, 267BMD, and 269

	Total Treatment Cycles*	Amenorrhea**	Prolonged Bleeding***
Race:			
▪ White	5515	1152 (21%)	2294(42%)
▪ Black	354	76 (21%)	156(44%)
▪ Mixed/Multiracial	684	218 (32%)	251 (37%)
▪ Asian or Pacific Islander	177	41 (23%)	77 (44%)
Baseline BMI (kg/m ²):			
▪ <20	1078	203 (19%)	463 (43%)
▪ Between 20 and 27	3967	891(22%)	1646 (41%)
▪ >27	1624	372 (23%)	665 (41%)
Use of CYP3A4 Inhibitors:			
▪ Yes	355	62(17%)	181 (51%)
▪ No	6355	1418 (22%)	2594 (41%)
Use of CYP3A4 Inducers:			
▪ Yes	239	38 (16%)	125 (52%)
▪ No	6471	1442 (22%)	2650 (41%)

*90-day intervals

**Patients with no bleeding or spotting throughout the 90-day interval

***A bleeding/spotting episode lasting 10 days or more starting in a 90-day interval

Source: Reviewer analysis of dataset EPISODE (Diary Summary - Bleeding Patterns) provided in Applicant's Integrated Assessment of Safety

Endometrial Histology

Endometrial histology and endometrial thickness data were available from a subset of women from Study 269. Expected endometrial changes occurred. There was a shift toward endometrial atrophy, insufficient tissue, and endometrial thinning, starting at 3 months and persisting through 12 months. (See Table 46).

Table 46. Endometrial Histology at Baseline and 12 Months

	Baseline N=164	12 Months N=110
Atrophic %	0.6%	30.9%
Proliferative %	37.8%	4.5%
Secretory %	43.3%	12.7%
Simple hyperplasia %	2.4%	1.8%
QNS %	14.0%	47.3%
Mean endometrial thickness (mm)	8.6*	4.6**

Source: Modified from Tables T6.1, T6.2 and T6.3, final study report for Study 269.

*N=153, **N=90

Five women had simple hyperplasia without atypia at baseline and 3 different women had simple hyperplasia on treatment. (See Table 47.) Except for 2 women who had subsequent biopsies labeled "atrophy", outcome was not recorded in the study report. However, no serious adverse

events, adverse events related to bleeding, or adverse events related to endometrial abnormalities were detected among these women.

Table 47. Women Who Had Biopsies Showing Simple Hyperplasia, Without Atypia, in Study 269

Patient Number	Screening Biopsy (endometrial thickness by ultrasound)	On-Treatment Biopsy (endometrial thickness on ultrasound)	Time on Treatment when Hyperplasia Diagnosed
508	Simple hyperplasia, without atypia (14 mm)	Quantity insufficient for diagnosis (not recorded)	0
628	Simple hyperplasia, without atypia (7 mm)	Atrophic (5.2 mm)	0
706	Simple hyperplasia, without atypia (6.1 mm)	Atrophic (2.8 mm)	0
713	Simple hyperplasia, without atypia (3.6 mm)	Not recorded (not recorded)	0
815	Biopsy suggesting a menstrual endometrium, but compare with the date of cycle to eliminate shedding of proliferative endometria with mild simple hyperplasia without atypia* (11.6 mm)	Not recorded (not recorded)	0
906	Secretory (4.0 mm)	Simple hyperplasia, without atypia (2.5 mm)	12
935	Proliferative (6.0 mm)	Simple hyperplasia, without atypia (not recorded)	9
1067	Secretory (8.0 mm)	Simple hyperplasia, without atypia (5.9 mm)	12

*This subject does not appear to have been included in the preceding table.

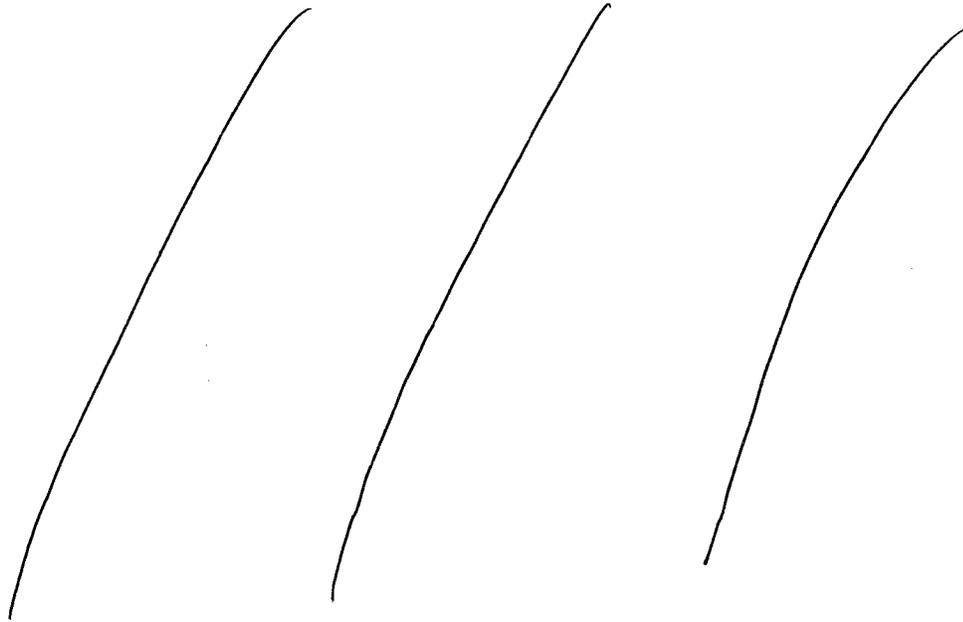
Source: Created by reviewer from datasets labeled GYHC.xpt and USMS.xpt in datasets for Study 269 and Study Report for Study 269, page 55

Thrombotic Events

Is MPA associated with thrombotic events? Opinions vary. From 1968 to the present, a history of thrombotic events has been a contraindication on the DMPA-IM label. The contraindication first appeared in 1968 in response to concern about thrombotic events in women using combination oral contraceptives, and case reports of thromboembolic events in women using DMPA-IM. However, the contraindication is *not* on the labeling for progestin-only oral contraceptives, none of which contain the progestin MPA.

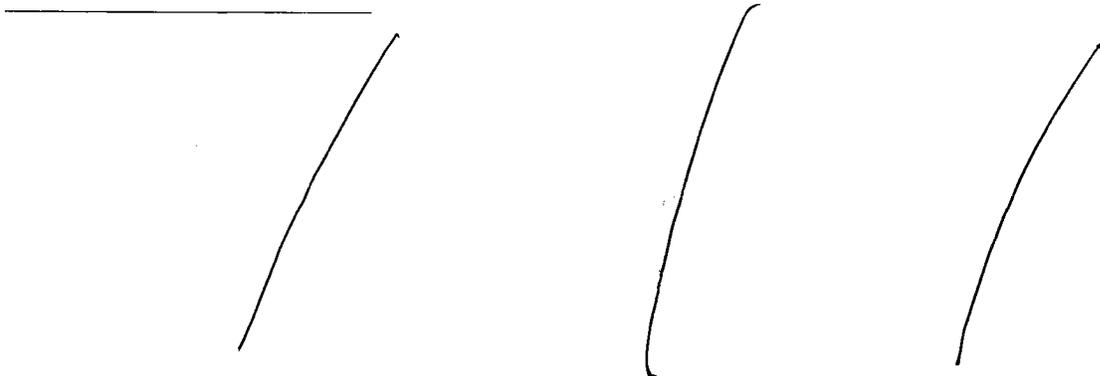
The Applicant's proposed label

/ / /



FDA has received numerous postmarketing reports of thrombotic events in women using DMPA-IM . Although reporting rates are lower than expected incidence rates for women of reproductive age, we know that most adverse events are not reported. Therefore, reporting rates should be considerably lower than incidence rates. According to the applicant, between 1999 and 2001 there were 1,586,767 women-years of DMPA-IM exposure in US women. In that same period, I found 27 cases of thrombotic events (found in FDA's AERS DataMart by searching for trade name ="Depo-Provera", reaction = "thrombosis", source = "domestic/unknown"). This is 0.2 VTEs in 10,000 women-years, somewhat lower than the estimated baseline risk of 1 per 10,000 women-years. However, the extent of underreporting is not known.

A clinical trial might seem to be a good way to estimate the incidence of thrombotic events, but the number of subjects in clinical trials is usually too small to detect an increased incidence of a rare event. However, DMPA-IM is an old product and has been used in a number of contraceptive trials. Therefore, I combined the data in the Phase 3 trials reported to the FDA to



see if I could estimate the incidence of VTEs in reproductive-aged women exposed to DMPA injections. Table 48 shows these data.

Table 48. Experience with VTEs in Phase 3 Clinical Trials Presented by the Applicant to Support Safety in This NDA

Study	Treatment*	VTEs	Time on Drug when AE First Reported	Women-years Exposure
Contraception Studies 267, 269, 267BMD	DMPA-SC or DMPA-IM	1 (Subject taking DMPA-IM)	9 months	1,717
Endometriosis Studies 268, 270	DMPA-SC	1 (intermediate probability V-Q scan and elevated d-dimers)	4 months	134
Contraception Study 144 (1960's)	DMPA-IM	**3	4 months, 5 months, 28 months	6,902
Contraception Study 148 (pre-1982)	DMPA-IM	0		320
Totals		5		9,073

*Treatment doses were standard: DMPA-IM, 150 mg every 3 months, or DMPA-SC, 104 mg every 3 months.

**One woman had a history of thrombophlebitis with a pregnancy, and 1 woman was found to have metastatic cancer. Three other women may have had thrombotic events but there is too little information to confirm (e.g. no venograms, no history of hospitalization.)

Since combination oral contraceptives increase the risk of thrombotic events, it is useful to compare clinical trial data for DMPA to clinical trial data for combination oral contraceptives. In an internal review of clinical trials for various combination oral contraceptives, 15 VTE's were seen in 28,830 women-years, which is 5.2 VTE's in 10,000 women-years.¹⁶ This is close to the expected rate based on published literature. Therefore, in clinical trials reviewed by the FDA, the incidence of thrombotic events in women receiving injections of DMPA for contraception does not appear different from the incidence of thrombotic events in women using combination oral contraceptives. (See Table 49.)

Table 49. FDA's Clinical Trial Experience with VTEs

Treatment	# VTEs	Women-years exposure	# VTEs per 10,000 women-years
DMPA-IM and DMPA-SC	5	9,073	5.5
Combination oral contraceptives	15	28,830	5.2

Source: Internal FDA review

Recently published data from the Women's Health Initiative provides further, albeit weak, support for the idea that MPA use may increase the risk of thrombotic events.^{17,18} The Women's

¹⁶ This review was done by Dr. Brenda Gierhart and Dr. Dan Davis, who extracted data from medical reviews of combination oral contraceptives reviewed at the FDA between 1983 and 1999. Reviews were of marketing applications for 20 different pills. All but 1 pill contained less than 50 ug ethinyl estradiol.

¹⁷ The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. JAMA 2004;291:1701-1712

Comments: Delayed return of ovulation and fertility may be a problem for some women and should be part of contraceptive counseling. Only 1 of 21 (5%) women who wanted a pregnancy was pregnant within 1 year of her last injection of DMPA-SC. In contrast, for rapidly reversible products such as IUDs or oral contraceptives, 85-90% of women who wish to become pregnant are pregnant within 1 year of discontinuing the product.

Pregnancy and Lactation

Since no pregnancies were detected in the clinical trials for DMPA-SC, there are no data about pregnancy outcome in subjects who become pregnant using DMPA-SC. However, studies in the medical literature address DMPA-IM exposure during pregnancy and lactation. There are a number of studies in the literature describing associations between MPA exposure and different birth defects. However, the findings are inconsistent. A Reprotox¹⁹ review of these studies done in August 2003 summarized findings as follows: "Medroxyprogesterone use during early pregnancy is not associated with an increase in adverse pregnancy outcome. Breastfeeding women may take this medication".

Another source of postmarketing data is the FDA's Adverse Event Reporting System (AERS). My search of FDA's AERS DataMart on January 28, 2004 revealed 131 reports coded as "congenital anomaly". Most of these case reports provide no further information. Among those with further medical information, I detected no pattern of malformations.

When progestin-only methods of contraception fail, there is usually a greater proportion of ectopic pregnancies to all pregnancies than is seen in the general population. Although ectopic pregnancies have been reported in DMPA-IM users, data are insufficient to indicate whether there is a greater than expected proportion of ectopic pregnancies. The clinical trials of DMPA have not been informative because of the small number of pregnancies. Also, DMPA-IM has not had a greater-than-expected proportion of ectopic:all pregnancies in postmarketing reports received by the FDA. (In our AERS DataMart on January 28, 2004 there were 12 case reports under the search term "ectopic pregnancy" and 1792 case reports under the search term "pregnancy".)

Regarding lactation, the Applicant did no studies of DMPA-SC in lactating women. However, there are published studies of DMPA-IM and lactation. The Reprotox summary (August 2003) of the literature follows:

"MPA administration immediately postpartum has not been shown to alter the duration of lactation (45,46) and children breastfed by MPA-receiving women demonstrate normal long-term growth and development (21,22). MPA is excreted in breast milk in small amounts (23,24); it is not believed that this exposure poses a hazard to the neonate (25,36,44)."

21. Jimenez J et al: Long-term follow-up of children breast-fed by mothers receiving depot-medroxyprogesterone acetate. *Contraception* 30:523-33, 1984.

¹⁹ The online publication of the Reproductive Toxicology Center, at <http://csi.micromedex.com/DATA/RX/RX2087.HTM?Top=Yes>

22. 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
23. Koetsawang S et al: Transfer of contraceptive steroids in milk of women using long-acting gestagens. *Contraception* 25:321-31, 1982.
24. Saxena BN et al: Levels of contraceptive steroids in breast milk and plasma of lactating women. *Contraception* 16:605-13, 1977.
25. Schwallie PC: The effect of depot-medroxyprogesterone acetate on the fetus and nursing infant: a review. *Contraception* 23:375-86, 1981.
36. The WHO Working Group, Bennet PN (ed): *Drugs and Human Lactation*. Elsevier, Amsterdam, New York, Oxford, 1988. pp. 168-9
44. Virutamasen P, Leepipatpaiboon S, Kriengsinyot R et al: Pharmacodynamic effects of depot-progesterone acetate (DMPA) administered to lactating women on their male infants. *Contraception* 1996;54:153-7.
45. Hannon PR, Duggan AK, Serwint JR, Vogelhut JW, Witter F, DeAngelis C. The influence of medroxyprogesterone on the duration of breast-feeding in mothers in an urban community. *Arch Pediatr Adolesc Med*. 1997 May;151(5):490-6.
46. Halerman LD, Nelson AL: Impact of early postpartum administration of progestin-only hormonal contraceptives compared with nonhormonal contraceptives on short-term breast-feeding patterns. *Am J Obstet Gynecol* 2002;186:1250

There have been 38 case reports coded as "suppressed lactation" or "failed lactation" reported in the FDA's AERS DataMart (searched on January 28, 2004).

Comments:

There does not appear to be a preponderance of a malformation in babies exposed to DMPA *in utero*.

The risk of ectopic pregnancy when DMPA fails has not been well-defined in clinical trials. Although it is reasonable to suppose that DMPA will behave like other progestin-only contraceptive methods, so far postmarketing reports have not suggested an increased proportion of ectopic pregnancies.

Postpartum lactation problems are a common clinical problem among all lactating women, and DMPA-IM is a widely used product that has been marketed for over 40 years. Therefore, the significance, if any, of 38 reports of lactation problems is unclear.

9.3.10 Postmarketing Data

Although DMPA-SC is not yet marketed, there is over 40 years of postmarketing experience with DMPA-IM. The Applicant summarized spontaneous reports from September 1999 through June 2002, as well as from December 1990 through September 1999. Based on vials of DMPA-IM sold, the Applicant estimates that the total US women-years of exposure from 1999 through 2001 is

Table 51. Spontaneous Reports in Applicant's Database

	Dec90 to Sep99 Number of Subjects	Sep99 to Jun02 Number of Subjects
Number of Subjects Reporting Serious Events	702	466
Number of Subjects Reporting Non-serious Events	14,620	1,871

According to the Applicant, none of the observed events gave any reason to re-evaluate the safety of DMPA-IM.

My review of postmarketing data consisted of a brief review of reports in FDA's AERS DataMart. On January 20, 2004, there were 9582 reports containing the term Depo-Provera in FDA's AERS DataMart. I limited my review to deaths. A total of 196 reports contain the outcome death. Most of these were fetal deaths from abortion or ectopic pregnancy. There have been 8 cases of death with the reaction code "pulmonary embolism". The significance of this is unclear for many reasons, including that the extent of underreporting is unknown.

9.3.11 Ongoing Studies of DMPA-IM

The Applicant has 2 ongoing studies that are summarized in Table 52.

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Table 52. Applicant's Ongoing Studies of DMPA-IM

Study ID	Objective(s) of Study	Design	DMPA Dose	N	Treatment Duration	Status
261	Evaluate BMD in adolescents during and for 2 years following treatment	Prospective surveillance. Control group not using hormones for contraception.	150 mg IM every 3 months	413 total	Up to 240 weeks	DMPA-IM arm stopped by Data Safety Monitoring Board because of BMD loss. Follow-up phase ongoing.
9	Evaluate BMD in adults age 18-35 and compare to women using Lunelle after 2 years of treatment.	Prospective surveillance. Lunelle comparator group.	150 mg IM every 3 months	241 DMPA users	2 years	Ongoing.

Source: Created by reviewer from information in NDA Section 2.7.4.6.5.

The SAEs detected so far do not raise unexpected safety concerns. In addition, there have been no thromboembolic SAEs in the ongoing studies.

9.3.12 Safety Update

The Applicant provided a safety update during the review cycle. The update included:

- An addendum to Study 267 including results from a substudy to assess return to ovulation
- An addendum to study 269 with results from a substudy to assess return to fertility
- A revision to Study 267BMD providing complete 1-year data for BMD. (A subsequent amendment provided complete 2-year BMD data.)
- List of SAEs for ongoing studies
- Interim report from Study 268, a Phase 3 endometriosis study
- Interim report from Study 270, a Phase 3 endometriosis study
- Interim Report from Study 261
- A postmarketing experience update

I reviewed the information in the update and incorporated findings into the corresponding sections of this review.

9.4. Adequacy of Safety Testing

Overall, total patient exposure met ICH guidelines for drug development and FDA recommendations for development of this product.

9.5 Summary of Critical Safety Findings and Limitations of Data

Although DMPA-SC users are exposed to less MPA than DMPA-IM users, no safety advantage was detected for DMPA-SC. In particular, endogenous hormone suppression, weight gain and bone mineral density loss were not different among users of either formulation.

/ / / / / /

Injection site reactions are a drawback of DMPA-SC compared with DMPA-IM. The reactions were usually rated as mild and not serious by investigators. Typical descriptions included "induration", "atrophy", or "dimpling", and one investigator stated the affected area was "about the size of a nickel." These reactions caused at least 10 women to stop treatment, and at least 7 of these 10 women had persistent induration at follow-up. Thin women may be more at risk for injection site reactions.

The design of the Case Report Forms allowed "withdrawal of consent" to be used too easily, and the opportunity to collect reasons for dropouts was lost. Consequently, adverse events associated with dropouts were probably underestimated.

Findings from the safety and efficacy review are incorporated into the proposed labeling changes in the Appendix. Highlights include

10 Dosing, Regimen, and Administration Issues

Although the Applicant reasonably chose the dose as the lowest dose to suppress ovulation,

11 Use in Special Populations

11.1 Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Not applicable.

11.2 Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

I detected no clinically significant effects of age or race on the safety or efficacy of DMPA-SC. Specific analyses are incorporated into the safety and efficacy section, above.

11.3 Evaluation of Pediatric Program

DMPA-SC is indicated only for females of reproductive age. With the possible exception of BMD loss, the risk/benefit profile is expected to be similar for postmenarcheal girls compared to older women of reproductive age. The Applicant is doing a large surveillance study to evaluate the reversibility of BMD changes in adolescent users of DMPA. Studies in older women suggest that BMD changes will be largely reversible.

11.4 Comments on Data Available or Needed in Other Populations

Although the IM formulation has been marketed for over 40 years, there are no studies in subjects with renal or hepatic impairment. Since DMPA is chiefly metabolized in the liver, severe hepatic dysfunction is a labeled contraindication. The effect of renal disease on the safety of DMPA is unknown.

12 Conclusions and Recommendations

12.1 Conclusions

DMPA-SC is a highly effective hormonal contraception with an efficacy and safety profile that is comparable to DMPA-IM. There were no confirmed pregnancies on treatment in 3 contraceptive trials. The Pearl Index pregnancy rate for women who were less than 36 years old at baseline, using only months when no barrier contraception was used, was 0 pregnancies per 100 women-years. The upper bound of the 95% confidence interval was 0.25 pregnancies per 100 women-years.

The 2-year data on BMD changes were not different between SC and IM formulations. Weight changes and hormonal changes were also not different between formulations.

A disadvantage of DMPA-SC compared with DMPA-IM is that injection site reactions occurred in women using DMPA-SC. About 5% of subjects using DMPA-SC reported injection site reactions as an adverse event.

The unresolved issue for both formulations remains the consequences, if any, of BMD loss. Data to 5 years suggest that BMD loss continues with every year of use. We do not know if losses plateau at some later point. Data also support that BMD losses are mostly reversible, although recovery was not complete almost 96 weeks after discontinuing therapy. However, since the

median time to return to ovulation after multiple doses was 10 months, 96 weeks post treatment (=22 months post treatment) may not be enough time to see maximal recovery. And finally, whether or not BMD loss in teens is more important than BMD loss in adults is unclear.

Labeling : ~~_____~~

12.2 Recommendations

I recommend approval of DMPA-SC pending changes to the proposed labeling. My labeling recommendations follow in the Appendix.

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13 Appendix

13.1 Review of Study 234

Title of Study: Assessment of Bone Mineral Density in Women Receiving Depo-Provera Contraceptive Injection

1. Background:

When the FDA approved Depo-Provera IM for contraception in 1992, the company made a postmarketing commitment to do a 7-year bone mineral density study. This document reviews the study report for the completed bone mineral density study. The approval letter for Depo-Provera IM described the commitment as "a bone mineral density study which examines the rate of bone mineral loss during the first five years of Depo-Provera Contraceptive Injection treatment and subsequent reversal of bone mineral loss following cessation of treatment."

2. Materials Reviewed:

- Final Study Report for Study 234, including BMD dataset
- Further sponsor analyses requested by the reviewer

3. Study Summary:

3.1 Objective

The primary objective was to evaluate BMD changes in women receiving Depo-Provera for up to 240 weeks and compare them to a cohort not using hormonal contraception, matched at each study site on the basis of race and current smoking status. Both Depo-Provera contraceptive users choosing to discontinue injections and non-exposed cohorts were to be further evaluated for BMD changes for an additional 96 weeks.

3.2 Design

The study design was open label, prospective, matched cohort. The matching was by race and current smoking status. Enrollment was 608 subjects (248 in Depo-Provera group and 360 in the control group). The women were healthy, aged 25 to 35 years, and not planning a pregnancy in the next 5 years. Women had to have regular menses, or, if they were breastfeeding, had to be at least 6 weeks postpartum. Exclusion criteria included the contraindications for Depo-Provera, as well as hyperthyroidism and BMD more than 2 standard deviations below normal for age.

Subjects in the treatment group received Depo-Provera as labeled, 150 mg/ml intramuscularly every 12 weeks.

The primary endpoint was the percentage change from screening in BMD measured at the spine, the femur, the femoral neck and the trochanter of the hip at 240 weeks.

Study procedures were as follows:

Visit (Weeks)	Treatment Phase						Post-Treatment Phase			
	Screen	0	24	48	72	96	24	48	96	
ALL SUBJECTS:										
Medical History	X									
Non-Investigational Medication	X									
Activity/Dietary Calcium Inquiry	X		X	X	X	X	Every 24 wks thru wk 240	X	X	X
Physical Exam	X			X	X	X	Every 48 wks thru wk 240	X	X	X
Pelvic Exam	X			X	X	X	Every 48 wks thru wk 240	X	X	X
Cervical Cytology	X			X	X	X	Every 48 wks thru wk 240	X	X	X
Bone Mineral Density (Spine and Hip)	X		X	X	X	X	Every 48 wks thru wk 240	X	X	X
Pregnancy Test	X									
Serum Estradiol	X		X	X		X	Every 48 wks thru wk 240	X	X	X
Osteocalcin	X		X	X		X	Every 48 wks thru wk 240	X	X	X
Serum Chemistry Profile	X		X	X		X	Every 48 wks thru wk 240	X	X	X
Lipids	X		X	X		X	Every 48 wks thru wk 240	X	X	X
Collagen Crosslinks	X		X	X		X	Every 48 wks thru wk 240	X	X	X
Thyroid Profile and Thyroid Stimulating Hormone	X			X		X	Every 48 wks thru wk 240	X	X	X
NON-EXPOSED SUBJECTS:										
Interval History:										
Non-Investigational Medication		X	X	X	X	X	Every 24 wks thru wk 240	X	X	X
Medical Event Form			X	X	X	X	Every 24 wks thru wk 240	X	X	X
Vital signs (Weight and Blood Pressure)		X	X	X	X	X	Every 24 wks thru wk 240	X	X	X
Pregnancy Test		As needed.								
EXPOSED SUBJECTS:										
DEPO-PROVERA Contraceptive Injection	Every 12 weeks: Week 0 through Week 228									
Interval History:										
Non-Investigational Medication	Every 12 weeks: Week 0 through Week 240							X	X	X
Medical Event Form	Every 12 weeks: Week 12 through Week 240							X	X	X
Vital signs (Weight and Blood Pressure)	Every 12 weeks: Week 0 through Week 240							X	X	X
Pregnancy Test	EXPOSED SUBJECTS: If injection interval is > 14 weeks.									

3.3 Results:

3.3.1 Subject Disposition:

Table 1 summarizes subject disposition. The DMPA-SC arm had a higher dropout rate than the control arm.

Table 1. Subject Disposition

Population	DEPO-PROVERA	Control
Enrolled	248	360
Received study medication	248	0
Completed study medication	42	118
ITT*	228	310
Reported post treatment data	91	138
Completed 96 week follow-up	44	87

*ITT = Intent to Treat: Subject should be enrolled into the study, have a measure at screening or baseline and at least one post-baseline measurement for any efficacy endpoint.

Source: Table on p. 36 of Study Report for Study 234

Table 2 shows the reasons for withdrawal. There were more withdrawals related to adverse events in the DMPA-IM group.

Table 2. Reasons for Withdrawal from Study 234

Reason	Treatment Phase n(%)		Post-Treatment Phase	
	DEPO- PROVERA n(%) N=248	Control n(%) N=360	DEPO- PROVERA n(%) N=248	Control n(%) N=360
Total withdrawn	206 (83)	242 (67)	47 (19)	51 (14)
Subject request	75 (30)	69 (19)	22 (8.9)	19 (5.3)
Non-serious medical event	62 (25)	16 (4.4)	9 (3.6)	4 (1.1)
Subject lost to follow-up	47 (19)	116 (32)	12 (4.8)	23 (6.4)
Ineligible after medication started	7 (2.8)	0	1 (0.4)	0
Protocol non-compliance	6 (2.4)	22 (6.1)	0	2 (0.6)
Serious medical event	1 (0.4)	1 (0.3)	1 (0.4)	0
Missing	0	0	1 (0.4)	2 (0.6)
Other	8 (3.2)	18 (5.0)	1 (0.4)	1 (0.3)

Source: Table on p.37 of Study Report for Study 234

Comment: Review of the listing of discontinuations related to adverse events did not reveal any discontinuations for loss of BMD.

3.3.2 Demographics:

Table 3 shows that the 2 groups were similar demographically.

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Table 3. Baseline Demographic Characteristics

Characteristic	DEPO-PROVERA N=248	Control N=360
Age in years		
Mean (SD)	30 (3.15)	32 (2.91)
Range	24-36	25-36
Race, n (%)		
White	180 (79)	245 (79)
Black	27 (12)	38 (12)
Oriental/Asian	3 (1.3)	1 (0.3)
Hispanic	17 (7.5)	26 (8.4)
Other	1 (0.4)	0
Weight (kg)		
Mean (SD)	67 (6.88)	65 (6.44)
Body Mass Index (kg/m²)		
Mean (SD)	25 (3.82)	24 (3.79)
Range	16-35	17-36
Smoking status, n (%)		
Non-smoker	170 (75)	257 (83)
< one pack/day	52 (23)	45 (15)
> one pack/day	6 (2.6)	8 (2.6)
Previously taken oral contraception? n (%)		
Yes	209 (92)	267 (86)
No	19 (8.3)	43 (14)
Physical exertion (hours/week)		
Mean (SD)	25 (22.64)	23 (20.93)
Range	0-98	0-90
Recreational activities (hours/week)		
Mean (SD)	3.8 (4.26)	3.8 (4.23)
Range	0-40	0-40
Calcium intake (mg/day)		
Mean (SD)	1042 (716.43)	839 (574.79)
Range	60-5781	60-3633

Source: Modified from table on p. 39 of Study Report for Study 234

3.3.3 Exposure:

Total DMPA-IM exposure for the ITT group was 534 women-years. (See Table 4 for exposure by numbers of injections.)

Table 4. Exposure as Number of Injections Received in ITT Group

Number of Injections	N	% of 228 Subjects
1	9	3.9
2	33	14.5
3	20	8.8
4	21	9.2
5	16	7.0
6	11	4.8
7	11	4.8
8	10	4.4
9	7	3.1
10	6	2.6
11	3	1.3
12	4	1.8
13	10	4.4
14	3	1.3
15	4	1.8
16	1	0.4
17	3	1.3
18	4	1.8
19	6	2.6
20	42	18.4
21	4	1.8

Source: Table T3.1, p. 99, Study Report for Study 234

3.3.4 Efficacy Endpoint:

Table 5 shows that women in the DMPA-IM group consistently and progressively lost BMD compared with the control group. There was partial recovery after treatment.

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Table 5. Percentage Change from Baseline in BMD (ITT Population)

Visit	DMPA-IM		Control		Difference [DMPA-IM – Control] Adjusted* mean change (95% CI)	P-Value
	n	Mean (SD)	n	Mean (SD)		
Femur Total BMD						
Week 24	108	-0.72 (2.07)	144	0.57 (2.32)	-1.34 (-1.93 - -0.76)	<0.001
Week 48	88	-1.56 (2.64)	125	0.95 (1.89)	-2.58 (-3.22 - -1.94)	<0.001
Week 96	57	-3.06 (2.93)	94	0.69 (3.12)	-3.59 (-4.64 - -2.55)	<0.001
Week 144	42	-3.89 (3.37)	77	-0.06 (2.72)	-3.66 (-4.80 - -2.53)	<0.001
Week 192	31	-4.52 (3.89)	70	-0.02 (2.76)	-4.34 (-5.75 - -2.93)	<0.001
Week 240	21	-5.16 (3.60)	65	0.19 (3.18)	-5.47 (-7.10 - -3.84)	<0.001
Week 24 post	36	-1.21 (4.04)	50	0.40 (3.04)	-1.61 (not done)	ND
Week 48 post	31	-0.70 (4.44)	54	0.65 (3.62)	-1.74 (-3.61 - 0.12)	0.066
Week 96 post	25	-0.20 (3.41)	43	0.84 (3.69)	-2.08 (-4.13 - -0.03)	0.047
Spine Total BMD						
Week 24	178	-1.41 (2.37)	291	0.19 (2.75)	-1.87 (-2.37 - -1.36)	<0.001
Week 48	135	-2.86 (2.47)	253	0.22 (2.81)	-3.11 (-3.72 - -2.51)	<0.001
Week 96	94	-4.11 (2.68)	197	0.29 (2.57)	-4.43 (-5.10 - -3.75)	<0.001
Week 144	71	-4.89 (3.16)	159	0.31 (2.75)	-5.21 (-6.06 - -4.35)	<0.001
Week 192	59	-4.93 (3.41)	137	0.35 (3.00)	-5.17 (-6.18 - -4.17)	<0.001
Week 240	33	-5.38 (3.57)	105	0.43 (3.27)	-5.65 (-7.06 - -4.23)	<0.001
Week 24 post	56	-3.48 (3.98)	92	0.33 (3.43)	-3.81 (not done)	ND
Week 48 post	45	-2.42 (3.73)	87	0.28 (3.53)	-2.82 (-4.26 - -1.38)	<0.001
Week 96 post	41	-1.19 (3.88)	66	0.47 (3.66)	-2.04 (-3.71 - -0.38)	0.017
Femoral Neck BMD						
Week 24	179	-1.24 (3.29)	289	0.22 (4.61)	-1.60 (-2.42 - -0.78)	<0.001
Week 48	137	-2.85 (3.66)	254	0.28 (4.34)	-3.23 (-4.10 - -2.35)	<0.001
Week 96	95	-3.99 (4.03)	195	-0.22 (4.75)	-3.50 (-4.66 - -2.34)	<0.001
Week 144	72	-4.80 (4.39)	159	-0.23 (3.87)	-4.45 (-5.63 - -3.27)	<0.001
Week 192	58	-5.90 (4.55)	138	-0.53 (4.03)	-4.79 (-6.12 - -3.45)	<0.001
Week 240	34	-6.12 (4.68)	106	-0.27 (5.22)	-5.75 (-7.86 - -3.64)	<0.001
Week 24 post	57	-2.99 (4.77)	92	-0.51 (4.46)	-3.5 (not done)	ND
Week 48 post	45	-3.04 (4.92)	86	-0.27 (4.90)	-2.88 (-4.78 - -0.98)	0.003
Week 96 post	42	-3.11 (4.28)	69	-0.36 (5.89)	-3.09 (-5.42 - -0.77)	0.010
Femoral Trochanter BMD						
Week 24	179	-1.22 (3.34)	289	0.60 (4.67)	-2.04 (-2.86 - -1.22)	<0.001
Week 48	137	-2.48 (4.38)	254	0.67 (4.47)	-3.30 (-4.23 - -2.37)	<0.001
Week 96	95	-4.29 (4.12)	195	0.41 (4.36)	-4.68 (-5.75 - -3.61)	<0.001
Week 144	72	-5.12 (4.74)	159	0.70 (4.30)	-5.82 (-7.12 - -4.53)	<0.001
Week 192	58	-5.37 (4.55)	138	0.00 (4.49)	-5.43 (-6.84 - -4.02)	<0.001
Week 240	34	-6.32 (5.55)	106	0.33 (4.62)	-6.55 (-8.46 - -4.65)	<0.001
Week 24 post	57	-1.70 (6.40)	92	0.50 (4.97)	-2.2 (Not done)	ND
Week 48 post	45	-0.83 (6.53)	86	0.68 (5.59)	-1.59 (-3.83 - 0.65)	0.161
Week 96 post	42	-0.43 (6.06)	69	0.93 (5.29)	-1.82 (-4.11 - 0.46)	0.116

*Covariates included in the analysis were race, smoking status, BMI, dietary calcium, the screening BMD, and exercise level.
Source: Modified from Applicant's table on p. 44 of Study Report for Study 234

Comments: Post-treatment BMD statistics include women who had varying amounts of treatment and therefore do not represent the amount of recovery for women exposed to treatment for 240 weeks.

Bone loss appears progressive. That is, the data do not indicate that % change in bone loss plateaus after any time interval.

Recovery of bone mass is incomplete 96 weeks (almost 2 years) after the last dose of DMPA.

Recovery is not clearly progressive from these numbers but it is possible that women with the least recovery were more likely to have longer follow-up.

When only the 37 DMPA-treated women with all 3 follow-up visits are evaluated, BMD recovery appears progressive, but the number of subjects is small. (See Table 6.)

Table 6. BMD Recovery in Subjects Treated with DMPA Who Had All 3 Follow-up Visits

Time Post-treatment	Spine Total BMD	Femur Total	Femoral Neck	Femoral Trochanter
	BMD % Change from Baseline (N)			
Week 24 Post	-4.4 (37)	-1.6 (26)	-4.0 (37)	-2.6 (37)
Week 48 Post	-2.8 (37)	-0.9 (26)	-3.4 (37)	-1.5 (37)
Week 96 Post	-1.3 (33)	-0.2 (23)	-3.0 (34)	-0.1 (34)

Source: Prepared by reviewer from Applicant's dataset called DBMDREAD.xpt using JMP software.

Similarly, when only the 11 DMPA-treated women who completed treatment with 20 doses of DMPA and had all 3 follow-up visits are evaluated, BMD recovery appears progressive, but the number of subjects is small. (See Table 7.)

Table 7. BMD Recovery in Subjects Who Had 20 Injections of DMPA and All 3 Follow-up Visits

Time	Spine Total BMD	Femur Total	Femoral Neck	Femoral Trochanter
	BMD % Change from Baseline (N)			
Week 240 Treatment	-6.1 (10)	-5.1 (6)	-7.1 (10)	-8.2 (10)
Week 24 Post	-5.0 (11)	-2.4 (7)	-6.5 (11)	-5.2 (11)
Week 48 Post	-3.7 (11)	-1.8 (7)	-6.2 (11)	-4.4 (11)
Week 96 Post	-3.0 (10)	-1.3 (7)	-5.8 (11)	-3.1 (11)

Source: Prepared by reviewer from sponsor's dataset called DBMDREAD.xpt using JMP software

Comments: Both tables suggest that

- BMD recovery is progressive
- recovery at the femoral neck is slower than at other sites
- recovery was incomplete 96 weeks following the last injection

However, numbers of subjects were small.

Table 8 shows that, on average, recovery was complete at 96 weeks for women who received treatment for 1 year or less. However, on average, women who had more than 1 year of treatment did not have complete recovery, and longer duration of treatment was associated with less recovery at 96 weeks post-treatment.

Table 8. Recovery at Week 96 Post-treatment by Number of Injections

Number of Injections	Spine Total BMD % Change from Baseline (N)	Femur Total BMD % Change from Baseline (N)	Femoral Neck BMD % Change from Baseline (N)	Femoral Trochanter BMD % Change from Baseline
1-4	1.26 (10)	0.15 (6)	0.02 (10)	2.29 (10)
5-8	-0.46 (9)	0.89 (7)	-2.10 (9)	1.76 (9)
9-12	0.33 (3)	0.20 (2)	-3.13 (3)	-1.27 (3)
13-16	-3.70 (3)	0.00 (2)	-3.90 (3)	-1.93 (3)
17-20	-2.94 (16)	-1.58 (8)	-5.34 (17)	-2.77 (17)
20	-3.13 (12)	-1.34 (7)	-5.38 (13)	-2.54 (13)

Source: derived from sponsor's Tables 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6 in Study Report for Study 234, analysis requested by reviewer

To see if women who had osteopenia or osteoporosis in the DMPA-IM group recovered BMD, the following subgroups were evaluated:

1. T-score > -1 at any time during treatment (normal)
2. T-score ≤ -1 , but > -2.5 (osteopenia) at any time during treatment
3. T-score ≤ -2.5 (osteoporosis) at any time during treatment

Table 9 shows that, on average, women who had osteopenia during the treatment phase had substantial recovery of BMD in the follow-up phase, although the number of women who had both osteopenia and follow-up BMD measurements was small.

Table 9. Recovery in Spine Total BMD% Change from Baseline by Spinal T-Score Subgroups, DMPA-IM Group

Subgroup by Spinal T-score at Any Time on Treatment	Mean Week 24 Post-treatment	Week 48 Post-treatment	Week 96 Post-treatment	Number of Observations on Treatment
	Mean Spine Total BMD % Change from Baseline			
Normal	-3.3 (N=52)	-2.5 (N=40)	-1.4 (N=37)	218
Osteopenia	-5.8 (N=12)	-2.3 (N=12)	-0.74 (N=10)	57
Osteoporosis				0

Source: Created by reviewer from Applicant dataset DBMDREAD.xpt, Study Report for Study 234, using JMP software

To see if recovery was similar for women losing different amounts of BMD, women who received DMPA-IM were subgrouped into 5 categories based on % change from baseline in

spine bone mineral density on treatment. Table 10 shows less recovery among women with the greatest BMD % change from baseline.

Table 10. Recovery in Spinal % Change from Baseline by % Change from Baseline Subgroups, DMPA-IM

Spinal % Change from Baseline on Treatment (=x)	Week 24 Post-Treatment	Week 48 Post-Treatment	Week 96 Post-Treatment	Number of Observations on Treatment
	Mean Spine Total BMD % Change from Baseline			
$x \geq -2.5\%$	-2.8 (N=42)	-1.6 (N=36)	-0.025 (N=32)	144
$-2.5\% > x \geq -5\%$	-4.6 (N=37)	-3.4 (N=31)	-2.1 (N=30)	125
$-5\% > x \geq -7.5\%$	-5.9 (N=22)	-4.6 (N=20)	-3.3 (N=18)	67
$-7.5\% > x \geq -10\%$	-7.1 (N=8)	-7.0 (N=8)	-5.3 (N=9)	26
$x < -10\%$	-8.0 (N=4)	-10.0 (N=2)	-7.1 (N=2)	9

Source: Created by reviewer from Applicant dataset DBMDREAD.xpt, Study Report for Study 234, using JMP software

To see if the bone loss led to detectable clinical consequences, adverse events related to fractures were evaluated. Table 11 lists the 5 fractures reported as serious adverse events (SAEs) on treatment.

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Table 11. Subjects with Fractures Recorded as SAEs during Treatment

Treatment	Subject	Fracture	Time in Study to Event	BMD Changes
Depo-Provera	61010	Compression fracture t11 – pain Possible nondisplaced fracture of sacrum pain, rollerblading fall	66 weeks	At Week 48, spinal T-score was -1.767 and spinal change from baseline was -3.7%.
Depo-Provera	101004	Fracture left femur	138 weeks	At Week 144, femur change from baseline was -5.9%, femur T-score was -0.693
Depo-Provera	111014	Fractured left patella	41 weeks	At Week 48, femur change from baseline was -3%, femur T-score was 0.113
Control	162013	Compound fracture right ankle	86 weeks	At Week 96, the spinal T-score was -.850 and spinal change from baseline was -0.9.
Control	102004	Left ankle fracture	36 weeks	At week 48, femur T-score was 0.348 and femur change from baseline was -2.9%.

Source: Modified from Table on page 59 of Applicant's Study Report for Study 234

Comment: There were no "spontaneous" fractures, and too few fractures to detect a difference between study groups.

3.3.5 Safety Results

There were no deaths. 5.9% of subjects in the Depo-Provera group and 9.6% of subjects in the control group had SAEs. There were no pregnancies, thrombotic events, or breast cancers in women using DMPA-IM. Review of SAEs did not reveal any unexpected events.

Reasons for treatment discontinuations were consistent with previous studies. (See Table 12.) There were no reports of discontinuations for adverse events related to BMD problems.

Table 12. Treatment Discontinuation Adverse Events Preferred Terms Reported by >1% of Subjects

Body System Adverse Event	DEPO-PROVERA n (%)
Number of Subjects	238
Subjects with at least one treatment discontinuation AE	68
Investigations	33 (14)
Weight increased	33 (14)
Psychiatric disorders	24 (10)
Depression NEC	5 (2.1)
Libido decreased	11(4.6)
Skin and subcutaneous tissue disorders	12 (5.0)
Acne NOS	6 (2.5)
Alopecia	4 (1.7)

% = (n/total reported) x 100

Abbreviations: NEC = not elsewhere classified

Source: Table on page 60 of Study Report for Study 234, Section 7.4.2.3

Weight changes merit comment because weight gain is a common problem for some DMPA users. Table 13 shows that women using DMPA-IM gained more weight than women in the control group. Although the differences between groups disappeared in the recovery period, the post treatment differences are unreliable because the DMPA group included women who were in the treatment phase of the study for varying amounts of time, and the control group included only women who completed 240 weeks in the "treatment" phase.

Table 13. Change from Baseline in Body Weight every 48 Weeks (ITT)

Visit	DEPO-PROVERA		Control		Difference DEPO-PROVERA – Control adjusted mean change in kg (95% CI)	P-Value
	n	Mean in kg (SD)	n	Mean in kg (SD)		
Week 48	141	1.25 (4.14)	261	0.37 (3.71)	1.08 (0.25 – 1.91)	0.011
Week 96	97	2.10 (5.36)	205	1.11 (4.28)	1.03 (-0.18 – 2.23)	0.094
Week 144	76	3.03 (6.15)	169	1.39 (5.19)	1.62 (-0.01 – 3.24)	0.051
Week 192	59	4.32 (6.73)	137	2.34 (5.77)	2.13 (0.17 – 4.09)	0.034
Week 240	41	5.09 (7.04)	114	2.93 (6.23)	2.19 (-0.28 – 4.67)	0.082
Week 24 post	66	4.84 (6.60)	102	3.51 (7.50)	1.40 (-1.01 – 3.81)	0.251
Week 48 post	51	4.51 (7.15)	93	3.75 (6.92)	0.22 (-2.42 – 2.86)	0.871
Week 96 post	45	4.96 (7.55)	86	4.34 (7.94)	-0.18 (-3.31 – 2.95)	0.911

Source: Applicant's Table on page 48 of study report for Study 234

Comment: The weight gain seen in Depo-Provera users is consistent with the current label.

Looking only at women who had 20 injections of DMPA and therefore completed 240 weeks of treatment, the week 96 post treatment weight gain 6.41 kg (SD=10.68, N=14),

compared with 4.34 kg in the control group. Therefore the study does *not* show recovery from DMPA-associated weight gain by 96 weeks post treatment.

4. Conclusions:

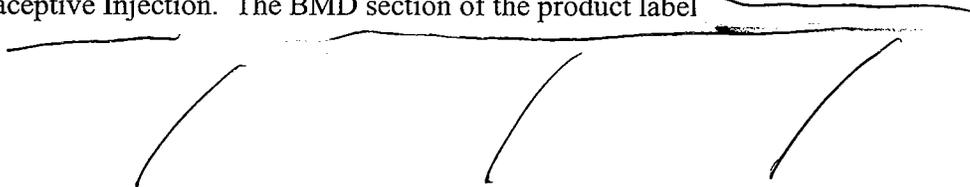
Women who used DMPA-IM experienced progressive BMD loss every year over 5 years. There was partial recovery over 96 weeks of post-treatment follow-up.

Exploratory analyses of the BMD data suggest that

- on average, women who had more than 1 year of treatment did not have complete recovery at 96 weeks post treatment
- longer duration of treatment was associated with less recovery at 96 weeks post treatment
- BMD recovery was progressive
- recovery at the femoral neck was slower than at other sites

The expected weight gain was observed. Weight gain differences appeared to persist at 96 weeks post treatment for women matched for the same length of time in the study, although numbers of subjects were small.

This study report satisfies the clinical Phase 4 postmarketing commitment for Depo-Provera Contraceptive Injection. The BMD section of the product label



13.2 Label

The following sections of labeling contains highlights of this reviewer's recommendations about labeling changes from the Applicant's proposed package insert. Single ~~strikeout~~ marks text for removal, and single underline marks text for addition. Explanatory comments are italicized. In addition to making conceptual changes, I tried to simplify language. FDA's Division of Drug Marketing, Advertising, and Communications provided comments in a review dated December 24, 2003, and I also addressed these comments in my review of the package insert.

The label will undergo additional changes during secondary review and discussions with the company. FDA and the Applicant had not yet agreed on a proprietary name when I did this labeling review (June 30, 2004).

13 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Leslie Ann Furlong
7/29/2004 01:47:40 PM
MEDICAL OFFICER

Scott Monroe
7/29/2004 02:36:04 PM
MEDICAL OFFICER

I concur with Dr. Furlong's recommendation regarding approvability.

Clinical Consultation

FROM: Theresa Kehoe, M.D.
Division of Metabolic and Endocrine Drug Products, HFD-510

THROUGH: David Orloff, MD Director, DMEDP

TO: Lesley Furlong, M.D., Medical Officer, Reproductive and Urologic, HFD-580
Charlene Williamson, Project Manager, Reproductive and Urologic, HFD-580

SUBJECT: Depo-Provera Contraceptive Injection and Bone Health

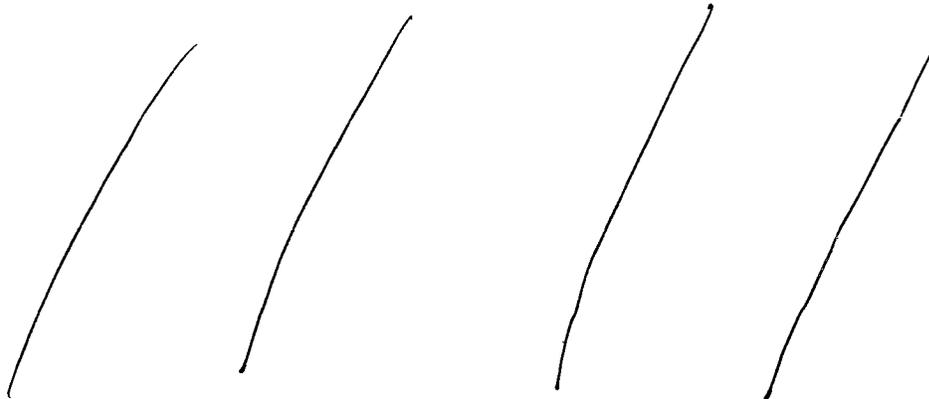
DATE CONSULT RECEIVED: May 10, 2004

DATE CONSULT COMPLETED: June 21, 2004

Material Received for Review: The consultation package included the electronic submission for NDA 21-583, including the final study report for study 267BMD, the final study report for study 234 and the interim study report for study 261.

Administrative Background: The Division of Reproductive and Urologic Drug Products seeks advice regarding a new formulation of Depo-Provera Contraceptive injection.

Requested action for DMEDP: Specific questions:

Four large, handwritten, diagonal scribbles, likely representing redacted information or a signature, arranged in a horizontal row.

Background: Medroxyprogesterone acetate (pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6 α)) (MPA) is a synthetic analogue of 17 α -hydroxyprogesterone. It has been marketed for many years in oral (PROVERA® Tablets) and intramuscular injection (DEPO-PROVERA®, DMPA-IM) formulations. The DMPA-IM injectable product is currently approved for use as a contraceptive and is given at a dose of 150 mg every 3 months. Pfizer has developed a new subcutaneous formulation of depot MPA (DMPA-SC) for the prevention of pregnancy in women.

The mechanism of action of DMPA is through inhibition of the hypothalamic-pituitary axis and gonadotropin secretion. Alteration of the axis results in prevention of follicular maturation and ovulation. One other consequence of DMPA use is estrogen deficiency. It is well known that postmenopausal estrogen deficiency is a major cause of bone loss in older women. Estrogen deficiency in young premenopausal women is of concern because maximum bone mineral accrual occurs during the teenage years with peak bone mass achieved between the ages of 20 and 30 years. Published literature suggests that DMPA use negatively affects BMD.

The focus of this review is the effect of DMPA on bone mineral density from three separate studies: study 267BMD, study 234 and the interim study report for study 261.

Study 839-FEH-0012-267BMD: Phase III Contraception Study of Depot Medroxyprogesterone Acetate Subcutaneous Injection (DMPA-SC) in Women of Childbearing Potential in the Americas: Substudy Comparing the Effects of DMPA-SC and DMPA-Intramuscular (IM) in Subjects Scheduled for Bone Mineral Density and Hormone Measurements (2 Year Report)

This study is a 3-year substudy (referred to as study 267BMD) of study 839-FEH-0012-267. Study 267BMD was conducted in a separate group of subjects (ages 18 to 35 years) to assess reduction in bone mineral density (BMD), which is known to accompany estrogen deficiencies in some populations. Study 267 was a 12-month open-label study conducted to determine the contraceptive efficacy, safety, and subject satisfaction of a subcutaneous formulation of DMPA in sexually active women between the ages of 18 and 49.

Objectives:

Primary:

The primary safety objective was to evaluate BMD changes in women receiving either DMPA-SC or DMPA-IM for up to 3 years of treatment with the 1-year time point being the interim analysis time point and the 2-year time point being the primary analysis time point.

The primary efficacy objective was to assess the contraceptive efficacy of DMPA-SC and DMPA-IM for up to 3 years with 1 and 2 year analysis time points as noted above.

Secondary:

The secondary safety objectives of this study were to assess the standard safety measurements of DMPA-SC and DMPA-IM contraceptive injection administered every 3 months for up to 3 years.

Secondary objectives also included assessment of subject experience with the treatment to which she was assigned, aspects of the treatment she liked and disliked, and the likelihood of selecting that method for future contraception.

Pharmacokinetic evaluations for MPA minimum plasma concentration (C_{min}) level determination was also performed

Study Design: Study 267BMD was a randomized, evaluator-blinded, 2-year comparison of approximately 500 subjects (250 subjects receiving DMPA-IM and 250 subjects receiving DMPA-SC) designed to assess BMD loss at 1 and 2 years relative to baseline. BMD loss was assessed by comparing DXA measurements taken at baseline and after 1 and 2 years of study treatment.

This study was an evaluator-blinded study. The principal investigator/evaluator, as well as any designated subinvestigators at each site, were blinded to the randomization of each subject. In order to maintain the evaluator blinding, a qualified, independent injectionist administered the study medication. The injectionist received the study syringes, maintained the randomization code, and administered the study drug.

Population: Approximately 500 subjects at selected sites in the BMD substudy were randomized in a 1:1 ratio to either DMPA-SC 104-mg or DMPA-IM 150-mg injection.

Inclusion Criteria

- *Being between the ages of 18 and 35 years*
- *Being sexually active*
- *Desiring long-term contraception (including women who currently used oral, intrauterine device [IUD], or barrier methods and wished to switch to DMPA contraception)*
- *Having been off oral contraceptives for the 2 months prior to enrollment when applicable, and having used a barrier (excluding IUD) method of contraception or having been sexually inactive during this prescreening period*
- *Having a negative urine pregnancy test*
- *Willing to rely upon DMPA-SC or DMPA-IM for contraception for at least 2 years (8 doses total)*
- *Menstruating regularly during the 3 months (cycle length of 25 to 35 days) prior to enrollment*
- *Willing to sign informed consent*
- *Willing and able to comply with the study-specific procedures*

Exclusion Criteria

- *Having been treated with oral contraceptives, contraceptive implants, or hormone medicated IUDs in the past 2 months or having had DMPA-IM administered in the 10 months prior to enrollment*
- *Having an increased risk of osteoporosis, defined by either lumbar spine or femur T-score of less than -1.0 or having a history of pathologic and/or compression fracture*
- *Having abnormal cervical cytology (Papanicolaou [Pap] test required within 12 months prior to enrollment), including any of the following results: atypical glandular cells of undetermined significance (AGUS), low-grade squamous intraepithelial lesions (LGSIL) or high-grade squamous intraepithelial lesions (HGSIL). However, subjects with a finding of atypical squamous cells of undetermined significance (ASCUS) were permitted in this study*
- *Having a history of breast cancer or having results from a mammogram that were suspicious of malignant disease or that required a 6-month follow-up*
- *Having a well-documented history of a thrombotic event such as stroke or venous thromboembolism (deep vein thrombosis or pulmonary embolus; this did not include superficial thrombophlebitis)*
- *Having undiagnosed abnormal genital bleeding*
- *Having a known or suspected pregnancy*
- *Having a history of alcoholism or other drug abuse within the 5 years prior to enrollment*
- *Having confirmed uncontrolled hypertension (ie, systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg) Having hypersensitivity to study medications or contraindication to progestin (as determined by the investigator)*
- *Concurrently using other investigational medication(s)*
- *Having previously participated in this study*
- *Having active hepatic or renal disease, or having a history of either, where hepatic disease was defined as having an aspartate aminotransferase/serum glutamate oxaloacetate transaminase (AST/SGOT) or alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT) or total bilirubin elevated by 2.5 times the upper limit of normal. Renal disease was defined as having a creatinine value of greater than 1.8 mg/dL.*

- *Having insulin-dependent diabetes mellitus or noninsulin-dependent diabetes mellitus that was poorly controlled*
- *Having had a tubal ligation, a known diagnosis of infertility, or having partner(s) who were sterile*
- *Taking Aminoglutethimide (anticancer agent)*
- *Having a condition (e.g., serious medical disease, psychiatric disturbances, or alcoholism) that might make strict compliance with the study instructions impossible*

COMMENT: Women with baseline low bone mass or fracture were appropriately excluded from the study. However, subjects with other metabolic bone diseases or medications that may affect bone density were not excluded from enrollment into the study.

Study Medication: In this study, 267BMD, subjects were randomized to receive either 104-mg of DMPA-SC or 150-mg of DMPA-IM at visit 1 and every 3 months thereafter for up to 2 years.

COMMENT: Baseline calcium and vitamin D supplementation was not required in this study. Other concomitant medications that may have affected BMD assessments (e.g., multivitamins, and/or other mineral supplements) were neither required nor prohibited by the protocol.

Study Methods: The primary safety variable was percent change from baseline for BMD after 2 years of treatment with either DMPA-SC or DMPA-IM. Lumbar spine (L₁-L₄) and femur (total femur) Bone Mineral Density (BMD) results were evaluated by Dual-energy X-ray Absorptiometry (DXA) at a screening visit for baseline data, at 1 year, and at the end of 2 years. Subjects were to be excluded from participating in the study if either their lumbar spine or femoral DXA resulted in a T-score of less than -1.0. The T-score was defined as the number of standard deviations from the mean BMD of a young normal Caucasian female reference population. The Caucasian reference group was used for all ethnicities.

BMD quality control consisted of centralized analysis and reporting of all BMD scans acquired by trained — research associates in order to maximize the precision and reproducibility of reported results. Instrument quality control and cross-calibration using a dedicated — was also performed on each instrument within the study group.

Withdrawal criteria: Treatment was discontinued at any time if the investigator considered it medically necessary or if the subject wished to do so. If any subject became pregnant or if the subject discontinued treatment to become pregnant, the pregnancy was followed to term.

Statistical Analyses: Changes in BMD at 1 and 2 years relative to baseline were compared between treatment groups. The BMD substudy was designed to show the superiority of DMPA-SC over DMPA-IM in reducing the amount of BMD loss after 2 years of treatment, with an interim analysis after 1 year of treatment. The BMD assessments for the treatment groups were compared at baseline and on the percent change from baseline at 1 year and 2 years using the Kruskal-Wallis test. Within-treatment group percent changes were compared using the Wilcoxon signed rank test. The BMD percent change from baseline analysis in the 1-year interim analysis reports was conducted at a significance level of 0.001 (i.e. a p-value of less than or equal to 0.001 was considered statistically significant for between treatment differences). The BMD

percent change from baseline analysis in this 2-year report was conducted at a significance level of 0.049 for between treatment differences since the overall type I error for the primary analysis time point at 2 years was to be ≤ 0.050 . The intent-to-treat (ITT) population was used for all analyses.

Protocol Amendments: Changes to the protocol were implemented with 10 amendments and 1 administrative protocol change. Only Amendments 1, 2, 10, A, B, C, and G and the administrative protocol change applied to the BMD substudy. Notable changes include:

- Statistical sections were expanded to describe BMD analysis, subgroup analyses of data from women taking medications that are metabolized by the CYP3A4 pathway, data from self-injection analysis (applicable to study 267 only), and data from barrier contraceptive use. (Amendment 1, February 2001)
- An extension to the BMD substudy for a further year with the same medication as previously used in the first 2 years of the study where further BMD data collection after 3 years of treatment or after 1 year off medication, if the subject did not elect to continue treatment. (Amendment 10, April 2003)
- The administrative protocol change clarified the unblinding of the treatment assignments after the second year of the study (the primary time point for evaluating the change in BMD). After the second year, the treatment assignments (both at the treatment group level and for an individual subject) were unblinded for use in this study report summarizing this data for regulatory submission purposes. However, since the subjects were still ongoing in the trial, the study remained evaluator-blinded through the third year (end of study). (December 2003)

Results

Patient Disposition: The ITT population consisted of 534 subjects (of the 535 subjects enrolled): 266 subjects received DMPA-SC and 268 subjects received DMPA-IM. As outlined in the table below, a total of 224 subjects (116 subjects in the DMPA-SC group and 108 subjects in the DMPA-IM group) completed the second year.

Study 267BMD: Disposition of Subjects at 2 Years		
	DMPA-SC	DMPA-IM
Enrolled	267	268
Treated	266	268
Discontinued	150	160
AE	46	59
Protocol Violations	11	5
Consent w/d	50	37
Lost to f/u	43	59
Completed 2 years	116	108

Demographics: Demographic characteristics were similar between the 2 treatment groups. The mean age was 25.9 years in the DMPA-SC group and 25.8 years in the DMPA-IM group. Most of the subjects were white (61.3% in the DMPA-SC group and 63.4% in the DMPA-IM group). There was a statistically significant difference ($p=0.032$) between the treatment groups for height. Mean height was 162.6 cm for the DMPA-SC group and 163.8 cm for the DMPA-IM

group. The clinical significance of this height difference is unclear. The mean weight in the DMPA-SC group was 69.3 kg and was 71.2 kg in the DMPA-IM group. The mean BMI values were similar between the 2 groups. The distribution of subjects by geographical location was similar in the 2 treatment groups.

Study 267BMD: Disposition		
Characteristic	DMPA-SC N = 266	DMPA-IM N = 268
Age (years)		
Mean ± SD	25.9 ± 4.9	25.8 ± 4.8
Range	18.0 - 35.9	18.0 - 35.7
< 25, n (%)	122 (45.9)	134 (50.0)
25 to ≤ 35, n (%)	144 (54.1)	134 (50.0)
Race, n (%)		
White	163 (61.3)	170 (63.4)
Black	39 (14.7)	42 (15.7)
Asian/Pacific Islander	10 (3.8)	7 (2.6)
Mixed/Multiracial	54 (20.3)	49 (18.3)
Weight (kg)		
Mean ± SD	69.3 ± 17.7	71.2 ± 19.0
Height (cm)		
Mean ± SD	162.6 ± 6.3	163.8 ± 6.8
Body Mass Index (kg/m²)		
Mean ± SD	26.1 ± 6.1	26.4 ± 6.4
Range	15.6 - 54.0	17.8 - 50.1
≤ 25, n (%)	142 (53.4)	142 (53.0)
> 25 to ≤ 30, n (%)	58 (21.8)	57 (21.3)
> 30, n (%)	65 (24.4)	69 (25.7)
Geographical Location, n (%)		
North America (Canada, US)	205 (77.1)	201 (75.0)
South America (Brazil)	61 (22.9)	67 (25.0)

Concomitant medications: In the DMPA-SC group, 75.6% of subjects reported taking at least 1 concomitant medication after the start of therapy. Concomitant medications taken by 10% or more of subjects in this group included paracetamol (31.2%), ibuprofen (23.3%), ascorbic acid (15.0%), ergocalciferol (14.3%), nicotinamide (14.3%), riboflavin (14.3%), retinol (13.9%), thiamine hydrochloride (13.5%), folic acid (13.2%), and panthenol (13.2%). In the DMPA-IM group, 71.6% (192/268) of subjects reported taking at least 1 concomitant medication after the start of therapy. Concomitant medications taken by 10% or more of subjects included paracetamol (25.7%), ibuprofen (18.7%), ascorbic acid (17.5%), nicotinamide (16.0%), riboflavin (16.0%), ergocalciferol (15.7%), retinol (15.7%), thiamine hydrochloride (14.9%), folic acid (14.6%), and panthenol (14.6%).

COMMENT: A total of 14.3% of subjects in the DMPA-SC group and 15.7% of subjects in the DMPA-IM group reported taking ergocalciferol during the study period. Few subjects (less than or equal to 3.4% of subjects in either group) reported use of calcium, calcium ascorbate, calcium carbonate, calcium citrate, calcium pantothenate, mineral supplements, minerals NOS, multivitamins with iron, or vitamins NOS at any time during the study.

Exposure: Exposure to DMPA-SC and DMPA-IM is summarized in the table below. In the DMPA-SC group, 47.0% (125/266) of subjects received all 8 injections, and in the DMPA-IM group, 44.8% (120/268) of subjects received all 8 injections.

Study 267BMD: Number of Injections Received				
Number of Injections	DMPA-SC N = 266		DMPA-IM N = 268	
	n	%	n	%
1	21	7.9	35	13.1
2	37	13.9	26	9.7
3	24	9.0	23	8.6
4	26	9.8	31	11.6
5	22	8.3	16	6.0
6	7	2.6	9	3.4
7	4	1.5	8	3.0
8	125	47.0	120	44.8

Bone Mineral Density: The primary safety endpoint of this substudy was the percent change from baseline in BMD after 2 years of treatment with DMPA-SC or DMPA-IM.

Median Percent Change from Baseline: The median percent change from baseline for BMD after the first and second year of treatment is summarized in the table below. In general, subjects in both treatment groups had modest decreases in femur and spinal BMD during the first year of treatment with BMD loss increasing further during the second year of treatment. At Year 2, the median percent change from baseline in the femur was -3.3% in the DMPA-SC group and -3.6% in the DMPA-IM group. At the lumbar spine, the median percent change from baseline at 2 years was -4.3% in the DMPA-SC group and -5.0% in the DMPA-IM group. Overall, at 24 months, 12% of subjects receiving DMPA developed low bone mass (T score less than -1.0) at the lumbar spine.

Study 267BMD: BMD Percent Change from Baseline (ITT Population)				
Visit		DMPA-SC	DMPA-IM	p-value
Baseline	Femur			
	N	264	267	
	Baseline BMD (g/cm ²)	1.03	1.03	0.922
	Baseline T score			
	Spine			
	N	264	268	
Month 12	Baseline BMD (g/cm ²)	1.16	1.15	0.840
	Baseline T score			
	Femur			
	N	166	162	
	Median Percent Change from Baseline	-1.4	-2.0	0.165
	Range	-19.9, 4.9	-18.0, 4.3	
Month 12	T score less than -1.0 [n (%)]	1 (0.6)	5 (3.1)	
	Spine			
	N	166	162	
	Median Percent Change from Baseline	-2.4	-3.4	0.021
	Range	-9.9, 4.2	-10.7, 3.5	

Study 267BMD: BMD Percent Change from Baseline (ITT Population)				
Visit		DMPA-SC	DMPA-IM	p-value
	T score less than -1.0 [n (%)]	14 (8.4)	18 (11.1)	
Month 24	Femur			
	N	106	101	
	Median Percent Change from Baseline	-3.3	-3.6	0.724
	Range	-22.7, 8.1	-18.3, 6.6	
	T score less than -1.0 [n (%)]	5 (4.7)	6 (5.9)	
	Spine			
	N	106	102	
	Median Percent Change from Baseline	-4.3	-5.0	0.191
Range	-10.8, 3.4	-11.8, 4.8		
	T score less than -1.0 [n (%)]	13 (12.3)	12 (11.8)	
Kruskal-Wallis test, significance defined at $p \leq 0.049$				
† Wilcoxon signed rank test, significance defined at $p \leq 0.050$				

Categorical Changes in BMD: The table below outlines the categorical changes in hip and spine BMD from baseline through 1 and 2 years of treatment. For Year 2, 13.2% (14/106) of DMPA-SC subjects and 15.8% (16/101) of DMPA-IM subjects had increases in femur total BMD, whereas, 86.8% (92/106) of DMPA-SC subjects and 84.2% (85/101) of DMPA-IM subjects had either no change or decreases in femur total BMD. At 2 years, 34.0% (36/106) of DMPA-SC subjects were in the same spine T-score category as they were at baseline, 63.2% (67/106) shifted to a lower T-score, and 2.8% (3/106) shifted to a higher T-score. For DMPA-IM subjects, 29.4% (30/102) were in the same spine T-score category as they were at baseline, 66.7% (68/102) shifted to a lower T-score, and 3.9% (4/102) shifted to a higher T-score at 2 years.

Of particular interest is the incidence of BMD loss of 5% or more. For year 2, 28.3% (30/106) of DMPA-SC subjects and 33.7% (34/101) of DMPA-IM subjects had a 5% or greater loss in femur total BMD. For year 2, 37.7% (40/106) of DMPA-SC subjects and 51.0% (52/102) of DMPA-IM subjects had a 5% or greater loss in spine total BMD. At 2 years, there was a greater difference between the treatment groups in spine total BMD loss of 5% or more than in femur total BMD loss of 5% or more.

Study 267BMD: Categorical Change in BMD from Baseline (ITT)					
Visit	Categorical Percent Change from Baseline	Total hip		Spine	
		SC	IM	SC	IM
		n (%)	n (%)	n (%)	n (%)
Month 12	2.6 to 5.0	4 (2.4)	6 (3.7)	4 (2.4)	4 (2.5)
	0.1 to 2.5	32 (19.3)	24 (14.8)	13 (7.8)	15 (9.3)
	-2.4 to 0	72 (43.4)	62 (38.3)	69 (41.6)	34 (21.0)
	-4.9 to -2.5	45 (27.1)	50 (30.9)	46 (27.7)	69 (42.6)
	-7.4 to -5.0	8 (4.8)	17 (10.5)	27 (16.3)	27 (16.7)
	-9.9 to -7.5	4 (2.4)	2 (1.2)	7 (4.2)	12 (7.4)
	≥ -10.0	1 (0.6)	1 (0.6)	0 (0)	1 (0.6)
	Total Reported	166	162	166	162
Month 24	7.6 to 10.0	1 (0.9)	0 (0)		
	5.1 to 7.5	0 (0)	1 (1.0)		
	2.6 to 5.0	2 (1.9)	5 (5.0)	2 (1.9)	3 (2.9)

Study 267BMD: Categorical Change in BMD from Baseline (ITT)					
Visit	Categorical Percent Change from Baseline	Total hip		Spine	
		SC	IM	SC	IM
		n (%)	n (%)	n (%)	n (%)
	0.1 to 2.5	11 (10.4)	10 (9.9)	10 (9.4)	2 (2.0)
	-2.4 to 0	27 (25.5)	23 (22.8)	16 (15.1)	18 (17.6)
	-4.9 to -2.5	35 (33.0)	28 (27.7)	38 (35.8)	27 (26.5)
	-7.4 to -5.0	21 (19.8)	18 (17.8)	30 (28.3)	37 (36.3)
	-9.9 to -7.5	6 (5.7)	13 (12.9)	8 (7.5)	10 (9.8)
	≥ -10.0	3 (2.8)	3 (3.0)	2 (1.9)	5 (4.9)
	Total Reported	106	101	106	102

BMD Subgroup Analyses: Subgroup analyses showed no obvious trends in the difference between treatments in median percent change from baseline values for BMD with regard to age (less than 25 years, and equal to 25 years to less than or equal to 35 years), race, or geographical location.

A trend in femur total BMD was reported with regard to BMI categories (less than or equal to 25 kg/m², greater than 25 kg/m² and less than or equal to 30 kg/m², greater than 30 kg/m²) in the treatment groups. At year 1, for both the DMPA-SC and DMPA-IM treatment groups, the BMD loss (as indicated by median percent change from baseline) in the femur total decreased as the BMI category increased. By year 2, this trend was still noted in the DMPA-IM treatment group only, although the lowest BMI category still had the highest BMD loss in both treatment groups.

No trend was detected in the BMD loss in the spine total in either treatment group at year 1. By year 2 the only trend detected was in the DMPA-IM group where the BMD loss increased as the BMI category increased. However, these differences must be carefully considered, as subjects with lower BMI tend to start out with lower absolute BMD at baseline.

Fracture as an Adverse Event: As outlined in the table below, five subjects (4 in the DMPA-SC group and 1 in the DMPA-IM group) sustained a fracture during the study. There was no consistent pattern of bone loss in these subjects. None of these events was considered to represent clinical osteoporotic fractures.

Study 267 BMD: Subjects with Fracture Adverse Events (ITT)							
Age	Adverse Event	AE Start Day	Study Visit	BMD			
				T-Scores		Percent Change from Baseline	
				Femur	Spine	Femur	Spine
DMPA-SC							
34	foot fracture	176	Baseline	2.242	0.908		
20	foot fracture	679	Baseline	0.300	-0.245		
			Month 12	0.147	-0.413	-1.9	-1.8
			Month 24	-0.255	-0.778	-6.9	-5.8
32	rib fracture	149	Baseline	0.100	-0.533		
			Early Discont (Day 273)	0.028	-0.719	-0.9	-2.0
27	ankle fracture	21	Baseline	1.523	0.878		
			Unscheduled	1.505	0.741	-0.2	-1.2

Study 267 BMD: Subjects with Fracture Adverse Events (ITT)							
Age	Adverse Event	AE Start Day	Study Visit	BMD			
				T-Scores		Percent Change from Baseline	
				Femur	Spine	Femur	Spine
			(Day 232)				
DMPA-IM							
25	wrist fracture	344	Baseline	2.042	0.483		
			Month 12	1.617	-0.042	-4.1	-5.1
			Month 24	1.233	-0.033	-7.8	-5.0

CONCLUSIONS: Bone mineral density decrease occurred with Depo Provera use. Although there was a trend toward greater BMD loss with DMPA-IM use, there was no statistically significant difference between the two routes of administration at 24 months. Overall, by Month 24, 44% of DMPA treated subjects lost greater than 5% BMD at the spine, while 31% of DMPA treated subjects lost greater than 5% BMD at the total hip. The 36 month extension data are not provided in this submission. No data are available from this study to assess recovery after treatment cessation.

Study M5400/0234: Assessment of Bone Mineral Density in Women Receiving DEPOPROVERA ® Contraceptive Injection.

This study was undertaken at the request of the FDA, as a Phase 4 condition for the approval of the DEPO-PROVERA Contraceptive Injection New Drug Application (NDA). It was a prospective controlled investigation of the effects of DMPA-IM injection on BMD in women who were new users and who terminated that use at a later date.

Objectives

Primary:

To evaluate bone mineral density (BMD) changes in women receiving DMPA-IM for up to 240 weeks as compared to a cohort not using hormonal contraception, matched at each study site on the basis of race and current smoking status. Both DMPA-IM contraceptive users choosing to discontinue injections and non-exposed cohorts will be further evaluated for BMD changes for up to an additional 96 weeks.

Secondary:

To evaluate lipid and weight changes over the same time periods as the primary objective.

Study Design: This was an open-label, prospective, matched cohort design; i.e., DMPA-IM users (DMPA-IM group) compared to a cohort not using hormonal contraception (Control group), matched at each study site on the basis of race and current smoking status. The Control group consisted of women who: had a tubal ligation, were using intrauterine device (IUD) or barrier contraception, or shared a monogamous relationship with a vasectomized partner.

Population: Approximately 500 subjects, aged 25-35 years, matched at each study site on the basis of race and current smoking status.

Inclusion Criteria

All Subjects:

1. Female subjects, aged 25 to 35 years, having regular menses, defined as 28 days \pm 5 days.
2. Postpartum, non-breast feeding subjects, aged 25 to 35 years, who have resumed menses.
3. Postpartum, breast feeding subjects, aged 25 to 35 years, who were 6 weeks post-delivery.
4. Had a negative pregnancy test.
5. Agreed to observe all of the program requirements, e.g., keeping appointments, BMD measurements, urine and blood tests, and annual physical exam at the requested time.
6. Reasonably capable of completing the 7 year study, i.e., not planning a family within five years.

Control Group Subjects:

1. Women with tubal ligation, using IUD or barrier contraception, or women in a monogamous relationship with a vasectomized partner.

Exclusion Criteria

All subjects:

1. Previous use of DEPO-PROVERA.
2. Known or suspected pregnancy.
3. Undiagnosed vaginal bleeding.
4. Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebrovascular disease.
5. Liver dysfunction or disease – aspartate transaminase >40 U/L or serum bilirubin >1.4 mg/dl.
6. Known or suspected malignancy of the breast, including abnormal breast exam, breast mass and nipple bleeding. Fibrocystic disease was not an exclusion.
7. Abnormal Cervical Cytology results reported as greater than Class II, or equivalent.
8. History of cancer, except for carcinoma in-situ of cervix (cervical intraepithelial neoplasia III, or squamous intraepithelial lesions) that had been treated, with normal cervical cytology subsequently, or basal cell cancer of the skin that had been treated.
9. Moderate Hypertension, defined as systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg.
10. Fasting serum glucose >115 g/dl or random serum glucose >160 mg/dl.
11. Renal disease, defined as blood urea nitrogen (BUN) >26 mg/dl, or serum creatinine >1.3 mg/dl.
12. Hyperthyroid subjects: Thyroxine (T4) ≥ 11.5 μ g/dL.
13. Present or past alcoholism or drug abuse.
14. BMD below acceptable criteria on screen: lumbar spine or hip, which is more than 2 standard deviations (SD) below normal for age, or history of pathologic and/or compression fracture.
15. Subjects $\geq 30\%$ of ideal body weight.
16. Previous participation in this study.

DMPA-IM Group Subjects:

1. Known sensitivity to DEPO-PROVERA (medroxyprogesterone acetate or any of its other ingredients).
2. Any subject for whom the investigator believes the use of DEPO-PROVERA Contraceptive Injection or participation in this study constitutes a contraindication.

COMMENT: BMD exclusion criteria was set at a T score of -2.0 for either hip or spine. Therefore, women with baseline low bone mass and a T score of -1 to -2 were included in the study. Subjects with a history of fracture were appropriately excluded from the study. Subjects with other metabolic bone diseases or medications that may affect bone density were not excluded from enrollment.

Study Medication: Subjects in the DMPA-IM group received intramuscular sterile aqueous suspension 150mg/ml every 12 weeks for up to 240 weeks. Both DMPA-IM and Control groups could not receive any other sex steroids during the study, unless approved by the study sponsor.

COMMENT: Baseline calcium and vitamin D supplementation was not required in this study. Other concomitant medications that may have affected BMD assessments (e.g., multivitamins, and/or other mineral supplements) were neither required nor prohibited by the protocol.

Efficacy Measures:

Primary Efficacy Endpoint: The primary efficacy endpoint is the percentage change from screening in BMD at 240 weeks. In the summary tables and text “screening” is referred to as “baseline”.

Secondary Efficacy Endpoints: The percentage change from screening in BMD (spine and hip) at Weeks 24, 48 and 96, then every 48 weeks until week 192. Then post-treatment at Weeks 24, 48 and 96.

Change in body weight from Week 0 at each visit until 96 weeks post-treatment.

Changes from screening in lipids [total low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL) and high-density lipoprotein (HDL) cholesterol and triglycerides] at Weeks 24, 48, and 96, then every 48 weeks until Week 240. Then post-treatment at Weeks 24, 48 and 96.

Changes from screening in biochemical markers of bone metabolism: osteocalcin and collagen crosslinks at Weeks 24, 48, and 96, then every 48 weeks until Week 240. Then post-treatment at Weeks 24, 48 and 96.

Withdrawal criteria: There were no stopping rules for BMD loss in this study.

Results

Patient Disposition: A total of 608 subjects were enrolled in the study, 248 in the DMPA-IM group and 360 in the Control group. Subject disposition and populations are summarized in the following table.

Study 0234:Disposition		
	DPMA IM	Control
Population	n(%)	n(%)
Enrolled	248	360
Received study medication	248 (100)	0
Completed study	42 (17)	118 (33)
ITT*	228 (92)	310 (86)
Evaluable**	92 (37)	291 (81)
Reported post treatment data	91	138
Completed 96 week follow-up	44 (48)	87 (63)
*ITT = Intent to Treat: Subject should be enrolled into the study, have a measure at screening or baseline and at least one post-baseline measurement for any efficacy endpoint.		
**Evaluable: Subject should have received treatment for at least 24 weeks, completed the visit at 24 weeks past screening and received injections within range.		
For the Control Group subject should have completed the visit at 24 weeks post screening and had BMD data collected at 24 weeks post screening.		

The discontinuation rate was higher in the DMPA group than the Control Group. The number of subjects ongoing for BMD evaluations at each visit is given in the following table.

Study 0234: Subjects Ongoing at Each Visit for BMD Evaluations		
Week	DMPA n(%)	Control n(%)
	N=248	N=360
Screening	247 (100)	357 (99)
Week 24	180 (73)	291 (81)
Week 48	140 (57)	255 (71)
Week 96	95 (38)	197 (55)
Week 144	72 (29)	161 (45)
Week 192	59 (24)	138 (38)
Week 240*	91 (37)	133 (37)
Post-Treatment Week 24	57 (23)	92 (26)
Post-Treatment Week 48	45 (18)	87 (24)
Post-Treatment Week 96	42 (17)	69 (19)

* Number of subjects shown as ongoing at Week 240 includes some subjects who had stopped treatment but for whom the investigator filled in a Week 240 visit in the CRF.

Demographics: The treatment groups were similar with respect to baseline and demographic characteristics (with the exception of the percentage of subjects greater than 35 years of age, which was higher in the Control group). These are summarized in the following table for the ITT population. A family medical history of osteoporosis was reported by 1% of the DMPA-IM group, and 5% of the Control group.

Study 0234: Summary of Demographic Characteristics (ITT)		
Characteristic	DMPA N=248	Control N=360
Age (yr)		
Mean (SD)	30 (3.15)	32 (2.91)
Range	24-36	25-36
<25, n (%)	4 (1.8)	1 (0.3)
25 -35, n (%)	217 (95)	264 (85)
>35 (n,%)	7 (3.1)	45 (15)
Race, n (%)		
White	180 (79)	245 (79)
Black	27 (12)	38 (12)
Oriental/Asian	3 (1.3)	1 (0.3)
Hispanic	17 (7.5)	26 (8.4)
Other	1 (0.4)	0
Weight (kg)		
Mean (SD)	67 (6.88)	65 (6.44)
Height (cm)		
Mean (SD)	166 (6.19)	165 (6.28)
Body Mass Index (kg/m²)		
Mean (SD)	25 (3.82)	24 (3.79)
Range	16-35	17-36
Smoking status, n (%)		
Non-smoker	170 (75)	257 (83)
< one pack/day	52 (23)	45 (15)
> one pack/day	6 (2.6)	8 (2.6)
Physical exertion (hours/week)		
Mean (SD)	25 (22.64)	23 (20.93)
Range	0-98	0-90
Recreational activities (hours/week)		

Study 0234: Summary of Demographic Characteristics (ITT)		
Characteristic	DMPA N=248	Control N=360
Mean (SD)	3.8 (4.26)	3.8 (4.23)
Range	0-40	0-40
Calcium intake (mg/day)		
Mean (SD)	1042 (716.43)	839 (574.79)
Range	60-5781	60-3633

Concomitant Medications taken During the Treatment Period: Medication was taken during the treatment period by 177 (83%) of the DMPA-IM group and 281 (90%) of the Control group. Medications taken during therapy that accounted for >10% included Amoxicillin (DMPA-IM 8.0%, Control 13%), Ibuprofen (DMPA-IM 14%, Control 13%), and Multivitamins (DMPA-IM 11% and Control 11%).

Exposure: Study medication was administered at 12 week intervals. Subjects in the DMPA-IM group had between one and 21 injections, 42 subjects received 20 injections which was the number required to complete the treatment phase.

Primary Efficacy Outcomes

Percent Change in Bone Mineral Density: Subjects in the DMPA-IM group had statistically significant and progressive decreases in BMD from baseline when compared with the Control group, as outlined in the table below. At the total hip, subjects in the DMPA-IM group lost 5.16% BMD compared with a 0.19% gain for the control group (treatment difference -5.47 %, p <0.001). Total spine BMD decreased 5.38% in the DMPA-IM group compared to a 0.43% gain for the control group (treatment difference -5.65 %, p <0.001). At the femoral neck, subjects in the DMPA-IM group lost 6.12% BMD compared to a 0.27% loss in the control group (treatment difference -5.75 %, p <0.001). Similar results are seen for the femoral trochanter, where the treatment difference was - 6.55% (p value <0.001).

On completion of the treatment phase, after 96 weeks off drug, bone mass recovery did occur, however, treatment differences remained. At the total hip, subjects in the DMPA-IM group continued to have a 0.20% BMD loss compared with a 0.84% gain for the Control group (treatment difference -2.08 %, p = 0.047). Total spine BMD loss remained at -1.19% in the DMPA-IM group compared to a 0.47% gain for the Control group (treatment difference -2.04 %, p = 0.017). At the femoral neck, subjects in the DMPA-IM group had a BMD loss of 3.11% compared to a loss of 0.36% in the Control group (treatment difference -3.09 %, p = 0.010). Similar results are seen for the femoral trochanter, with a loss of 0.43 in the DMPA-IM group, compared to a 0.96% gain in the Control group (treatment difference was -1.82%, p = 0.116).

Study 0234: Percentage Change from Baseline in BMD (ITT)						
Visit	DMPA-IM		Control		Difference [DMPA – Control] adjusted mean change (95% CI)	P-Value
	n	Mean (SD)	n	Mean (SD)		
Femur Total BMD						
Week 24	108	-0.72 (2.07)	144	0.57 (2.32)	-1.34 (-1.93 - -0.76)	<0.001
Week 48	88	-1.56 (2.64)	125	0.95 (1.89)	-2.58 (-3.22 - -1.94)	<0.001
Week 96	57	-3.06 (2.93)	94	0.69 (3.12)	-3.59 (-4.64 - -2.55)	<0.001

Study 0234: Percentage Change from Baseline in BMD (ITT)						
Visit	DMPA-IM		Control		Difference [DMPA – Control] adjusted mean change (95% CI)	P-Value
	n	Mean (SD)	n	Mean (SD)		
Week 144	42	-3.89 (3.37)	77	-0.06 (2.72)	-3.66 (-4.80 - -2.53)	<0.001
Week 192	31	-4.52 (3.89)	70	-0.02 (2.76)	-4.34 (-5.75 - -2.93)	<0.001
Week 240 OC	21	-5.16 (3.60)	65	0.19 (3.18)	-5.47 (-7.10 - -3.84)	<0.001
Week 24 post	36	-1.21 (4.04)	50	0.40 (3.04)	Not done	ND
Week 48 post	31	-0.70 (4.44)	54	0.65 (3.62)	-1.74 (-3.61 - 0.12)	0.066
Week 96 post	25	-0.20 (3.41)	43	0.84 (3.69)	-2.08 (-4.13 - -0.03)	0.047
Spine Total BMD						
Week 24	178	-1.41 (2.37)	291	0.19 (2.75)	-1.87 (-2.37 - -1.36)	<0.001
Week 48	135	-2.86 (2.47)	253	0.22 (2.81)	-3.11 (-3.72 - -2.51)	<0.001
Week 96	94	-4.11 (2.68)	197	0.29 (2.57)	-4.43 (-5.10 - -3.75)	<0.001
Week 144	71	-4.89 (3.16)	159	0.31 (2.75)	-5.21 (-6.06 - -4.35)	<0.001
Week 192	59	-4.93 (3.41)	137	0.35 (3.00)	-5.17 (-6.18 - -4.17)	<0.001
Week 240 OC	33	-5.38 (3.57)	105	0.43 (3.27)	-5.65 (-7.06 - -4.23)	<0.001
Week 24 post	56	-3.48 (3.98)	92	0.33 (3.43)	Not done	ND
Week 48 post	45	-2.42 (3.73)	87	0.28 (3.53)	-2.82 (-4.26 - -1.38)	<0.001
Week 96 post	41	-1.19 (3.88)	66	0.47 (3.66)	-2.04 (-3.71 - -0.38)	0.017
Femoral Neck BMD						
Week 24	179	-1.24 (3.29)	289	0.22 (4.61)	-1.60 (-2.42 - -0.78)	<0.001
Week 48	137	-2.85 (3.66)	254	0.28 (4.34)	-3.23 (-4.10 - -2.35)	<0.001
Week 96	95	-3.99 (4.03)	195	-0.22 (4.75)	-3.50 (-4.66 - -2.34)	<0.001
Week 144	72	-4.80 (4.39)	159	-0.23 (3.87)	-4.45 (-5.63 - -3.27)	<0.001
Week 192	58	-5.90 (4.55)	138	-0.53 (4.03)	-4.79 (-6.12 - -3.45)	<0.001
Week 240 OC	34	-6.12 (4.68)	106	-0.27 (5.22)	-5.75 (-7.86 - -3.64)	<0.001
Week 24 post	57	-2.99 (4.77)	92	-0.51 (4.46)	Not done	ND
Week 48 post	45	-3.04 (4.92)	86	-0.27 (4.90)	-2.88 (-4.78 - -0.98)	0.003
Week 96 post	42	-3.11 (4.28)	69	-0.36 (5.89)	-3.09 (-5.42 - -0.77)	0.010
Femoral Trochanter BMD						
Week 24	179	-1.22 (3.34)	289	0.60 (4.67)	-2.04 (-2.86 - -1.22)	<0.001
Week 48	137	-2.48 (4.38)	254	0.67 (4.47)	-3.30 (-4.23 - -2.37)	<0.001
Week 96	95	-4.29 (4.12)	195	0.41 (4.36)	-4.68 (-5.75 - -3.61)	<0.001
Week 144	72	-5.12 (4.74)	159	0.70 (4.30)	-5.82 (-7.12 - -4.53)	<0.001
Week 192	58	-5.37 (4.55)	138	0.00 (4.49)	-5.43 (-6.84 - -4.02)	<0.001
Week 240 OC	34	-6.32 (5.55)	106	0.33 (4.62)	-6.55 (-8.46 - -4.65)	<0.001
Week 24 post	57	-1.70 (6.40)	92	0.50 (4.97)	Not done	ND
Week 48 post	45	-0.83 (6.53)	86	0.68 (5.59)	-1.59 (-3.83 - 0.65)	0.161
Week 96 post	42	-0.43 (6.06)	69	0.93 (5.29)	-1.82 (-4.11 - 0.46)	0.116

Categorical Percent Change from Baseline: The table below outlines the categorical changes in hip and spine BMD. By Week 240 of the study, 95.2% (20/21) of DMPA-IM subjects and 52.3% (34/65) of Control subjects had either no change or decreases in total hip BMD, whereas 4.8% (1/21) of DMPA-IM subjects and 47.7% (31/65) of Control subjects had increases in total hip BMD. At the spine, BMD decreased or did not change in 97.0% (32/33) of DMPA-IM subjects and of 50% (52/105) Control subjects; while increases occurred in 3% (1/33) of DMPA-IM subjects and 50% (53/105) of Control subjects.

Of particular interest is the incidence of BMD loss of 5% or more. At the end of the treatment phase, 52.4% (11/21) of DMPA-IM subjects and 4.6% (3/65) of Control subjects had a 5% or

greater loss in total hip BMD while 54.5% (18/33) of DMPA-IM subjects and 1.9% (2/105) of Control subjects had a 5% or greater loss in spine BMD. After the Week 96 post-treatment phase, recovery had occurred such that only one subject in the DMPA-IM group and 2 subjects in the Control group had a 5% or greater loss in total hip BMD. At the spine, 17% (7/41) of DMPA-IM subjects and 8% (5/66) of Control subjects continued to have a 5% or greater loss in BMD at the end of the post-treatment phase.

Study 0234: Categorical Percent Change in BMD				
% Change	Week 240 Observed Case		Week 96 post-treatment	
	DMPA IM	Control	DMPA IM	Control
	n (%)	n (%)	n (%)	n (%)
Femur Total BMD				
>10	0	0	0	0
7.6 to 10.0	0	2 (3.1)	0	1 (2.3)
5.1 to 7.5	0	2 (3.1)	1 (4.0)	4 (9.3)
2.6 to 5.0	0	9 (14)	3 (12)	10 (23)
0.1 to 2.5	1 (4.8)	18 (28)	7 (28)	11 (26)
-2.4 to 0	5 (24)	23 (35)	9 (36)	10 (23)
-4.9 to -2.5	4 (19)	8 (12)	4 (16)	5 (12)
-7.4 to -5.0	5 (24)	3 (4.6)	0	1 (2.3)
-9.9 to -7.5	3 (14)	0	1 (4.0)	1 (2.3)
<= -10.0	3 (14.3)	0	0	0
Total reported	21 (100)	65 (100)	25 (100)	43 (100)
Spine Total BMD				
>10	0	0	0	0
7.6 to 10.0	0	1 (1.0)	1 (2.4)	2 (3.0)
5.1 to 7.5	0	10 (9.5)	1 (2.4)	7 (11)
2.6 to 5.0	0	15 (14)	3 (7.3)	9 (14)
0.1 to 2.5	1 (3.0)	26 (25)	11 (27)	15 (23)
-2.4 to 0	7 (21)	33 (31)	11 (27)	21 (32)
-4.9 to -2.5	7 (21)	18 (17)	7 (17)	7 (11)
-7.4 to -5.0	11 (33)	2 (1.9)	4 (10)	4 (6.1)
-9.9 to -7.5	4 (12)	0	3 (7.3)	1 (1.5)
<= -10.0	3 (9.1)	0	0	0
Total reported	33 (100)	105 (100)	41 (100)	66 (100)
Femoral Neck BMD				
>10	0	3 (2.8)	0	2 (2.9)
7.6 to 10.0	1 (2.9)	3 (2.8)	0	2 (2.9)
5.1 to 7.5	0	10 (9.4)	0	6 (8.7)
2.6 to 5.0	0	10 (9.4)	8 (19)	13 (19)
0.1 to 2.5	2 (5.9)	14 (13)	2 (4.8)	13 (19)
-2.4 to 0	4 (12)	31 (29)	8 (19)	14 (20)
-4.9 to -2.5	4 (12)	20 (19)	12 (29)	5 (7.2)
-7.4 to -5.0	9 (27)	8 (7.5)	6 (14)	7 (10)
-9.9 to -7.5	9 (27)	7 (6.6)	3 (7.1)	3 (4.3)
<= -10.0	5 (15)	0	3 (7.1)	4 (5.8)
Total reported	34 (100)	106 (100)	42 (100)	69 (100)
Femoral Trochanter BMD				
>10	0	1 (0.9)	2 (4.8)	3 (4.3)
7.6 to 10.0	0	6 (5.7)	1 (2.4)	2 (2.9)
5.1 to 7.5	0	10 (9.4)	3 (7.1)	10 (15)
2.6 to 5.0	1 (2.9)	10 (9.4)	7 (17)	10 (15)

Study 0234: Categorical Percent Change in BMD				
% Change	Week 240 Observed Case		Week 96 post-treatment	
	DMPA IM	Control	DMPA IM	Control
	n (%)	n (%)	n (%)	n (%)
0.1 to 2.5	2 (5.9)	31 (29)	5 (12)	12 (17)
-2.4 to 0	6 (18)	18 (17)	7 (17)	13 (19)
-4.9 to -2.5	6 (18)	19 (18)	9 (21)	12 (17)
-7.4 to -5.0	6 (18)	5 (4.7)	4 (9.5)	2 (2.9)
-9.9 to -7.5	6 (18)	4 (3.8)	2 (4.8)	5 (7.2)
<= -10.0	7 (21)	2 (1.9)	2 (4.8)	0
Total reported	34 (100)	106 (100)	42 (100)	69 (100)

T-Scores: A baseline T-score of -2.0 or less was an exclusion criteria for this study. As outline in the table below, the percentage of DMPA-IM subjects with T-Scores less than -1.00 increased by Week 240, but declined in the post-treatment phase back to a similar level as at screening. In the Control Group the percentage of T-Scores less than -1.00 showed no clear trend over the period of the study. No subjects in either treatment group became osteoporotic (T score less than -2.5 SD below peak bone mass).

Study 0234: T-Scores Less Than -1 (ITT Population)						
T - Score	Screening		Week 240 (OC)		Week 96 post	
	DMPA-IM	Control	DMPA-IM	Control	DMPA-IM	Control
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Femur Total BMD						
-1.49 to -1.00	11 (8.2)	16 (10.5)	3 (9.4)	11 (11)	2 (5.6)	7 (10)
-1.99 to -1.50	1 (0.7)	1 (0.7)	0	3 (3.0)	0	1 (1.5)
<= -2.00	0	1 (0.7)	0	0	0	0
Spine Total BMD						
-1.49 to -1.00	18 (7.9)	21 (6.8)	5 (15.2)	5 (4.8)	4 (9.8)	6 (9.1)
-1.99 to -1.50	11 (4.8)	15 (4.9)	2 (6.1)	3 (2.9)	1 (2.4)	2 (3.0)
<= -2.00	2 (0.9)	0	0	1 (1.0)	0	1 (1.5)
Femoral Neck BMD						
-1.49 to -1.00	22 (9.6)	32 (10)	7 (21)	11 (10.4)	4 (9.5)	5 (7.2)
-1.99 to -1.50	2 (0.9)	10 (3.2)	1 (2.9)	5 (4.7)	1 (2.4)	3 (4.3)
<= -2.00	0	0	0	0	0	0
Femoral Trochanter BMD						
-1.49 to -1.00	15 (6.6)	27 (8.7)	3 (8.8)	8 (7.5)	1 (2.4)	5 (7.2)
-1.99 to -1.50	5 (2.2)	8 (2.6)	1 (2.9)	1 (0.9)	0	1 (1.4)
<= -2.00	0	1 (0.3)	0	1 (0.9)	0	0

Change in Biochemical Markers of Bone Metabolism: There was no consistent change in bone biomarkers serum osteocalcin levels or urine pyridinium collagen crosslinks during the study.

Fracture as an Adverse Event: As outlined in the table below, six subjects (3 in the DMPA-IM group and 3 in the Control group) sustained a fracture during the study. There was no consistent pattern of bone loss in these subjects. None of these events was considered to represent a clinical osteoporotic fracture.

Study 0234: Subjects with Fracture Adverse Events (ITT)							
Age	Adverse Event	AE Week	Study Visit	BMD			
				Tscore		Percent Change from Baseline	
				Femur	Spine	Femur	Spine
DMPA-IM							
31	T-11 comp fx Sacral fx	66	Baseline	-0.39	-1.46		
			Week 24	-0.33	-1.62	0.9	-2.1
		66	Week 48	-0.27	-1.77	1.7	-3.7
			Week 240	-0.46	-1.82	-1	-4.4
28	Patella, left	41	Baseline	0.36	-1.82	0.1	-7.7
			Week 24	0.32	-2.11	-0.5	-3.6
			Week 48	0.11	-1.55	-3	3.3
			Week 96	0.20	-1.72	-1.9	1.1
34	Femur, left	138	Baseline	-0.25	-1.21		
			Week 24	-0.42	-1.28	-2.4	-0.7
			Week 96	-0.52	-1.24	-3.7	-0.3
			Week 240	-0.38	-1.22	-1.9	-0.2
Control							
35yo	Rib	298	Baseline	-1.06	-0.11		
			Week 24	-1.07	0.03	-0.2	1.4
			Week 96	-1.15	-0.12	-1.4	-0.1
			Week 240	-1.41	-0.20	-5.4	-0.8
29	Ankle, left	36	Baseline	0.59	1.68		
			Week 24	0.47	1.56	-1.5	-1.1
			Week 96	0.45	1.56	-1.7	-1.1
			Week 240	0.71	1.56	1.4	-1.1
162013 35y	Ankle, right	86	Baseline		-0.77		
			Week 24		-0.76		0.1
			Week 96		-0.85		-0.9
			Week 240	0.56	-0.66		1.2

Medical Officer Conclusions: This open label cohort study clearly shows that Depo-Provera use is associated with significant BMD loss at both the hip and spine. Statistically significant losses were seen as early as 24 weeks and progressively declined throughout the 240 weeks of treatment with DMPA-IM. At the end of the treatment phase, 52.3% of DMPA-IM had a greater than 5% loss of BMD at the total hip, while 54.5% had a greater than 5% loss of BMD at the spine. No subjects in either treatment group developed T scores of -2.5 SD below peak bone mass. Recovery of bone mass does occur after cessation of DMPA therapy though at 2 years post therapy, full recovery had not been achieved. No consistent change in bone biomarkers was observed. In subjects sustaining fractures as adverse events, there was no consistent pattern of bone loss seen.

Study Z5400/0261: DEPO-PROVERA: Evaluation of Bone Mineral Density and Total Body Calcium in Adolescent DP150CI Users and Non-Hormonal Contraceptive Users

Background: This is an interim report for study 0261. On February 25, 2003, the data safety monitoring board made a decision to discontinue exposure to Depo-Provera in this study. Full study details are not currently available.

Safety Categories: For the purpose of monitoring, the DSMB classified subjects into four mutually exclusive categories, according to their bone mineral density (BMD) assessed by DEXA at the lumbar spine, total hip and femoral neck. A subject was classified in only one of the categories and remained classified in the most serious category thereafter for the duration of the study. The categories are defined as:

- **5% BMD loss:** Any subject with a single documented BMD value which was between 5% and 8% below baseline at any time in the study
- **8% BMD loss:** Any subject with a single documented BMD value which was 8% or more below baseline at any time in the study
- **Persistent 5% BMD loss:** Any subject who had more than one consecutive documented BMD loss between 5% and 8%.
- **Progressive and Persistent BMD loss:** Any subject with a progressive decline in BMD of 8% or more below baseline defined as at least 1 value which was between 5% and 8% below baseline and at least 1 consecutive value which was 8% or more below baseline

Study Design: This was a non-randomized, open-labeled study in which participants were free to switch back and forth between different methods of contraception. DMPA-IM injections were given every 12 weeks. Consequently, study visits were scheduled at Baseline and at 12-week intervals thereafter until Week 240. Two additional follow-up visits were to occur at 60 and 120 weeks post discontinuation of DMPA-IM. DXA scans were performed at Baseline and then at study weeks 24, 60, 84, 120, 144, 180, 204 and 240. Two additional scans were to be performed at the two follow-up visits. The study was divided into 60 week blocks. A DMPA-IM user was defined as a subject who has received at least two consecutive injections of DMPA-IM in each 60-week period. Subject classification is outlined in the table below.

Study 0261: Classification of Depo-Provera Users	
Class	Definition
Constant	A subject who is initiated on DMPA-IM and continues to receive at least two consecutive DMPA-IM injections per 60-week interval.
Converted	A) A subject who was on DMPA-IM at study start and later switched to another form of contraception or B) A subject who was not on DMPA-IM at the beginning of the study and switched to DMPA-IM at a later time point
Conservative	A subject who has received two consecutive DMPA-IM injections at any time during the study

Disposition: The first subject was enrolled in April of 1998 and the last subject was enrolled in Oct of 1999. The information presented reflects a snapshot of the data in Pharmacia's database at the beginning of February 2003, when the DSMB requested the analyses. The data available is outlined in the table below. At the time of the analyses, few records were available for the Week 240 visit, therefore, the Week 180 visit was the last visit used for data evaluation.

Study 0261: Disposition of Study Subject Data			
Time	Subjects Completed	Subjects Between Visits	Data Records Being Queried
Baseline	388	-	-

Study 0261: Disposition of Study Subject Data			
Time	Subjects Completed	Subjects Between Visits	Data Records Being Queried
At Least 60 Weeks	320	0	0
At Least 120 Weeks	255	0	7
At Least 180 Weeks	158	30	25
240 Weeks	14	155	9

As outlined in the table below, a total of 178 subjects discontinued prematurely from the study. The majority of these subjects discontinued during the first 60 weeks of the study.

Study 0261: Discontinued subjects	
Time of Discontinuation	Subjects
0 - 60 Weeks	68
60 - 120 Weeks	58
120 - 180 Weeks	42
180 - 240 Weeks	10
Total	178

Results

As most of the subjects attained the 180-week mark in the study, the data were examined up to and including week 180. In subjects that completed the first 180 weeks of the study, significant bone loss was observed in constant Depo Provera users with 42% experiencing loss at the spine, 76% with bone loss at the total hip and 78% with bone loss at the femoral neck (see Table below).

Study 0261: Subjects who completed at least the first 180 weeks in the study						
Number of 60 week Intervals with DMPA-IM	Total # Subjects	Nonconsecutive 5% Loss	Nonconsecutive 8% Loss	Persistent	Persistent & Progressive	Any Category
Lumbar spine						
0	80	1 (1.3)	--	--	1 (1.3)	2 (2.6)
1	15	2 (13.3)	--	--	--	2 (13.3)
2	13	4 (30.8)	--	--	2 (15.4)	6 (46.2)
3	50	7 (14.0)	1 (2.0)	5 (10.0)	8 (16.0)	21 (42.0)
Total Hip						
0	80	6 (7.5)	--	1 (1.3)	--	7 (8.8)
1	15	--	1 (6.7)	2 (13.3)	--	3 (20.0)
2	13	1 (7.7)	--	3 (23.1)	4 (30.8)	8 (61.5)
3	50	6 (12.0)	1 (2.0)	13 (26.0)	18 (36.0)	38 (76.0)
Femoral Neck						
0	80	7 (8.8)	--	1 (1.3)	2 (2.5)	10 (12.5)
1	15	4 (26.7)	--	--	--	4 (26.7)
2	13	1 (7.7)	--	2 (15.4)	4 (30.8)	7 (53.8)
3	50	11 (22.0)	--	8 (16.0)	20 (40.0)	39 (78.0)

As outlined in the table below, when evaluated by the number of DMPA-IM injections received 41.7%, 75.0% and 77.1% of subjects who received more than 80% of the prescribed number of injections in the 180-week interval experienced some form of bone loss at the lumbar spine, total hip and femoral neck, respectively.

Study 0261: Subjects who completed at least the first 180 weeks in the study						
Number Injections	Total # Subjects	Nonconsecutive 5% Loss	Nonconsecutive 8% Loss	Persistent	Persistent & Progressive	Any Category
Lumbar spine						
2-4	8	1 (12.5)				1 (12.5)
5-8	10	3 (30.0)				3 (30.0)
9-12	12	3 (25.0)			2 (16.7)	5 (41.7)
13-16	48	6 (12.5)	1 (2.1)	5 (10.4)	8 (16.7)	20 (41.7)
Total Hip						
2-4	8		1 (12.5)	1 (12.5)		2 (25.0)
5-8	10			2 (20.0)	1 (10.0)	3 (30.0)
9-12	12	2 (16.7)		2 (16.7)	4 (33.3)	8 (66.7)
13-16	48	5 (10.4)	1 (2.1)	13 (27.1)	17 (35.4)	36 (75.0)
Femoral Neck						
2-4	8	3 (37.5)				3 (37.5)
5-8	10	2 (20.0)		1 (10.0)		3 (30.0)
9-12	12	1 (8.3)		2 (16.7)	4 (33.3)	7 (58.3)
13-16	48	10 (20.8)		7 (14.6)	20 (41.7)	37 (77.1)

When using a conservative definition for Depo-Provera user (i.e. any subject who received at least 2 consecutive DMPA-IM injections at any point during the study)

Study 0261: BMD Safety Classification, All Study Data						
	Total # Subjects	Nonconsecutive 5% Loss n (%)	Nonconsecutive 8% Loss n (%)	Persistent n (%)	Persistent & Progressive n (%)	Any Category n (%)
Lumbar Spine						
DMPA IM	180	24 (13.3)		10 (5.6)	17 (9.4)	51 (28.3)
Non User	208			2 (1.0)	1 (0.5)	3 (1.5)
Total Hip						
DMPA IM	180	20 (11.1)	2 (1.1)	28 (15.6)	29 (16.1)	79 (43.9)
Non User	208	8 (3.9)		5 (2.4)		13 (6.3)
Femoral Neck						
DMPA IM	180	32 (17.8)	1 (0.6)	16 (8.9)	39 (21.7)	88 (48.9)
Non User	208	16 (7.7)		4 (1.9)	4 (1.9)	24 (11.5)

In subjects with uninterrupted DMPA-IM use, percent change in BMD is listed in the table below. Treatment with Depo-Provera is associated with statistically significant BMD deficits at all time points examined, out to 180 weeks. Control subjects increased BMD more at the lumbar spine than they did at the hip. Depo-Provera subjects lost more bone at the hip than they did at the spine. The magnitude of the mean deficit, after two years (120 weeks) of uninterrupted therapy, ranged from -6.1% at the lumbar spine to -8.4% at the femoral neck.

Study 0261: Percent Change from Baseline in BMD (g/cm ²)						
Visit		DMPA-IM		Control	Difference	P-Value
	n	Mean (SD)	n	Mean (SD)	[DMPA-IM - Control]	
Total Hip BMD						
Week 24	148	-1.47 (2.14)	205	0.76 (2.38)	-2.20 (-2.74 - -1.65)	<0.001

Study 0261: Percent Change from Baseline in BMD (g/cm ²)							
Visit		DMPA-IM		Control		Difference	P-Value
	n	Mean (SD)	n	Mean (SD)	[DMPA-IM - Control]		
Week 60	103	-2.82 (3.18)	171	1.32 (2.80)	-4.19 (-5.03 - -3.34)	<0.001	
Week 84	78	-4.45 (2.97)	155	1.69 (3.57)	-5.76 (-6.83 - -4.70)	<0.001	
Week 120	58	-5.26 (3.42)	110	2.09 (4.44)	-6.97 (-8.58 - -5.37)	<0.001	
Week 144	45	-6.16 (3.15)	111	1.74 (4.47)	-7.29 (-9.16 - -5.43)	<0.001	
Week 180	30	-7.06 (3.07)	77	2.25 (5.78)	-8.28 (-10.89 - -5.68)	<0.001	
Femoral Neck BMD							
Week 24	148	-1.68 (3.17)	205	0.99 (2.95)	-2.70 (-3.43 - -1.98)	<0.001	
Week 60	103	-3.05 (4.17)	171	1.87 (3.65)	-4.31 (-5.41 - -3.21)	<0.001	
Week 84	78	-4.21 (4.37)	155	2.39 (4.11)	-5.77 (-7.11 - -4.44)	<0.001	
Week 120	58	-5.76 (4.48)	110	2.76 (5.44)	-8.37 (-10.33 - -6.41)	<0.001	
Week 144	45	-6.01 (4.61)	111	2.54 (5.95)	-7.15 (-9.62 - -4.69)	<0.001	
Week 180	30	-6.87 (4.40)	77	2.60 (6.78)	-8.74 (-11.94 - -5.55)	<0.001	
Spine BMD							
Week 24	149	-1.23 (2.01)	207	1.66 (2.26)	-2.57 (-3.06 - -2.08)	<0.001	
Week 60	104	-2.42 (2.79)	171	3.47 (3.31)	-5.33 (-6.18 - -4.49)	<0.001	
Week 84	80	-3.02 (3.27)	154	4.26 (4.06)	-6.39 (-7.48 - -5.30)	<0.001	
Week 120	58	-2.62 (3.81)	110	5.23 (5.60)	-6.07 (-7.78 - -4.35)	<0.001	
Week 144	46	-2.78 (4.03)	111	5.41 (5.49)	-7.01 (-8.98 - -5.04)	<0.001	
Week 180	29	-2.43 (4.48)	77	6.77 (6.92)	-6.61 (-9.55 - -3.67)	<0.001	

Bone Mineral Content: The bone mineral content (BMC) of the lumbar spine, hip and femoral neck decreased in DMPA-IM treated subjects and increased in Control subjects, similar to changes seen in BMD. Whole body bone mineral content (BMC) increased in both DMPA-IM users and in Controls. The rate of increase was slower in those subjects taking Depo-Provera.

Recovery: The current protocol plans to follow subjects for 2 years following their last DMPA-IM injection in order to assess BMD recovery. Initial data on subject who had received all scheduled doses of Depo-Provera is presented in the table below. It is important to note that subjects stopped treatment at various time points throughout the study, so these recovery data represent subjects who received all scheduled doses of Depo Provera, but not necessarily a full 5 years of treatment. The results suggest that a substantial degree of BMD recovery does occur in the first two years of post-treatment follow-up. Only 13 subjects had 3 years (180 weeks) of post-treatment follow-up. Their results suggest that improvement in BMD may continue beyond two years.

Study 0261: BMD Recovery		
Follow up Visit	n	DMPA-IM % Change (SD)
Spine BMD		
Recovery Baseline	179	-2.09 (4.00)
Week 60 f/up	58	0.21 (4.32)
Week 120 f/up	25	2.78 (3.76)
Week180 f/up	13	4.16 (3.68)
Total Hip BMD		
Recovery Baseline	178	-3.82 (4.49)
Week 60 f/up	58	-1.67 (4.56)
Week 120 f/up	25	-0.16 (4.18)
Week180 f/up	13	1.83 (5.03)

Study 0261: BMD Recovery		
Follow up Visit		DMPA-IM
	n	% Change (SD)
Femoral Neck BMD		
Recovery Baseline	178	- 4.08 (5.35)
Week 60 f/up	58	-2.80 (6.42)
Week 120 f/up	25	0.54 (4.71)
Week180 f/up	13	1.83 (5.78)

Medical Officer Conclusions: These analyses demonstrated to the DSMB that sufficient data had been collected for the purposes of this study to document the effect of Depo-Provera on BMD in this adolescent cohort. Clearly, adolescent users of Depo Provera sustain significant bone loss. This loss occurs at a critical age when bone mass accrual is maximal. Given the age of the population studied, any further evaluation of this study data should use Z scores (age matched) rather than T scores, as this age group has not reached peak bone mass and would be better assessed against age matched peers.

One remaining clinical question is whether adolescents who use Depo Provera will have complete bone mass recovery once drug use stops. Initial recovery data suggests that bone density will recover after Depo Provera is discontinued. This data is preliminary and more analysis is needed as follow up continues. The clinical impact of Depo-Provera use on future fracture risk is not clear. In general, risk of fracture is low in young individuals with low bone mass. Future studies should include baseline calcium and vitamin D replacement, which while not typical to this population, may help ameliorate the bone loss seen.

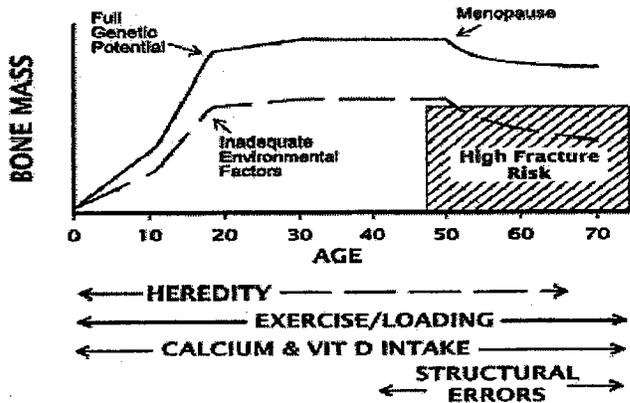
Discussion: The studies reviewed herein clearly show that areal BMD (aBMD) decreases progressively with use of Depo-Provera. In adult premenopausal women, approximately 53% of subjects treated with Depo-Provera lost greater than 5% of bone density and 65% of subjects shifted to a lower BMD T-score category during 2 years of treatment (study 267BMD).

While in postmenopausal women, aBMD loss of this magnitude is associated with increased short-term fracture risk, there are no data to support such an association in premenopausal subjects. In other words, all else being equal, age is an independent and direct correlate of fracture risk. This is best illustrated in young patients treated with glucocorticoids, who despite significant reduction in aBMD, do not appear to have an increased short-term risk for osteoporotic fractures. (Persistently low aBMD would increase the risk for osteoporotic fracture later in life, however.)

An issue specific to the population of women who use hormonal birth control is that of peak bone mass, which depending on the skeletal site and whether one measures areal or volumetric BMD, is generally achieved in females between late adolescence and 30 years of age. As shown in the figure¹ below, any factor that prevented or significantly lessened the attainment of peak bone mass would in theory increase the risk for osteoporotic fracture in later life.

¹ Figure taken from: Heaney RP, et al. Peak bone mass. Osteoporosis International. 2000. 11:985-1009.

While data from the studies reviewed for this consult indicate the at least partial recovery of bone mass occurs following discontinuation of Depo-Provera, it is unknown if use of this contraceptive agent during adolescence or early adulthood would prevent the attainment of peak bone mass even if the drug were discontinued during or immediately after this critical period of bone mass accrual.



Response to Questions from HFD-580

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