CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-584

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM TO CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-584
Submission Dates:	January 27, 2005
Generic Name:	Medroxyprogesterone acetate injectable suspension
Brand Name:	depo-subQ provera 104™
Sponsor:	Pfizer Inc.
Date:	March 18, 2005
Reviewer:	Myong-Jin Kim, PharmD, HFD-870

Background:

NDA 21-583 (depo-subQ provera 104™) is currently approved for the prevention of pregnancy in women of child bearing potential. NDA 21-584 supports the management of endometriosis-associated pain [redacted]. NDA 21-584 received an approvable action on October 18, 2004. The sponsor seeks a combined label for NDA 21-583 and 21-584. The Clinical Pharmacology section of the label for NDA 21-583 and 21-584 is the same.

In response to October 18, 2004 approvable letter for NDA 21-584, the sponsor submitted an amendment on January 27, 2005 (Amendment No. 16). This amendment contains an updated physician insert, patient insert, container and package (carton) labeling and safety update.

Recommendation:

The labeling changes to the Clinical Pharmacology section of the label (NDA 21-584) are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II.

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/s/

Myong-Jin Kim
3/18/05 01:55:07 PM
PHARMACOLOGIST

Ameeta Parekh
3/24/05 09:56:59 AM
BIOPHARMACEUTICS
I concur

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	**21-584**
Brand Name:	**Pending**
Generic Name:	**Medroxyprogesterone Acetate Injectable Suspension**
Sponsor:	**Pfizer Inc.**
Relevant IND(s):	**61,389**
Date(s) of Submission:	**December 18, 2003**
Type of Submission:	**Original NDA**
Formulation:	**Subcutaneous Injection**
Strength:	**104 mg/0.65 mL**
Indication:	**Management of endometriosis-associated pain**
Reviewer:	**Myong-Jin Kim, Pharm.D.**
Team Leader:	**Ameeta Parekh, Ph.D.**
OCPB Division:	**DPE-II**
OND Division:	**Reproductive & Urologic Drug Products**

Table of Contents

1. Executive Summary

The sponsor seeks approval of a new, subcutaneous formulation of depot medroxyprogesterone acetate (DMPA-SC) for the indication of endometriosis-associated pain in women. The recommended dose of DMPA-SC is 104 mg administered by subcutaneous (SC) injection into the anterior thigh or abdomen, once every 3 months.

Medroxyprogesterone acetate (MPA) is a synthetic analog of 17α-hydroxyprogesterone. MPA has been marketed for many years as oral (Provera® Tablets) and intramuscular injection formulations (Depo-Provera® Contraceptive Injection and Depo-Provera® Sterile Aqueous Suspension). Provera® is indicated for the treatment of secondary amenorrhea, for abnormal uterine bleeding due to hormone imbalance, and for the prevention of endometrial hyperplasia in non-hysterectomized postmenopausal women taking conjugated estrogen. Depo-Provera® Contraceptive Injection (DMPA-IM) is approved for use as a contraceptive in the U.S. (NDA 20-246, approved in 1992). It is to be administered by a healthcare professional at a single dose of 150 mg intramuscularly every 3 months in the gluteal or deltoid muscle. Depo-Provera® Sterile Aqueous Suspension (400 mg/mL) is indicated for the adjunctive and palliative treatment of endometrial or renal cell carcinoma. To present, no formulation of MPA is approved for the management of endometriosis-associated pain in the United States. Currently approved drugs for endometriosis are danazol and gonadotropin-releasing hormone against, such as leuprolide, nafarelin and goserelin.

The endometriosis studies are supported by 3 Phase 1/2 clinical pharmacology studies (Studies 265, 271, and 272), which were originally submitted in support of the contraceptive program (NDA 21-583, 'approvable' action on August 2, 2004). These single dose studies were conducted to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of MPA. The to-be-marketed formulation was used in the Phase 1/2 and clinical studies except in a dose-finding study (Study 265). In addition to these studies, the sponsor submitted the multiple-dose PK data (Study 267 BMD). This was a 2-year study to compare the effects of DMPA-SC with those of DMPA-IM on bone mineral density (BMD) in women who received treatment with DMPA-SC or DMPA-IM every 3 months. The MPA data after multiple doses of DMPA-SC were obtained in a subset of study subjects.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-584 submitted on December 18, 2003. The overall Human Pharmacokinetic Section is *acceptable*. Labeling comments outlined in the labeling section should be conveyed to the sponsor. An addendum will be added to this review when agreement on labeling is reached.

1.2 Phase IV Commitments

None.

On July 15, 2004, the sponsor had agreed to undertake an in-vitro metabolism study as a Phase IV commitment for NDA 21-583. The sponsor submitted additional review of literature pertaining to potential effect of drug inducers on MPA following SC injection to address this issue. The sponsor provided the literature data to suggest that CYP3A4 appears to be one of the metabolic pathways of MPA. In addition, the sponsor provided documentation to support that the induction

of MPA is more likely with oral administration and less likely with SC administration. We agree with this scientific basis and this justification satisfies the Phase IV commitment and no further studies are recommended (teleconference minutes dated September 22, 2004).

1.3 Summary of CPB Findings

The PK and PD of MPA were characterized in women of reproductive age following a single dose of DMPA-SC in 3 Phase 1/2 studies. These studies included dose-range Study 265 with ovulation suppression as the primary endpoint, PK/PD Study 271 in Asian women, and return of ovulatory function in Study 272. In addition, the potential effects of body mass index (BMI), race/ethnicity, and the SC injection sites (anterior thigh vs. abdomen) on the PK/PD profiles of MPA were evaluated. Subgroup analyses for primary efficacy endpoints based on age, race, or body weight did not suggest any differential responsiveness within these groups.

Following a single SC administration of DMPA-SC, considerable inter-subject variability in MPA concentrations was apparent. Serum MPA concentrations peaked approximately 9 days (range, 2 – 80 days) after dosing. The mean MPA C_{max} was approximately 1.56 ng/mL (range, — ng/mL) with a mean apparent terminal $t_{1/2}$ of 43 days. The mean trough MPA concentration of 0.402 ng/mL (range, — ng/mL) was observed at 91 days.

	C_{max} (ng/mL)	T_{max} (day)	C_{91} (ng/mL)	$AUC_{0-\tau}$ (ng·day/mL)	$AUC_{0-\infty}$ (ng·day/mL)	$t_{1/2}$ (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min		2.0		20.63	31.36	16
Max		80.0		139.79	162.29	114

Multiple-Dose PK

No unexpected accumulation of MPA was observed following multiple SC injections. Mean (SD) MPA trough concentrations were 0.67 (0.36) ng/mL (n=157) and 0.79 (0.36) ng/mL (n=144) at 6 and 12 months, respectively. The *R* value (accumulation constant) calculated from a mean K value of 0.0195 $days^{-1}$ and a dosing interval of 90 days was 1.21. The observed accumulation based upon the ratio of the trough concentrations observed at 6 months from the main protocol dataset (0.67 ng/mL, n=157) and after the single dose administration (0.40 ng/mL, n=42) was 1.68. The observed and calculated accumulation estimates were similar given the observed variability in the parameters and the limitations of a cross-study comparison.

Linearity

Following a single SC administration of doses ranging from 50 to 150 mg, the AUC and C_{min} ($C_{91\ day}$) increased with increasing doses of DMPA, but there was large overlap across dose levels (Study 265). There was no evidence of nonlinearity in the PK profile of MPA over the dose range of 50 to 150 mg after SC administration of DMPA-IM formulation. Serum MPA concentrations at Day 91 increased in a dose proportional manner but C_{max} did not appear to increase proportionally with increasing doses of DMPA-IM given subcutaneously. The AUC data were suggestive of dose linearity (r=0.6851, p=0.0001). The dose-normalized AUC and C_{max} were statistically different among treatments.

Race

Race had no significant effect on the PK of MPA after DMPA-SC administration. Following a single SC administration of DMPA-SC, there were no statistically significant differences in the PK parameter estimates for MPA among the subgroups with the exception of t_{max}. The t_{max} appeared to be longer in black women. The proposed SC dosing regimen was effective in suppressing ovulation, thereby providing adequate coverage in women regardless of their race. Progesterone concentrations were suppressed in 23 of 24 Asian women for at least 112 days after the SC dosing. In addition, a single dose of DMPA-SC effectively suppressed ovulation for 13 ± 1 weeks in all evaluable subjects (Study 272).

Injection Site

The location of SC injection site (anterior leg or abdomen) did not appear to affect the overall PK profile of MPA. There were no statistically significant differences in MPA parameter estimates obtained for the 2 injection sites, except for C_{max}. The C_{max} was higher in women receiving the injection in the anterior leg relative to the abdomen. MPA trough concentrations were similar.

BMI

MPA concentrations had tendency to be lower in women with BMI >38 kg/m^2, but trough concentrations (C_{91}) remained ≥ 0.2 ng/mL. The total MPA exposure (AUC_{inf}) was lower in obese subjects (>38 kg/m^2), than healthy or overweight subjects after a single DMPA-SC administration. Although no statistically significant difference was observed in MPA concentrations on day 91 among different BMI categories, MPA trough concentrations tended to be lower in obese subjects with a higher BMI (> 38 kg/m^2).

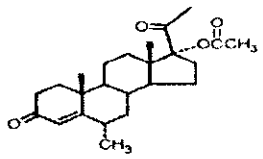
2. Question-Based Review

2.1 General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Physico-chemical properties

- Structural formula:



- IUPAC Name: 17-hydroxy-6α-methylpregn-4-ene-3,20-dione 17-acetate
- Molecular Weight: 386.53
- Molecular Formula: $C_{24}H_{34}O_4$
- Chemical Name: 17-alpha-acetoxy-6-alpha-methylprogesterone

Description	Medroxyprogesterone Acetate occurs as a white or almost white, powder
pKa	N/A
pH	N/A
Optical Rotation	+45 to +51 degrees
Aqueous Solubility	Medroxyprogesterone acetate is practically insoluble in water
Non-aqueous Solubility	Medroxyprogesterone acetate is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and in methanol, and slightly soluble in ether
Melting Range/Decomposition	205°C to 209°C
Solid-State Forms	
Hygroscopicity	

Drug Formulation

The DMPA-SC formulation is similar to the marketed Depo-Provera® IM contraceptive formulations (DMPA-IM) except for a few new excipients have been added in the DMPA-SC formulations (i.e., methionine, phosphate [redacted], povidone) (see **General Biopharmaceutics**). Since the active ingredient, MPA, is insoluble in water, both the marketed DMPA-IM and the new DMPA-SC formulations are formulated as a sterile aqueous suspension.

Throughout the DMPA-SC development, only one formulation (104 mg/0.65 mL per injection) was used in all clinical trials. The one exception was the first, dose-finding Study 265. The formulations used in Study 265 were the marketed DMPA-IM products (Depo-Provera Sterile Aqueous Suspension, 400 mg/mL, and Depo-Provera Contraceptive Injection, 150 mg/mL), diluted with sterile saline to achieve appropriate dose levels for SC administration at a constant volume. The sponsor did not conduct a bridging study to link these two formulations.

What is the proposed mechanism of action?

DMPA-SC, when administered subcutaneously at 104 mg/0.65 mL to women every 3 months, inhibits the secretion of gonadotropins, which in turn, prevents follicular maturation and ovulation, decreases estrogen secretion, and results in endometrial thinning. This underlies the primary therapeutic effect of DMPA-SC.

What are the proposed indication, dosage and route of administration?

The proposed indication of DMPA-SC is management of endometriosis-associated pain [redacted] The recommended dose of DMPA-SC is 104 mg administered by subcutaneous injection into the anterior thigh or abdomen, once every 3 months.

2.2 General Clinical Pharmacology

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

DMPA-SC inhibits the secretion of gonadotropins, which in turn, prevents follicular maturation and ovulation, decreases estrogen secretion, and results in endometrial thinning. This underlies the primary therapeutic effect of DMPA-SC. Ovulation suppression followed by recurrence of ovulation was monitored as evidenced through changes in serum progesterone, estradiol, LH and FSH concentrations. Progesterone concentrations $\geq$ 4.7 ng/mL were used as a threshold level for occurrence of ovulation.

The primary efficacy endpoint was patient response to treatment at 6 months with respect to 5 endometriosis sign/symptom categories: dysmenorrheal, (pelvic) induration, pelvic pain, pelvic tenderness, and (if sexually active) dyspareunia. Each category was rated as none, mild, moderate, or severe at baseline and all scheduled visits. For each category, a positive response was defined as an improvement of at least 1 point in the score after 6 months of treatment relative to baseline. In women with baseline scores for each of the 5 categories, a mean decrease of 4 points within the treatment groups after 6 months of treatment relative to baseline was considered clinically meaningful.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Blood samples for determination of MPA, progesterone, estradiol, LH and FSH were collected after drug administration.

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Based on the clinical PK/PD data, a concentration-response relationship has been established for MPA and the duration of ovulation suppression, as determined by serum progesterone hormone. The established threshold for serum MPA concentrations ranges from 0.10 to 0.20 ng/mL, using GC/MS analytical method (Rahimy MH *et al.* Contraception 1999;60:209-14). The sponsor used MPA trough concentrations (C_{91}) and ovulation suppression as criteria for selecting the DMPA-SC dose in the dose-finding study.

The proposed dose of 104mg/0.65mL was determined based on a dose-finding study (Study 265) evaluating the suppression of ovulation, and not on the suppression of estradiol. The 150-mg dose was effective in suppressing ovulation for > 112 days but the individual MPA profiles indicated that this dose was higher than needed. The 100-mg dose was effective in suppressing ovulation for > 112 days. The observed ovulation suppression and PK results of the dose-finding study suggest that 104 mg/0.65 mL would be an effective dose given SC every 3 months. No threshold MPA concentration has been established for estradiol suppression, which is the likely mechanism of mitigating symptoms of endometriosis. Study 265 evaluated estradiol concentrations following administration of one of four doses of DMPA-SC ranging from 50-150 mg. Reduction in serum estradiol concentrations showed a dose-response, with mean concentrations of 100-150 pg/ml, 50-100 pg/ml and 50 pg/ml following the 50 mg, 75-100 mg and 150 mg dose of MPA, respectively.

Dose of 100-mg DMPA

- Progesterone concentrations were suppressed in 11 of 12 women for ≥ 112 days.
- Ten of 12 subjects exhibited MPA trough concentrations (C_{91}) ≥ 0.2 ng/mL. One woman (Subject No. 26) showed a significant burst effect immediately after dosing, followed by a rapid decline in serum MPA concentrations approaching = ng/mL by Day 49.

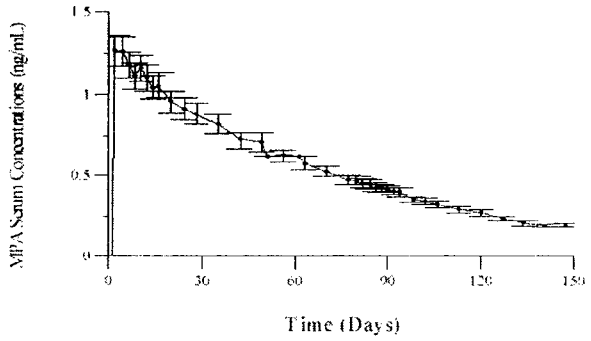
What are the characteristics of drug absorption?

Table 1. Summary of MPA PK Parameters after a Single DMPA-SC Dose (n=42) (Study 272)

PK Parameter	MEAN	STD	MEDIAN	MIN	MAX
AUC0-91 (ng.day/mL)	66.98	24.90	67.22		
AUC0-t(last) (ng.day/mL)	80.79	25.28	80.86		
AUC0-∞ (ng.day/mL)	92.84	23.46	95.23		
Cmax (ng/mL)	1.56	0.67	1.49		
tmax (day)	8.8	13.2	5.0		
t1/2,z (day)	43.2	20.8	37.8		
CL91 (ng/mL)	0.402	0.147	0.388		

- Considerable inter-subject variability in MPA concentrations was apparent.
- Serum MPA concentrations peaked approximately 9 days after dosing.
- The mean MPA C_{max} was approximately 1.56 ng/mL with a mean apparent terminal $t_{1/2}$ of 43 days.

Figure 1. Mean (SEM) Serum MPA Concentration-Time Profile after a Single Dose of DMPA-SC (n=42) (Study 272)



Effect of Injection Site

There were no statistically significant differences in MPA parameter estimates obtained for the 2 injection sites (abdomen vs. leg). The location of SC injection site (anterior leg or abdomen) did not appear to affect the overall PK profile of MPA. In the Phase 3 studies (Studies 268 and 270), DMPA-SC was administered into the anterior thigh or abdominal wall. There were no differences in efficacy.

Figure 2. MPA Concentration-Time Profile after a Single DMPA-SC Dose in Asian Women by Injection Site (n=12) (Study 271)

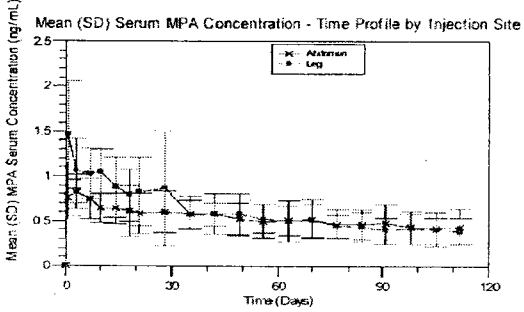


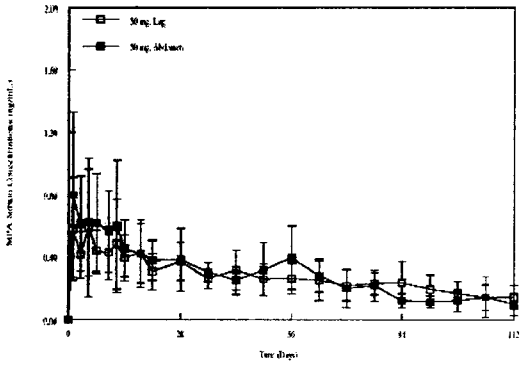
Table 2. Summary Statistics of MPA PK Parameters after a Single DMPA-SC in Asian Women by Injection Site (Study 271)

PK Parameter	Abdomen (n=12)			Anterior thigh (n=12)			ANOVA p-value
	Mean	Median	Range	Mean	Median	Range	
AUC0-91	60.03	65.93		67.75	67.89		.2530
AUC0-t(last)	60.15	66.01		68.17	68.06		0.2399
AUC0-∞	123.75	84.02		112.52	101.44		0.6916
Cmax	0.943	0.920		1.652	1.775		0.0019
tmax	21.9	8.5		4.3	1.0		0.0615
λz	0.0100	0.007		0.0110	0.0110		0.5489
t1/2,z	103.7	87.3		80.9	65.9		0.3642
C91	0.470	0.379		0.412	0.426		0.4394

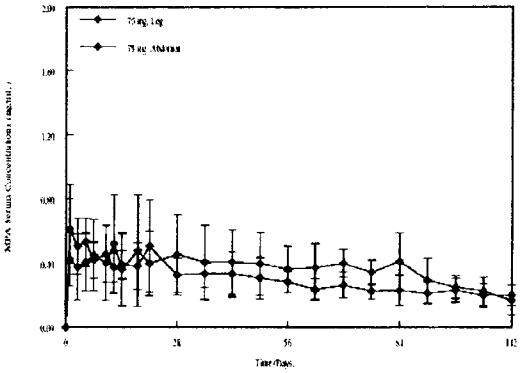
- There was no statistically significant difference in MPA parameter estimates obtained for the 2 injection sites, except for C_{max}.
- The C_{max} was higher in women receiving the injection in the anterior leg relative to the abdomen. This increase in mean C_{max} was primarily due to one subject.

Figure 3. Mean (SD) Serum MPA Concentration-Time Profile after the (A) 50-mg, (B) 75-mg, (C) 100-mg, or (D) 150- mg DMPA Dose by Injection Site (Study 265)

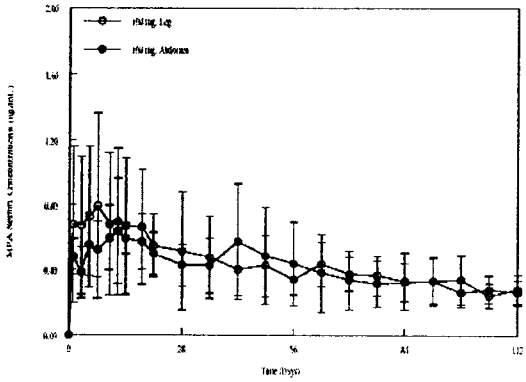
(A) 50-mg



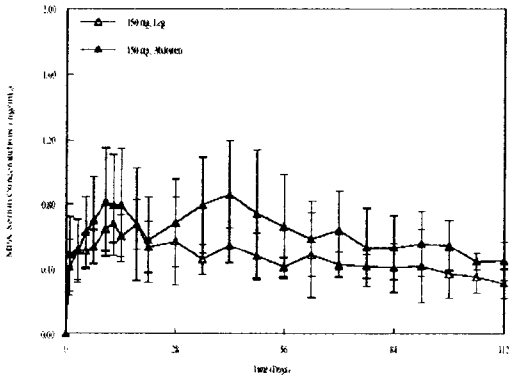
(B) 75-mg



(C) 100-mg



(D) 150-mg



- The location of SC injection site (anterior leg or abdomen) did not appear to affect the overall PK profile of MPA.

What are the characteristics of drug distribution?

Formal assessment of protein binding was not conducted during the DMPA-SC development program. Published literature data indicate that plasma protein binding of MPA is about 86%. MPA binding occurs primarily to serum albumin. No binding of MPA occurs with sex-hormone-binding globulin (SHBG).

What are the characteristics of drug metabolism?

MPA is extensively metabolized in the liver by P450 enzymes. CYP3A4 appears to be one of the metabolic pathways of MPA (Kobayashi et al, Clin Cancer Res 2000;6:3297-303). A number of MPA metabolites (>10) have been identified in the plasma. The main routes of MPA metabolism appear to be A ring and/or side-chain reduction, loss of the acetyl group, hydroxylation preferentially in the 2-, 6-, and 21-positions, or a combination of these positions, resulting in more than 10 metabolites. Hydroxylation in the 2-position can be followed by reduction of the 3-keto group or by dehydration.

What are the characteristics of drug excretion?

MPA administered parenterally or orally is eliminated primarily via fecal excretion by the human. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates. No unchanged MPA is excreted in urine after oral administration of MPA.

Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Following a single SC administration of doses ranging from 50 to 150 mg, the AUC and C_{min} ($C_{91\ day}$) increased with increasing doses of DMPA, but there was considerable overlap across dose levels. There was no evidence of nonlinearity in the PK profile of MPA over the dose range of 50 to 150 mg after SC administration. Serum MPA concentrations at Day 91 increased in a dose proportional manner but C_{max} did not appear to increase proportionally with the increasing doses of DMPA given subcutaneously. The AUC data were suggestive of dose linearity (r=0.6851, p=0.0001). The dose-normalized AUC and C_{max} were statistically different among treatments.

Figure 4. Mean Serum MPA Concentration-Time Profiles after a Single SC Administration of DMPA-IM Formulation (Study 265)

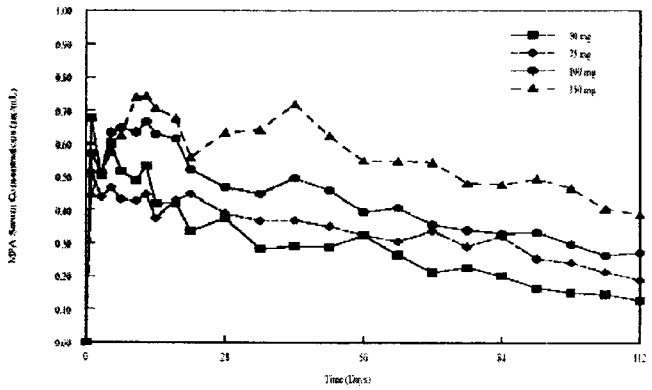


Table 3. Mean (SD) MPA Parameter Estimates after a Single SC Administration of DMPA-IM Formulation (Study 265)

Parameter	Treatment (mg MPA per 0.5 mL injection)				ANOVA p-value*
	50	75	100	150	
AUC_{0-91} (ng day/mL)	29.2 (6.23)	32.6 (9.29)	41.5 (13.4)	53.3 (16.4)	0.0001
$AUC_{0-\infty}$ (ng day/mL)	37.7 (8.41)	43.2 (13.1)	54.0 (15.9)	79.3 (26.9)	0.0001
C_{max} (ng/mL)	0.831 (0.387)	0.780 (0.226)	0.889 (0.353)	0.947 (0.277)	0.6179
C_{91} (ng/mL)	0.174 (0.0822)	0.253 (0.111)	0.332 (0.137)	0.495 (0.215)	0.0001
t_{max} (day)	16 (28)	18 (21)	21 (21)	25 (27)	0.8058
$t_{1/2}$ (day)	31.4 (20.8)	31.8 (18.2)	27.0 (11.7)	37.3 (18.9)	0.6033
Dose Normalized†					
AUC_{0-91} (ng day/mL)	29.2 (6.23)	21.8 (6.19)	20.8 (6.69)	17.8 (5.46)	0.0008
$AUC_{0-\infty}$ (ng day/mL)	37.7 (8.41)	28.8 (8.76)	27.0 (7.97)	26.4 (8.97)	0.0120
C_{max} (ng/mL)	0.831 (0.387)	0.520 (0.151)	0.445 (0.177)	0.316 (0.092)	0.0001
C_{91} (ng/mL)	0.174 (0.082)	0.169 (0.074)	0.166 (0.069)	0.165 (0.072)	0.9930

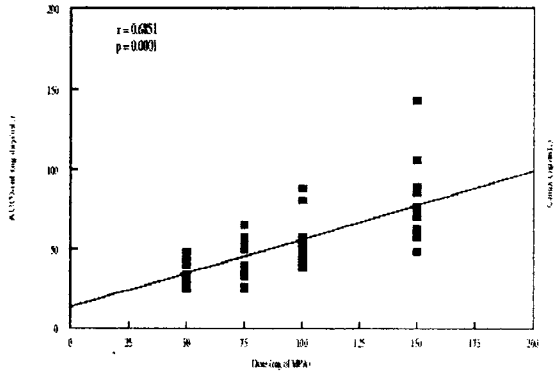
Source: Section 5.3.3.1.1, Table 2.

* p-value for overall treatment differences by Analysis of Variance (ANOVA).

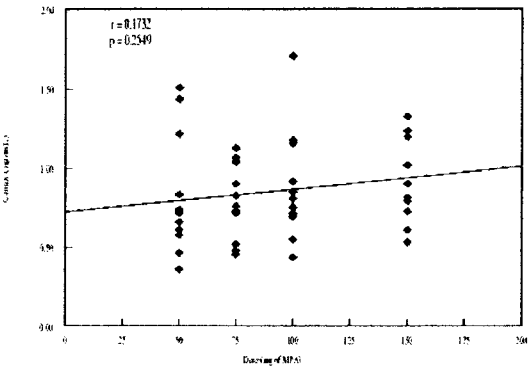
† Dose-normalized parameters to a 50-mg dose.

Figure 5. Relationship between (A) AUC_{0-inf}, (B) C_{max}, or (C) C_{91} and SC Administration of DMPA-IM Formulation (Study 265)

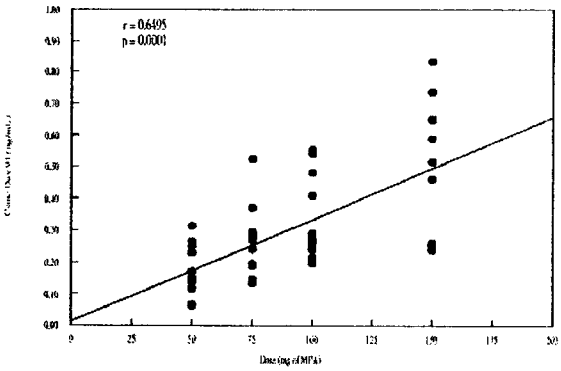
(A) AUC



(B) C_{max}



(C) C_{91}



How do the PK parameters change with time following chronic dosing?

No unexpected accumulation of MPA was observed following multiple SC injections. Trough concentrations were collected at 6, 12 and 24 months for the subjects who participated in the BMD substudy of protocol 267. Mean (SD) MPA trough concentrations were 0.67 (0.36) ng/mL (n=157) and 0.79 (0.36) ng/mL (n=144) at 6 and 12 months, respectively.

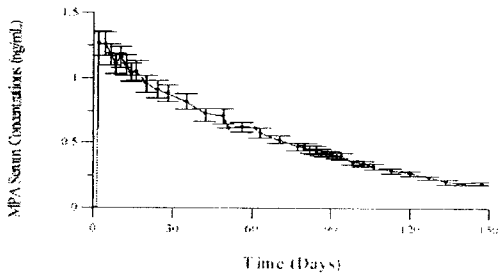
The *R* value (accumulation constant) calculated from a mean K value of 0.0195 $days^{-1}$ and a dosing interval of 90 days was 1.21. The observed accumulation based upon the ratio of the trough concentrations observed at 6 months from the larger main protocol dataset (0.67 ng/mL, n=157) and after the single dose administration (0.40 ng/mL, n=42) equals 1.68. The observed and calculated accumulation estimates are similar given the observed variability in the parameters and the limitations of a cross-study comparison.

Table 4. Summary Statistics for MPA Concentrations by Timepoint

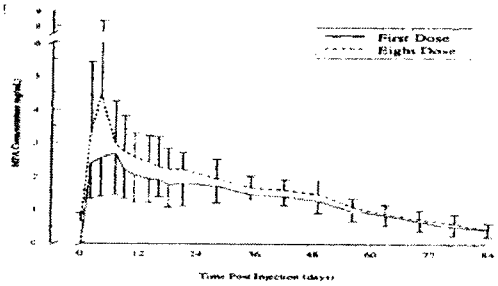
	6-Month	12-Month	2nd Year – Within 1 Dosing Interval*						24-Month
			2 Week	4 Week	6 Week	8 Week	10 Week	12 Week	
N	8	8	7	8	8	8	7	8	2
Mean	0.59411	0.96900	1.70171	1.48525	1.31563	1.09850	0.93686	0.94313	0.77300
Min	0.098	0.314	0.902	0.542	0.495	0.384	0.304	0.291	0.298
Max	1.18	2.61	2.36	2.25	2.34	1.70	1.38	1.35	1.25
SD	0.34615	0.72854	0.60469	0.52604	0.52871	0.38986	0.36107	0.35677	0.67458

Figure 6. Mean Serum MPA Concentration-Time Profile after a Single Dose of DMPA-SC (A) (Study 272) and a Single and Multiple Doses of DMPA-IM Given Every 3 Months (B) (Data from NDA 20-246)

(A) DMPA-SC (n=42)



(B) DMPA-IM (n=9)



What is the intersubject variability of PK parameters in volunteers, and what are the major causes of variability?

There was considerable intersubject variability in MPA concentrations and the derived PK parameters.

Table 5. Mean (SD) PK Parameters of MPA after a Single SC Administration of DMPA

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

+ Dose was 100 mg per 0.5 mL

- The estimates obtained in the dose-finding Study 265 for C_{max} and AUC were lower by about 30 % to 50 % compared with the estimates obtained in 2 other studies. The apparent difference could be due to high inter-subject variability in MPA concentrations and the derived PK parameters, changes in the formulations, or dilutional factor.

- The $t_{1/2}$ estimate (~91 days) from Study 271 (a single SC administration of DMPA-SC in Asian women) was several-fold greater than the estimate (~20 days) obtained in the dose-finding study (Study 265). The difference in $t_{1/2}$ is likely because of high variability in the estimate of the apparent terminal rate constant used in computing the $t_{1/2}$. In some study subjects, the last 3 to 4 time points on the terminal log-linear region of the concentration-time curves appeared flat, or occasionally with upward tendency, thus making it difficult to obtain reasonable λ_z estimates, using least-squares regression.
- It should be noted that Kinetica™ was used to determine PK parameters in Study 271 whereas CPAP (Clinical Pharmacokinetics Analysis Package) was used in the dose-finding study (Study 265).

2.3 Intrinsic Factors

What intrinsic factors (age, race, body mass index, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Subgroup analyses for primary efficacy endpoints based on age, race, or body weight did not suggest any differential responsiveness within these groups.

Age

Safety and effectiveness of DMPA-SC in pediatric patients have not been established. Studies involving DMPA-SC in geriatric women have not been conducted.

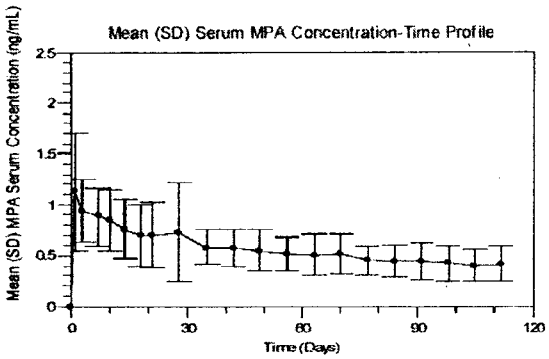
Race

The patient population in the clinical studies (Studies 268 and 270) was primarily white. In Study 268, the percentages of white and black were 90.4% and 7.4%, respectively. In Study 270, there were 56% white, 2% black, 17.6% Asian/Pacific Islander, and 24% mixed/multiracial.

Following a single SC administration of DMPA-SC, there was no statistically significant difference in the PK parameter estimates for MPA among the subgroups with the exception of t_{max}. The t_{max} appeared to be longer in black subjects, as several subjects showed prolonged, flat MPA profiles with no apparent C_{max} concentration.

Since the proposed dosing regimen for DMPA-SC (104 mg/0.65 mL) utilized a reduced MPA dose compared to DMPA-IM (150 mg/mL), and the DMPA-SC dose has been selected based on dose-finding data in Caucasian women, a study was undertaken to evaluate the duration of ovulatory suppression after a single dose of DMPA-SC in Asian women. The proposed SC dosing regimen was effective in suppressing ovulation, thereby providing adequate coverage in Asian women (Study 271). Progesterone concentrations were suppressed in 23 of 24 women for at least 112 days after the SC dosing. In addition, a single dose of DMPA-SC effectively suppressed ovulation for 13 ± 1 weeks in all evaluable subjects (white, black, Asian) regardless of their race (Study 272).

Figure 7. MPA Concentration-Time Profile after a Single DMPA-SC Dose in Asian Women (n=24) (Study 271)



- MPA concentrations were sustained throughout the targeted dosing interval of 91 days indicating that MPA absorption from the SC injection site was prolonged in these Asian women.

Table 6. PK Parameters of MPA after a Single DMPA-SC Dose in Asian Women (Study 271)

AUC0_91	24	63.893	16.2443	65.9336
AUC0N	24	64.163	16.4195	66.0123
AUCTOT	24	118.135	67.1614	93.0457
CMAX	24	1.298	0.6024	1.0550
TMAX	24	13.125	23.1842	3.0000
LZ	23	0.011	0.0066	0.0091
THALF	23	91.864	58.6432	76.5477
C_91	24	0.441	0.1776	0.4090

- The mean (SD) MPA C_{max} was 1.30 (0.60) ng/mL and the t_{max} was approximately 2 weeks after dosing (range, 1-91 days).
- The mean (SD) $t_{1/2}$ was about 92 (59) days and highly variable (range, 21-261 days).

Table 7. Mean MPA PK Parameters by Ethnicity after DMPA-SC Dose (Study 271)

PK Parameter	Chinese (n=4)	Filipino (n=2)	Malayan (n=6)	Thai (n=2)	Indian (n=10)	ANOVA p-value
AUC0-91 (ng.day/mL)	60.46	83.29	52.64	77.99	65.32	0.0968
AUC0-∞ (ng.day/mL)	135.22	139.92	92.05	132.75	119.67	0.8575
Cmax (ng/mL)	1.010	1.915	1.171	1.655	1.294	0.4343
tmax (day)	5.2	35.0	2.3	5.5	19.9	0.3465
t1/2,z (day)	130.4	83.9	71.8	73.2	93.9	0.6516
C91 (ng/mL)	0.410	0.598	0.331	0.544	0.468	0.3114

- There was no apparent difference in PK parameter estimates among the 5 Asian ethnic subgroups.
- The AUC and C_{max} appeared to be greater in the Filipino women but the increase was due primarily to one time point (Day 28) in the concentration-time data of Subject No.3.

Table 8. MPA Pharmacokinetic Parameters by Race after DMPA-SC Administration (Study 272)

Pharmacokinetic Parameter	Asian (n = 4)	Black (n = 14)	White (n = 27)	ANOVA p-value
AUC0-91 (ng-day/mL)	57.54	62.65	69.58	0.0609
AUC0-t(last) (ng-day/mL)	80.14	75.88	83.36	0.6778
AUC0-∞ (ng-day/mL)	97.52	86.75	95.83	0.5026
Cmax (ng/mL)	—	1.377	1.677	0.3201
tmax (day)	4.0	16.1	5.3	0.0384
λz	0.0198	0.0191	0.0197	0.9792
$t_{1/2}$ (day)	35.0	42.7	43.8	0.9138
C91 (ng/mL)	—	0.397	0.403	0.9692

- There was no statistically significant difference in the PK parameter estimates for MPA among the subgroups with the exception of t_{max}. The t_{max} appeared to be longer in black subjects, as several subjects showed prolonged, flat MPA profiles with no apparent C_{max} level.

Body Mass Index (BMI)

There was no difference in efficacy by BMI in the Phase 3 clinical studies (Studies 268 and 270). The mean BMI of subjects in Study 268 and Study 270 were 25.8±5.9 kg/m^2 (range, 17.8 – 47.3) and 23.6±3.9 kg/m^2 (range, 16.1 – 35.0), respectively.

MPA concentrations had tendency to be lower in women with BMI >38 kg/m^2, but trough concentrations (C_{91}) remained ≥ 0.2 ng/mL. The total MPA exposure (AUC_{inf}) was lower in obese subjects (>38 kg/m^2), than healthy or overweight subjects after a single DMPA-SC administration. However, suppression of ovulation was maintained in obese subjects.

Table 9. MPA Pharmacokinetic Parameters by BMI after DMPA-SC Administration (Study 272)

PK Parameter	BMI			ANOVA p-value		BMI			ANOVA p-value
	≤25 (n=13)	>25-30 (n=10)	>30 (n=19)			≤28 (n=19)	>28-38 (n=18)	>38 (n=5)	
AUC0-91 (ng•day/mL)	68.50	74.79	61.83	0.4075		71.55	67.89	46.33	0.1279
AUC0-t(last) (ng•day/mL)	84.71	88.22	74.21	0.2986		86.39	81.45	57.18	0.0671
AUC0-∞ (ng•day/mL)	99.31	98.09	85.65	0.1977		99.30	92.44	69.75	0.0389
Cmax (ng/mL)	1.647	1.765	1.400	0.3305		1.735	1.534	1.021	0.0982
tmax (day)	4.2	17.5	7.5	0.0424		9.5	9.3	4.4	0.7354
λz	0.0175	0.0233	0.0188	0.2595		0.0198	0.0201	0.0159	0.6363
$t_{1/2}$ (day)	46.9	35.6	44.8	0.4041		43.2	39.8	55.9	0.3189
C91 (ng/mL)	0.445	0.443	0.351	0.1218		0.431	0.411	0.259	0.0618

- The BMI in the DMPA-SC group ranged from 18.2 to 46.7 kg/m^2, with the majority in the overweight/obese categories.
- The analysis used a BMI classification based on Dietary Guideline for Americans 2000 (healthy: BMI 18.5 – 25 kg/m^2; overweight: BMI 25 – 30 kg/m^2; obese: BMI>30 kg/m^2) and the BMI stratification used at the time of randomization: (1) BMI 18-28 kg/m^2, (2) BMI >28-38 kg/m^2, and (3) BMI>38 kg/m^2.
- Dietary Guideline for Americans: there were no significant differences in the MPA parameter estimates of AUC, C_{max}, λz, and $t_{1/2}$ among the 3 BMI categories. The AUC_{inf} was lower in subjects with a BMI >38 kg/m^2.

- Although no statistically significant difference was observed in MPA concentrations on day 91 among different BMI categories, MPA trough concentrations tended to be lower in obese subjects with a higher BMI (> 38 kg/m^2).

Renal Impairment

No formal studies have evaluated the effect of renal disease on the PK of DMPA-SC.

Hepatic Impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of DMPA-SC. However, steroid hormones may be poorly metabolized in patients with severe liver dysfunction.

2.4 Extrinsic Factors

Drug-Drug Interactions

Formal assessments of drug-drug interactions involving DMPA-SC were not conducted. Aminoglutethimide administered concomitantly with DMPA-SC may decrease the serum concentrations of MPA thereby possibly decreasing the efficacy of DMPA-SC.

2.5 General Biopharmaceutics

DMPA-SC contains the active ingredient MPA. The preparation is presented as a pre-filled, single-use glass syringe, which delivers 104 mg of MPA in 0.65 mL.

The drug substance, MPA, used in the DMPA-SC formulation is same as that used in the marketed Depo-Provera IM, in terms of physical-chemical characteristics, specifications, synthetic route, sterilization method, manufacturing and sterilization sites. The acceptance criteria of

Table 10. Formulation of the DMPA-SC pre-filled syringes

Names of Ingredients	Quantity (Percentage w/v)	Function	Reference to Quality Standards
Medroxyprogesterone Acetate (MPA)		Active Ingredient	USP plus in house Standard
Other Ingredients:			
Methylparaben			USP/NF
Propylparaben			USP/NF
Sodium Chloride			USP
Polyethylene Glycol			USP/NF
[redacted]			
Polysorbate 80			USP/NF
Monobasic Sodium Phosphate • 1 H_2O			USP
Dibasic sodium Phosphate • 12 H_2O			USP
Methionine			JSP
Povidone			USP
Sodium Hydroxide or Hydrochloric Acid	QS	pH adjustment	USP/NF
Water for injection	QS to	Solvent	USP

Table 11. Comparison of the to-be-marketed DMPA-SC and marketed DMPA-IM (used in Study 265) formulations

Substance	DMPA-IM (w/v)	DPMA-SC (w/v)
Drug		
MPA		
Excipients		
Methylparaben		
Propylparaben		
Sodium Chloride		
Polyethylene Glycol		
Polysorbate 80		
Monobasic Sodium Phosphate •1 H_2O		
Dibasic Sodium Phosphate •12 H_2O		
Methionine		
[redacted]		
Sodium Hydroxide or Hydrochloric Acid*	QS	
Water for Injection		QS to
Dose	150 mg MPA	104 mg MPA
Injection Volume	1 mL	0.65 mL

* As necessary to obtain desired pH.
Abbreviations: QS=as needed; w/v=weight/volume ratio

The sponsor stated that a bridging study was not deemed necessary to link Study 265 findings with the DMPA-SC database given minor differences between the formulations. All excipients present in the marketed IM formulation are also present in the SC formulation although the quantities are slightly different in some cases. This was to accommodate the increase in MPA concentration (w/v) in comparison with the IM formulation (w/v). The methionine and phosphate were added to the SC formulation to

What are the differences between the clinical and the to-be-marketed formulations?

The Phase 3 trials were performed with the to-be-marketed formulation and dose/volume of administration.

2.6 Analytical

Human serum samples were quantitated for MPA using a sensitive and selective

This method was developed and validated at This method was cross-validated for use of either plasma or serum. All clinical studies in this application collected serum for quantitation of MPA. Quantitation of E2, progesterone, LH, and FSH in serum was performed by using an

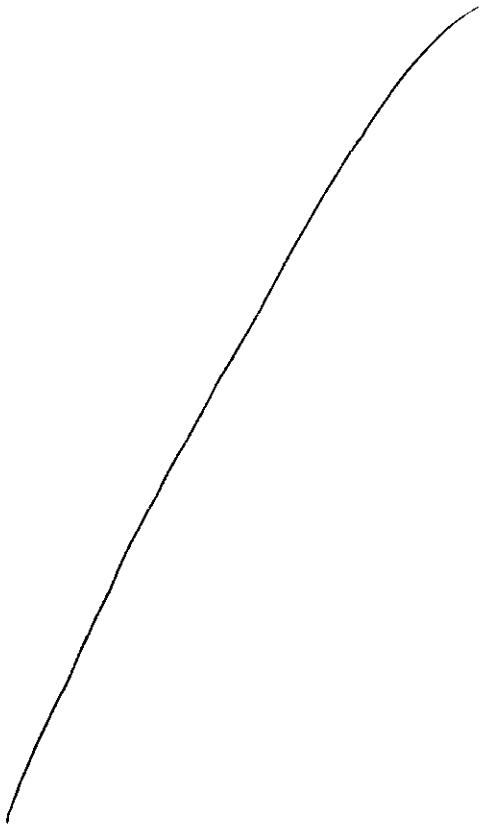
Calibration standard responses were linear over the MPA range of ng/mL using a weighted (1/concentration^2) linear, least squares regression. Results below the lower limit of quantitation (LLOQ) were reported in the final data report as 'BLQ'; the LLOQ equals ng/mL. No clinical sample responses exceeded the calibration range. Correlation coefficients were all ≥ CV% were used to express the precision of the back-calculated CS. The eight CS points had CVs that were with mean accuracy between Inter-day accuracy and precision was further monitored by analysis of three MPA quality control (QC) standards with target concentrations of ng/mL. Inter-day precision for the three QC standards was with assay accuracy from

The lower limit of quantitation for estradiol was — pg/mL. Inter-assay precisions were — , for the — pg/mL QC standards, respectively. Mean accuracies were — pg/mL AC standards, respectively.

The lower limit of quantitation for progesterone was — pg/mL. Inter-assay precisions were — QC standards, respectively. Mean accuracies were —

3. **Detailed Labeling Recommendations**

CLINICAL PHARMACOLOGY



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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

4. Appendices

4.1 Individual Study Reviews

Study 272 "A Prospective, Evaluator-blinded, Randomized, Single-center Trial Comparing Suppression of Ovulation, Duration of Ovulation Suppression, and Return of Ovulation Following a Single Injection of DMPA-SC or DMPA-IM"

A prospective, evaluator-blinded, randomized, single-dose, single-center study was conducted in 68 healthy female subjects aged 18-40 to compare ovulation suppression, duration of ovulation suppression, and return to ovulation following a single injection of either DMPA-SC or DMPA-IM. The PK of MPA was determined in subjects enrolled in the DMPA-SC arm. Subjects with confirmed ovulation were stratified by BMI and then randomized to either DMPA-SC (n=45) or DMPA-IM (n=23) in an approximate 2:1 ratio into the DMPA-SC or DMPA-IM group, respectively. Subjects received a treatment injection within 3 days of their menses.

The PK of MPA was determined from the 42 DMPA-SC subjects (39 clinically evaluable, 3 nonevaluable). Suppression followed by the recurrence of ovulation was monitored thereafter through changes in serum and urine hormone levels and sonogram readings. The return to ovulation was defined by a serum progesterone level ≥ 4.7 ng/mL, or urinary levels of Pd-3-G (pregnanediol-3-glucuronide) that were ≥ 3 times its mean baseline level for at least 3 consecutive samples. Subgroup analyses for selected endpoints were performed for race subgroups (white, black, and Asian/Pacific Islander) and 3 BMI ranges (18-28 kg/m^2, 28-38 kg/m^2 and >38 kg/m^2). No formal statistical analysis was planned for the PD data generated in this study. The relationship between PK parameters (e.g., C_{91} days) and suppression followed by resumption of ovulation was explored by correlation analysis.
For the analyses of MPA, progesterone, E_2, LH and FSH, blood samples were collected at the following times: Day 0 (pre-dose), and on Days 1 (24 hr post-dose), 3, 5, 7, 9, 11, 13, 15, 19, 23, 27, 34, 41, 48, 55, 62, 69, 76, 79, 81, 83, 85, 89, 91, 93, 97, 101, 105, 112, 119, 126, 133, and 140.

The mean age of 39 subjects (25 white, 13 black, and 1 Asian) in the DMPA-SC group was 33.8 ± 5.5 (range, 21 – 40), and the mean BMI was 28.7 ± 6.3 (range, 18.2 – 46).

Table 12. MPA Pharmacokinetic Parameters after DMPA-SC Administration (n=42)

Pharmacokinetic Parameter	MEAN	STD	MEDIAN	MIN	MAX
AUC0-91 (ng•day/mL)	66.98	24 90	67 22		
AUC0-t(last) (ng-day/mL)	80.79	25 28	80.86		
AUC0-∞ (ng-day/mL)	92 84	23 46	95 23		
Cmax (ng/mL)	1.56	0 67	1 49		
tmax (day)	8.6	13 2	5 0		
λz	0 0195	0 0088	0 0183		
$t_{1/2}$ (day)	43 2	20 8	37 8		
C_{91} (ng/mL)	0.402	0.147	0 388		

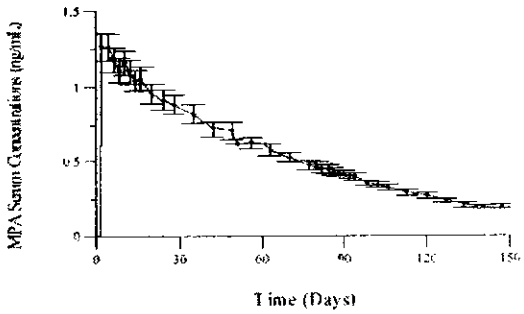
N = 42 subjects

- All individual MPA profiles demonstrated serum concentrations ≥ 0.2 ng/mL by 24 hour and were sustained throughout the targeted dosing intervals of 13 ± 1 weeks in all but 2 subjects.

- Considerably inter-subject variability in MPA concentrations was apparent. Serum MPA concentrations peaked approximately 9 days after dosing.
- The mean MPA C_{max} was about 1.56 ng/mL with a mean apparent terminal $t_{1/2}$ of 43 days.

Figure 8. Mean Serum MPA Concentration-Time Profile after (A) DMPA-SC and (B) DMPA-IM Administration (Data from NDA 20-246)

(A) DMPA-SC (n=42)



(B) DMPA-IM (n=9)

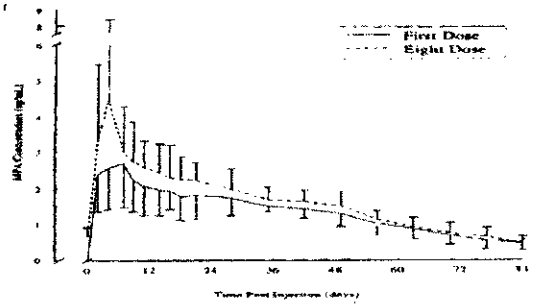


Table 13. MPA Pharmacokinetic Parameters by Race after DMPA-SC Administration

Pharmacokinetic Parameter	Asian (n = 1)	Black (n = 14)	White (n = 27)	ANOVA p-value
AUC0-91 (ng•day/mL)	57.54	62.65	69.58	0.6609
AUC0-t(last) (ng•day/mL)	80.14	75.88	83.38	0.6778
AUC0-∞ (ng•day/mL)	97.52	86.75	95.83	0.5026
Cmax (ng/mL)	—	1.377	1.677	0.3201
tmax (day)	4.0	16.1	5.3	0.0384
λz	0.0198	0.0191	0.0197	0.9792
$t_{1/2}$ (day)	35.0	42.7	43.8	0.9138
C91 (ng/mL)	—	0.397	0.403	0.9692

- There was no statistically significant difference in the PK parameter estimates for MPA among the subgroups with the exception of t_{max}. The t_{max} appeared to be longer in black subjects, as several subjects showed prolonged, flat MPA profiles with no apparent C_{max} level.

Table 14. MPA Pharmacokinetic Parameters by BMI after DMPA-SC Administration

PK Parameter	BMI ≤25 (n=13)	BMI >25-30 (n=10)	BMI >30 (n=19)	ANOVA p-value	BMI ≤28 (n=19)	BMI >28-38 (n=18)	BMI >38 (n=5)	ANOVA p-value
AUC0-91 (ng•day/mL)	68.50	74.79	61.83	0.4075	71.55	67.82	46.33	0.1279
AUC0-t(last) (ng•day/mL)	84.71	88.22	74.21	0.2586	86.39	81.45	57.18	0.0671
AUC0-∞ (ng•day/mL)	99.31	98.09	85.85	0.1977	99.30	92.44	69.75	0.0369
Cmax (ng/mL)	1.647	1.766	1.460	0.3305	1.735	1.534	1.021	0.0982
tmax (day)	4.2	17.8	7.8	0.0424	9.5	9.3	4.4	0.7354
λz	0.0175	0.0233	0.0186	0.2595	0.0198	0.0201	0.0159	0.5363
$t_{1/2}$ (day)	46.9	35.6	44.8	0.4041	43.7	39.6	55.9	0.3189
C91 (ng/mL)	0.445	0.443	0.351	0.1218	0.431	0.411	0.259	0.0618

- The BMI in the DMPA-SC group ranged from 18.2 to 46.7 kg/m^2, with the majority in the overweight/obese categories.
- The analysis used a BMI classification based on Dietary Guideline for Americans 2000 (healthy: BMI 18.5 – 25 kg/m^2; overweight: BMI 25 – 30 kg/m^2; obese: BMI>30 kg/m^2)

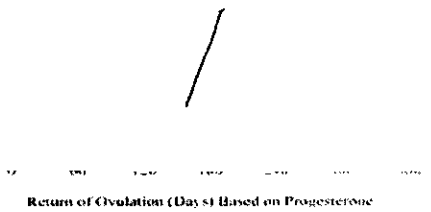
and the BMI stratification used at the time of randomization: (1) BMI 18-28 kg/m^2, (2) BMI >28-38 kg/m^2, and (3) BMI>38 kg/m^2.

- Dietary Guideline for Americans: there were no significant differences in the MPA parameter estimates of AUC, C_{max}, λz, and $t_{1/2}$ among the 3 BMI categories.
- There were no significant differences in the parameter estimates of AUC_{91}, AUC_{last}, C_{max}, λz, and $t_{1/2}$ among BMI categories used at the time of randomization. The AUC_{inf} was lower in subjects with a BMI >38 kg/m^2.
- Although no statistically significant difference was observed in MPA concentrations on day 91 among different BMI categories, MPA trough concentrations tended to be lower in obese subjects with a higher BMI (> 38 kg/m^2).

A single dose of DMPA-SC effectively suppressed ovulation for 13 ± 1 weeks in all evaluable subjects, regardless of race and body weight. The earliest return to ovulation was 15 weeks and the median return was 30 weeks, as measured by a serum progesterone level ≥4.7 ng/mL. By the end of 1 year, the cumulative rate of return to ovulation was 97.4% (38/39) in the DMPA-SC group. By the end of 1-year, the cumulative rate of return to ovulation was 97.4% after DMPA-SC administration.

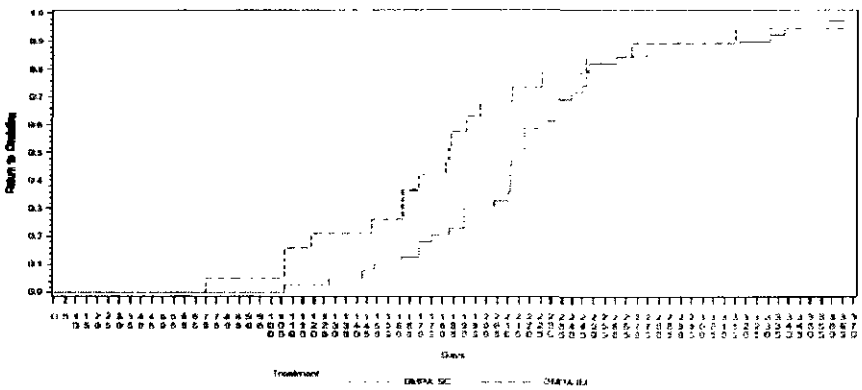
PK/PD Correlation

Figure 9. Individual Subject MPA Concentration at Day 91 (C_{91}) vs. Return of Ovulation Based on Serum Progesterone in the DMPA-SC Group



- The correlation coefficient was 0.035 and the coefficient of determination was 0.0012. The low coefficient of determination indicates that the C_{91} parameter is not predictive of the return of ovulation following DMPA-SC administration.

Figure 10. Time to Return of Ovulation Based on Progesterone Concentrations (≥ 4.7 ng/mL) in Evaluable Subjects



The cumulative rate of ovulation at the end of 12 months post-injection in evaluable subjects was 97.4 % (38/39) in the DMPA-SC group. The median time of return to ovulation, based on progesterone concentrations ≥ 4.7 ng/mL in evaluable subjects, was 212 days for the DMPA-SC group by Kaplan-Meier analysis.

Study 265 "MPA Injectable Sterile Suspension: A PK and PD Study after Single SC Administration of 50-mg, 75-mg, 100-mg, or 150-mg Dose in Women with Menstrual-ovulatory Cycle"

A single center, open-label, randomized, single-dose (4 levels), outpatient, parallel group, PK/PD study was conducted in 47 healthy women aged between 18 and 45 years to determine the PK and PD of MPA after a single SC 0.5 mL injection of either a 50-mg, 75-mg, 100-mg, or 150-mg dose level administered in the leg or in the abdomen.

Based on the observed ovulation suppression and PK results of the dose-finding study, it was concluded that 100 mg per 0.5 mL suspension would be an effective contraceptive dose given SC every 3 months. Since the SC formulation being developed for this protocol and for the Phase III program is 16% w/v (a concentration of 100 mg MPA per 0.625 mL), the injection volume was rounded to 0.65 mL for practical reasons, thus yielding a dose of 104-mg MPA per injection.

Objectives:

- To determine the dose-response (suppression of ovulation) relationship after a single SC administration of 50mg, 75mg, 100mg, or 150mg MPA in women with confirmed menstrual-ovulatory cycles
- To determine the PK of MPA after SC administration of 50-, 75-, 100-, and 150-mg doses, comparison of two SC injection locations, and to explore possible relationships between select PK parameters (eg, AUC, C_{91}) and the PD response (suppression of ovulation) at each dose level
- To identify a lowest MPA dose that effectively suppresses ovulation when administered SC every 3 months, for further investigation of DMPA-SC in Phase III trials for prevention of pregnancy, and the treatment of symptoms of endometriosis in women

Subjects were randomized to receive a single injection of a 50-mg, 75-mg, 100-mg, or 150-mg dose of MPA in the leg (anterior) or the abdomen. Serum concentrations of progesterone, E_2, LH and FSH were monitored for 112 days for evidence of suppression followed by resumption of ovulation. In women randomized into the 100-mg dose, vaginal ultrasounds were also performed during the pretreatment and treatment phases to determine the status of follicular development. Endometrial thickness was assessed in those women who underwent vaginal ultrasound.

The following marketed products were used to produce the subcutaneously administered 50-, 75-, 100-, and 150-mg MPA per 0.5-mL dose levels: Depo-Provera® Contraceptive Injection (150 mg/mL), and Depo-Provera® Sterile Aqueous Suspension (400 mg/mL). The 50- and 75-mg doses were prepared from Depo-Provera CI (150 mg/mL), while the 100- and 150-mg doses were prepared from Depo-Provera SAS (400 mg/mL). Both Depo-Provera-IM products were diluted with sterile saline to yield the appropriate dose levels for DMPA-SC administration. Blood samples were collected at the following times to determine the concentrations of MPA, progesterone, E_2, LH and FSH: Day 0 (pre-dose), and on Days 1 (24 hrs post-dose), 3, 5, 7, 10, 12, 14, 18, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, and 112.

Figure 11. (A) Mean Serum MPA Concentration-Time and (B) Log-Linear Mean Serum MPA Concentration-Time Profiles after a Single DMPA Dose

(A) (B)

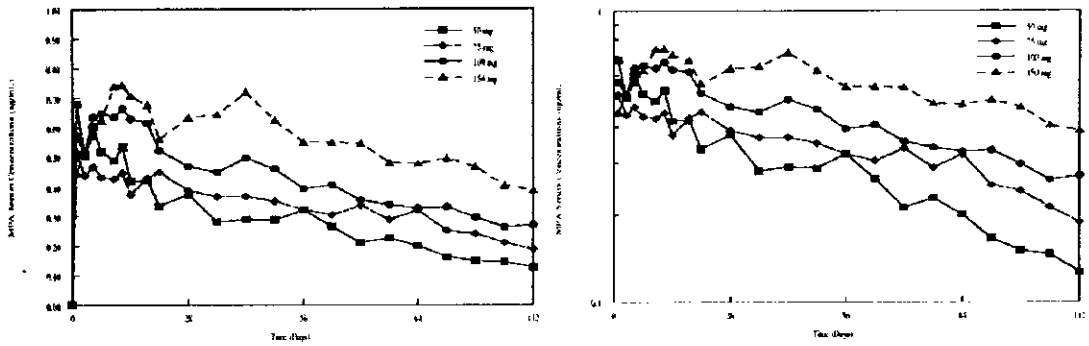


Table 15. Mean (SD) MPA Pharmacokinetic Parameters after a Single DMPA Dose

Parameter	Treatment*				ANOVA p-value†	Pairwise Comparison‡
	A	B	C	D		
AUC (ng day/mL)	37.7 (8.41)	43.2 (13.1)	54.0 (15.9)	79.3 (26.9)	0001	ABC, BC
AUC0-tt (ng day/mL)	29.2 (6.23)	32.8 (9.29)	41.5 (13.4)	53.3 (16.4)	0001	AB, BC
Cmax (ng/mL)	0.831 (0.387)	0.780 (0.226)	0.889 (0.353)	0.947 (0.277)	6179	-
Cτ (ng/mL)	0.174 (0.0822)	0.253 (0.111)	0.332 (0.137)	0.495 (0.215)	0001	AB, BC
tmax (day)	16 (28)	18 (21)	21 (21)	25 (27)	8058	--
t1/2 (day)	31.4 (20.8)	31.8 (18.2)	27.0 (11.7)	37.3 (18.9)	6033	--
Dose Normalized§						
AUC (ng day/mL)	37.7 (8.41)	28.8 (8.76)	27.0 (7.97)	26.4 (8.97)	0120	BCD
AUC0-tt (ng day/mL)	29.2 (6.23)	21.8 (6.19)	20.8 (6.69)	17.8 (5.46)	0008	BCD
Cmax (ng/mL)	0.831 (0.387)	0.520 (0.151)	0.445 (0.177)	0.316 (0.0922)	0001	BC, CD
Cτ (ng/mL)	0.174 (0.0822)	0.169 (0.0738)	0.166 (0.0687)	0.165 (0.0718)	9939	--

* Treatment A: 50 mg MPA per 0.5 mL
Treatment B: 75 mg MPA per 0.5 mL
Treatment C: 100 mg MPA per 0.5 mL
Treatment D: 150 mg MPA per 0.5 mL

† p-value for overall treatment differences by Analysis of Variance (ANOVA)

‡ Pairwise comparisons made by LSD (least significant-difference test). Treatments that are grouped together are not significantly different from each other ($p>.05$)

§ Dose-normalized parameters to a 50-mg dose

- Serum MPA concentrations peaked approximately 2 to 3 weeks after dosing and apparently independent of dose.
- MPA concentrations were sustained throughout the targeted dosing interval of 91 days, particularly at the higher dose levels, indicating that MPA absorption from the SC injection site is prolonged.
- The AUC and C_{min} ($C_{91\ day}$) increased with higher doses of DMPA, but there was considerable overlap across dose levels.
- Serum MPA concentrations at Day 91 increased in a dose proportional manner but C_{max} did not appear to increase proportionally with the higher doses of DMPA given subcutaneously.
- The $t_{1/2}$ appeared to be independent of dose. The mean $t_{1/2}$ estimated from plasma concentrations 70-112 days post-dosing were highly variable, ranging from 27 to 37 days for different dose groups. The dose-normalized AUC and C_{max} were statistically different among treatments.

Figure 12. Relationship between $AUC_{0\text{-inf}}$, C_{max}, or C_{91} and DMPA Dose

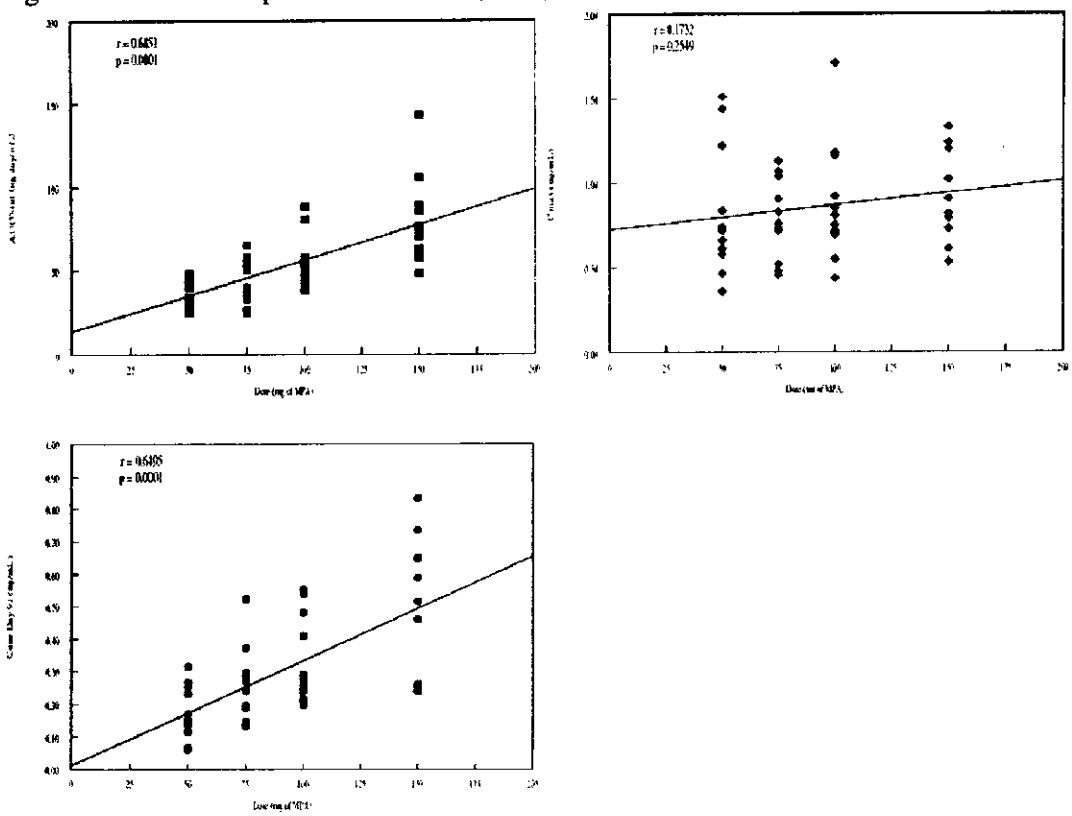
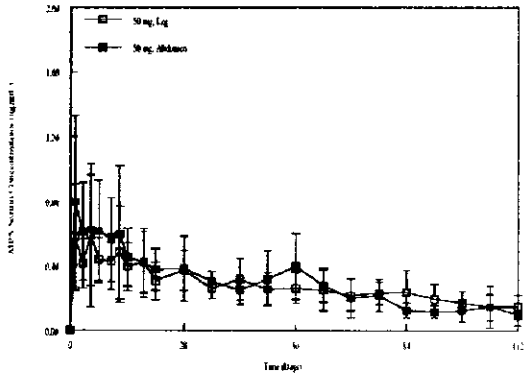
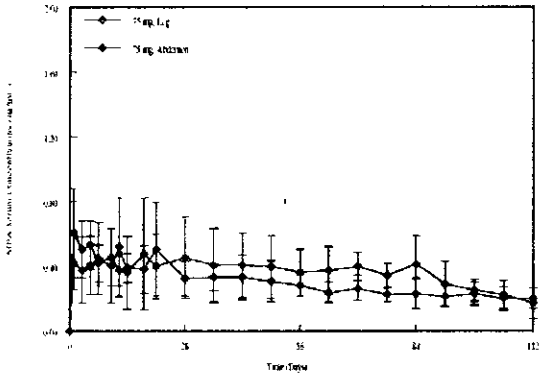


Figure 13. Mean (SD) Serum MPA Concentration-Time Profile after the (A) 50-mg, (B) 75-mg, (C) 100-mg, or (D) 150- mg DMPA Dose by Injection Site

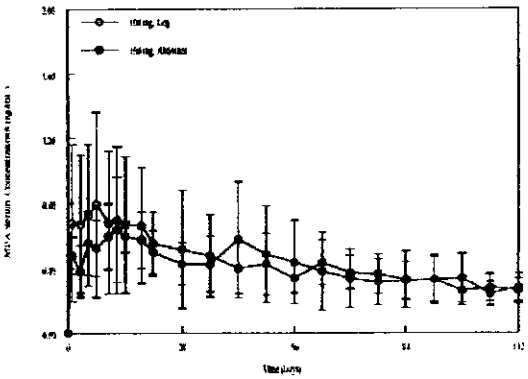
(A) 50-mg



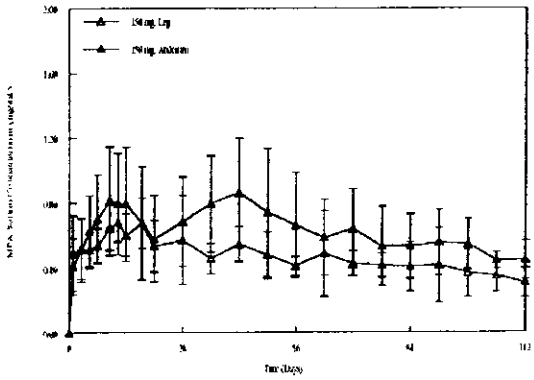
(B) 75-mg



(C) 100-mg



(D) 150-mg



- The location of SC injection site (anterior leg or abdomen) did not appear to affect the overall PK profile of MPA.

Ovulation Suppression and PK of MPA

- The higher the DMPA-SC dose, the magnitude and duration of estradiol suppression was greater. Serum estradiol concentrations on average were 100-150 pg/mL, 50-100 pg/mL, or about 50 pg/mL following the 50-, 75-/100-, or the 150mg dose, respectively.
- Circulating levels of estradiol observed during the 3 treatment months after the SC injection of doses from 50 to 100 mg DMPA were comparable to those found in the early to mid-follicular phase of the control cycle.

50-mg DMPA

- Progesterone concentrations were suppressed in 8 of 11 women for ≥ 112 days.
- One woman (Subject No. 42) showed ovulatory progesterone levels — g/mL) on Day 5 post-injection, too early for an actual ovulatory cycle. It appears that variation in the menstrual cycle length of this subject may have led to inaccurate timing of the injection.
- In 2 women (Subject No. 38 & 24), although progesterone concentrations increased to — ng/mL (Day 98) and — ng/mL (Day 112), respectively, the observed progesterone concentrations did not reach ovulatory threshold. One woman (Subject No. 23) missed 2 consecutive visits from Day 70 through Day 91 with some indication of return to ovulation.
- Seven of 11 subjects (64 %) had MPA trough concentrations below 0.20 ng/mL.

75-mg DMPA

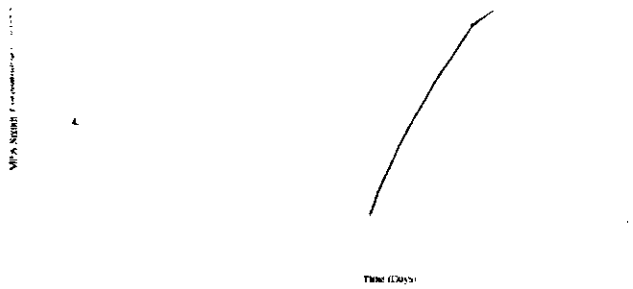
- No ovulation (based on serum progesterone) occurred during the dosing interval of 91 days.
- One woman ovulated (confirmed by progesterone levels >4.7 ng/mL) on Day 98 after the SC injection. This ovulation is considered an efficacy failure as the actual ovulation/lutenization (LH surge) has most likely occurred 1-2 weeks earlier (within the dosing interval of 91 days).
- Five of 12 subjects (42 %) had trough serum MPA concentrations below 0.20 ng/mL on Day 91.

100-mg DMPA

- Progesterone concentrations were completely suppressed in 11 of 12 women for ≥ 112 days.
- One woman (Subject No. 26) ovulated on Day 70 post-injection. This subject failed efficacy clearly because of an unexpected pharmacokinetic profile. This subject was excluded from the 100-mg dose for further PK/PD analysis.

- Ten of 12 subjects exhibited MPA trough concentrations (C_{91}) ≥ 0.2 ng/mL. One woman (Subject No. 26) showed a significant burst effect immediately after dosing, followed by a rapid decline in serum MPA concentrations approaching 0.167 ng/mL by Day 49.

Figure 14. Composite of Individual Subject Serum MPA Concentration-Time Profiles after the 100-mg DMPA Dose Including Subject 26



150-mg DMPA

- Serum progesterone concentrations were effectively suppressed in all 11 women completing the 112 day time course.
- All women showed MPA C_{91} ≥ 0.2 ng/mL.

Study 271: "A PK and PD Study after a Single Administration of DMPA-SC (104 mg/0.65 mL) in Asian Women with Menstrual-Ovulatory Cycles"

A single center, open-label, single-dose, outpatient, parallel-group study was conducted in 24 healthy Asian women (age, 18-40 years old, BMI, 18-28) with confirmed ovulation involving a single SC dose administration of DMPA-SC within the first 5 days of the onset of menstrual bleeding. The DMPA-SC suspension was administered in either the leg (anterior) or the abdomen in a 1:1 ratio.

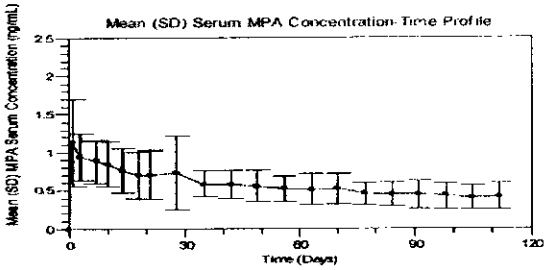
Objectives:

- To determine the duration of ovulation suppression in Asian women after SC administration of DMPA-SC with serum progesterone as the primary indicator of ovulation
- To determine the PK of MPA after SC administration of DMPA-SC
- To evaluate the effect of SC injection location (anterior leg vs. abdomen) on the PK/PD profiles
- To assess whether Asian ethnic groups exhibit major differences in PK/PD profile of DMPA-SC

Suppression followed by recurrence of ovulation was monitored as evidenced through changes in serum progesterone, E_2, LH and FSH concentrations. Progesterone concentrations ≥ 4.7 ng/mL were used as a threshold level for occurrence of ovulation. An increase in serum concentrations of E_2 ≥ 150 pg/mL and of progesterone ≥ 3 ng/mL were considered to be indicative of ovarian follicular and luteal phase activity, respectively. No formal statistical analysis was planned for the pharmacodynamic data generated in this study.

Blood samples for MPA, progesterone, E_2, LH and FSH were collected at the following times after drug administration: Day 0 (prior to dosing), and on Days 1 (24 hr post-dose), 3, 7, 10, 14, 18, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105 and 112.
Twenty-four women had a mean age of 33.8 (range, 23 – 40) years and a mean BMI of 22.4 (range, 17.6 – 27.2) kg/m^2. There were 4 Chinese, 2 Filipino, 10 Indian, 6 Malayan and 2 Thai women.

Figure 15. MPA Concentration-Time Profile after a Single DMPA-SC Dose in Asian Women (n=24)



- MPA concentrations of ≥ 0.20 ng/mL were observed for > 91 days in 23 of 24 women after SC administration of DMPA-SC.
- MPA concentrations were sustained throughout the targeted dosing interval of 91 days indicating that MPA absorption from the SC injection site was prolonged in these Asian women.

Table 16. PK Parameters of MPA after a Single DMPA-SC Dose in Asian Women

AUC0_91	24	63.893	16.2443	65.9336
AUCON	24	64.163	16.4195	66.0123
AUCTOT	24	118.135	67.1614	93.0457
CMAX	24	1.298	0.6024	1.0550
TMAX	24	13.125	23.1842	3.0000
LZ	23	0.011	0.0066	0.0091
THALF	23	91.864	58.6432	76.5477
C_91	24	0.441	0.1776	0.4090

- The mean (SD) MPA C_{max} was 1.30 (0.60) ng/mL and the t_{max} was approximately 2 weeks after dosing (range, 1-91 days).
- The mean (SD) $t_{1/2}$ was about 92 (59) days and highly variable (range, 21-261 days).

Figure 16. MPA Concentration-Time Profile after a Single DMPA-SC Dose in Asian Women by Injection Site (n=12)

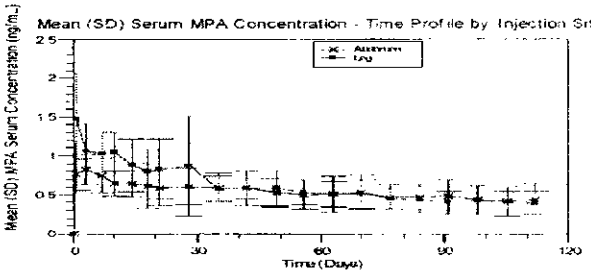


Table 17. PK Parameters of MPA after a Single DMPA-SC in Asian Women by Injection Site

AUC0_91	60.032	67.754	0.25299
AUC0N	60.155	68.171	0.23996
AUCTOT	123.748	112.522	0.69163
CMAX	0.943	1.652	0.00189
TMAX	21.917	4.333	0.06146
LZ	0.010	0.011	0.54896
THALF	103.748	80.971	0.36430
C_91	0.470	0.412	0.43939

- There was no statistically significant difference in MPA parameter estimates obtained for the 2 injection sites, except for C_{max}. The C_{max} was higher in women receiving the injection in the anterior leg relative to the abdomen.

Table 18. PK Parameter Summary Statistics by Injection Site

Abdomen

AUC0_91	12	60.032	16.3399	65.9336
AUC0N	12	60.155	16.3480	66.0123
AUCTOT	12	123.748	84.4139	84.0200
CMAX	12	0.943	0.2059	0.9200
TMAX	12	21.917	29.8830	8.5000
LZ	11	0.010	0.0057	0.0079
THALF	11	103.748	71.5215	87.2551
C_91	12	0.470	0.2214	0.3795

Leg

AUC0_91	12	67.754	15.8817	67.889
AUC0N	12	68.171	16.1678	68.060
AUCTOT	12	112.522	47.2960	101.441
CMAX	12	1.652	0.6649	1.775
TMAX	12	4.333	7.8894	1.000
LZ	12	0.011	0.0074	0.011
THALF	12	80.971	44.2389	65.965
C_91	12	0.412	0.1231	0.426

Table 19. Concentration Summary by Injection Site

0	0.00000	0.00000	.
1	0.75482	1.46892	0.00111
3	0.82375	1.06283	0.05392
7	0.74958	1.02836	0.01476
10	0.64167	1.04858	0.00014
14	0.63717	0.87917	0.04080
18	0.60675	0.76758	0.13346
21	0.57942	0.83008	0.05974
28	0.60467	0.86533	0.20294
35	0.58742	0.57473	0.86514
42	0.57783	0.58000	0.97697
49	0.52367	0.58150	0.50270
56	0.50250	0.52664	0.74855
63	0.50609	0.50930	0.97188
70	0.52828	0.50492	0.77608
77	0.46567	0.44333	0.70583
84	0.46225	0.43267	0.66260
91	0.46983	0.41225	0.43939
98	0.42542	0.41367	0.87151
105	0.41350	0.39850	0.82443
112	0.44000	0.39558	0.54363

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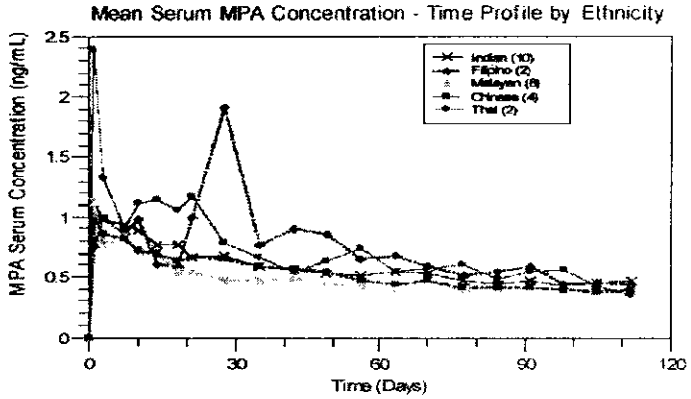
Figure 17. MPA Concentration-Time Profile after a Single DMPA-SC in Asian Women by Ethnicity



- One Filipino woman (Subject No. 3, leg injection site, 29 years old, BMI of 20) showed a high serum MPA (~2 ng/mL) 28 days after dosing, likely an assay interference.

Table 20. PK Parameters of MPA after a Single DMPA-SC in Asian Women by Ethnicity

AUCD_91	60.460	83.288	52.6409	77.996	65.317	0.09679
AUCON	60.555	84.158	52.8612	78.497	65.522	0.09187
AUCTOT	135.220	179.920	92.0494	132.747	119.674	0.85747
CMAX	1.010	1.915	1.1712	1.655	1.294	0.43430
TMAX	5.250	35.000	2.3333	5.500	19.900	0.34654
LZ	0.007	0.009	0.0120	0.019	0.010	0.27906
THALF	130.405	83.912	71.8472	73.206	93.993	0.65159
C_91	0.410	0.598	0.3307	0.544	0.468	0.31138

- The mean (SD) serum MPA concentrations at the expected time of the next injection (Day 91) were 0.41 (0.08), 0.60 (0.23), 0.33 (0.18), 0.54 (0.15) and 0.47 (0.19) ng/mL in Chinese, Filipino, Malayan, Thai and Indian women, respectively.
- The AUC and C_{max} appeared to be greater in the Filipino women but the increase was due primarily to one time point (Day 28) in the concentration-time data of Subject No.3.
- There was no significant difference in serum MPA concentration data among 5 ethnic subgroups, with the exception of one time point at Day 28.

Duration of Ovulation Suppression

- Progesterone concentrations were suppressed in 23 of 24 women for at least 112 days after the SC dosing.
- One Filipino woman (Subject No. 3, leg injection site, 29 years old, BMI of 20) showed an increase in serum progesterone (~16 ng/mL) 57 days after injection. The secondary biomarkers of ovulation (E_2, LH, FSH) as well as the MPA concentration-time profile were not collectively in agreement with the progesterone data. None of these secondary endpoints indicated occurrence of an ovulation in this woman, particularly the absence of follicular activity. Her serum progesterone data revealed values <0.5 ng/mL on Day 50, ~16 ng/mL (the repeat assay confirmed the levels) on Day 57, and 0.57 ng/mL on Day 64. The sponsor states that based on their past experience with this type of study design, ovulations have been observed during two consecutive weekly rises in serum

progesterone when a weekly blood-sampling scheme is used. It is speculated that an interference in the progesterone assay may have caused a high reading on Day 57.

Figure 18. Mean and Median Concentration-Time Profiles for Progesterone after a Single DMPA-SC Dose in Asian Women

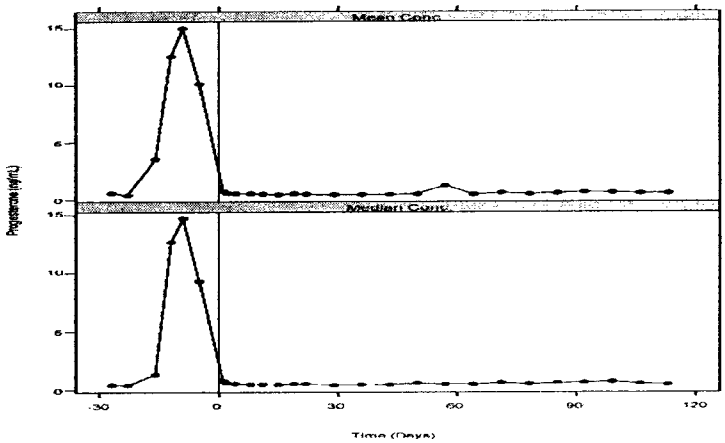


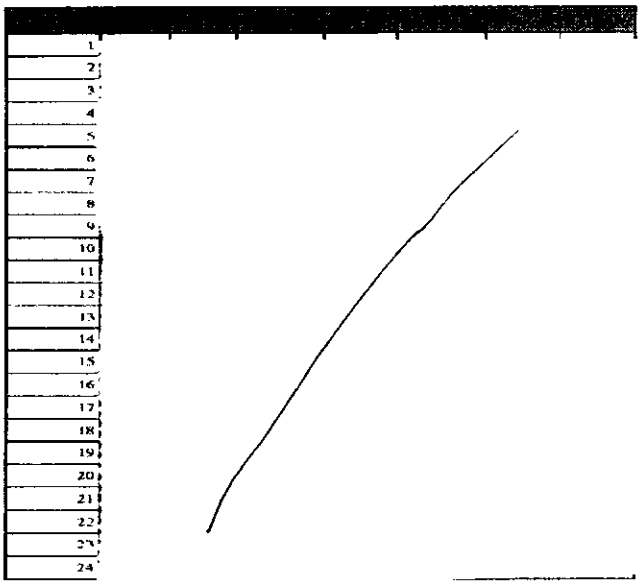
Table 21. Return of Ovarian Function Following a Single Administration of DMPA-SC

Subject	Inj Site	PK/PD Parameters				
		E2*		Progesterone†		MPA
		Time (Days)	Conc (pg/mL)	Time (Days)	Conc (ng/mL)	C91 Days (ng/mL)
1	Abdomen	>112	-----	112	-----	
2	Abdomen	>112	-----	>112	-----	
4	Abdomen	>112	-----	>112	-----	
5	Abdomen	>112	-----	>112	-----	
6	Abdomen	4		>112	-----	
7	Abdomen	4		112	-----	
9	Abdomen	>112	-----	>112	-----	
10	Abdomen	>112	-----	>112	-----	
12	Abdomen	>112	-----	>112	-----	
13	Abdomen	22		>112	-----	
21	Abdomen	22		>112	-----	
22	Abdomen	>112	-----	>112	-----	
3	Leg	>112	-----	57		
8	Leg	>112	-----	112	-----	
11	Leg	>112		>112	-----	
14	Leg	64		112	-----	
15	Leg	>112	-----	>112	-----	
16	Leg	57		>112	-----	
17	Leg	>112	-----	>112	-----	
18	Leg	112		>112	-----	
19	Leg	85		>112	-----	
20	Leg	22		>112	-----	
23	Leg	>112	-----	>112	-----	
24	Leg	99		>112	-----	

* E2 ≥ 150 pg/mL

† Progesterone levels > 4.7 ng/mL.

Table 22. Pharmacokinetics of MPA Following a Single SC administration of DMPA-SC in Each Subject



Study 267 BMD "Phase III Contraception Study of DMPA-SC in Women of Childbearing Potential in the Americas: Substudy Comparing the Effects of DMPA-SC and DMPA-IM in Subjects Scheduled for BMD and Hormone Measurements"

An evaluator-blinded, controlled, two-year study was conducted to compare the effects of DMPA-SC with those of DMPA-IM on bone mineral density (BMD) in women who received treatment with DMPA-SC or DMPA-IM every 3 months for 2 years. An amendment was added to the protocol in order to obtain MPA data after multiple doses of DMPA-SC in a subset of study subjects. Six blood draws were collected in the 2nd year of the BMD substudy at selected centers in Canada. The blood samples were drawn every 2 weeks beginning at Week 2 after a dose of study medication in 8 subjects.

The trough concentrations of MPA from the post one-year dosing interval were compared to other trough concentration data collected in these same subjects at 6, 12 and 24-months. Trough concentrations were also collected at 6, 12 and 24-months for the rest of the subjects who participated in the BMD substudy of protocol 267. An accumulation constant (R) was calculated from single dose data to assess the approximate pharmacokinetic behavior of multiple DMPA-SC injections using the following equation:

$R = 1 / (1-e^{-K\tau})$

where K was the mean terminal rate constant and τ was the dosing interval.

Table 23. Listing of 8 Subjects and MPA C_{min} Concentrations by Timepoint

Subject	6-Month (ng/mL)	12-Month (ng/mL)	2nd Year – Within 1 Dosing Interval*						24-Month (ng/mL)
			2 Week (ng/mL)	4 Week (ng/mL)	6 Week (ng/mL)	8 Week (ng/mL)	10 Week (ng/mL)	12 Week (ng/mL)	
2312									
2354									
2382									
2383									
2398									
2413									
2433									
2450									

Table 24. Summary Statistics for MPA Concentrations by Timepoint

	6-Month	12-Month	2nd Year – Within 1 Dosing Interval*						24-Month
			2 Week	4 Week	6 Week	8 Week	10 Week	12 Week	
N	8	8	7	8	8	8	7	8	2
Mean	0.59411	0.96900	1.70171	1.48525	1.31563	1.09850	0.93686	0.94313	0.77300
Min									
Max									
SD	0.34615	0.72854	0.60469	0.52604	0.52871	0.38986	0.36107	0.35677	0.67458

- Serum MPA concentrations indicate that steady state was achieved over the 6-month to 24-month sample collection period in these 8 subjects. No unexpected accumulation of MPA was observed following multiple SC injections.
- Trough concentrations were collected at 6, 12 and 24 months for the rest of the subjects who participated in the BMD substudy of protocol 267. Mean (SD) MPA trough concentrations at 6 months were 0.67 (0.36) ng/mL (n=157) and at 12 months were 0.79 (0.36) ng/mL (n=144).

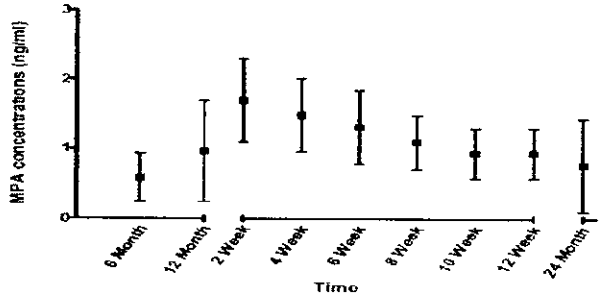
Table 25. Analysis of MPA Concentration Based on Subject and Timepoint

	6-Month	12-Month	Week 12 of Year 2 Interval*	24-Month	ANOVA P-Value
Mean MPA Concentration	0.59411	0.96900	0.94313	0.77300	0.0949

*Subjects had 6 bi-weekly MPA concentrations drawn during one dosing interval in the 2nd year of the study.

- No statistical significance was observed between the mean MPA trough concentrations after 6 months.

Figure 19. Mean (SD) MPA Concentrations at 6 Months, 12 Months and 24 Months (trough values) and at Bi-Weekly Intervals in the Second Year of Dosing Administration



The *R* value calculated from a mean K value of 0.0195 $days^{-1}$ and a dosing interval of 90 days was 1.21. The observed accumulation based upon the ratio of the trough concentrations observed at 6 months from the larger main protocol dataset (0.67 ng/mL, n=157) and after the single dose administration (0.40 ng/mL, n=42) equals 1.68. The observed and calculated accumulation

estimates are approximately the same given the observed variability in the parameters and the limitations of a cross-study comparison.

"DMPA-IM (NDA 20,246), originally reviewed by Dr. Ron Kavanagh dated January 8, 2001"

The PK of MPA following the 1st and the 8th doses of DMPA-IM were evaluated in 9 healthy Caucasian female subjects (mean age, 30±8 years old, range 21-44) with a history of regular menses (28 ± 5 days). Blood samples were obtained prior to 1st and 8th doses and on Days 3, 5, 8, 10, 12, 15, 17, 19, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85 (Week 0, Day 1 and Week 84, Day 1). The site of injection was not mentioned or specified in the protocol. Serum samples were quantitated for MPA using GC-MS method.

Figure 20. Mean (SD) Serum Concentration-Time Profile of MPA Following the 1st or the 8th IM injection of DPMA-IM (n=9)

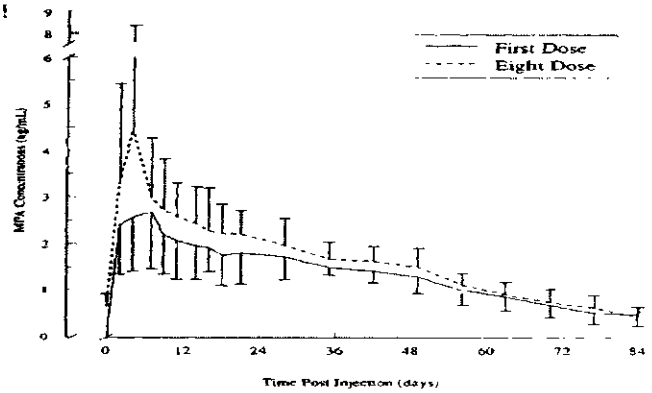


Table 26. Mean (SD) PK Parameters of MPA Following the 1st or the 8th IM Administration of DMPA-IM

Parameters	Doses		Analysis
	First n = 9	Eighth n = 9	Sign Rank p Value
Cmax (ng/mL)	2.90 (1.13)	4.67 (3.60)	0.0742
Tmax (days)	7.22 (4.18)	12.89 (13.39)	0.3828
AUC_{0-84} (ng.day/mL)	114.65 (19.58)	139.14 (23.68)	0.0117*
$AUC_{0-\infty}$ (ng.day/mL)	135.34 (18.47)	nc	-
λz ($days^{-1}$)	0.033 (0.014)	0.033 (0.015)	0.7344
$t_{1/2}$ (days)	26.71 (14.96)	26.02 (16.33)	0.6523
C_{84} days (ng/mL)	0.478 (0.222)	0.446 (0.210)	1.0000

* Indicates significant difference.
nc Not computed

- In a cross-study comparison, the mean values of C_{max} and AUC_{inf} of MPA following a single SC administration of DMPA-SC (NDA 21-583, Study No. 272) were about 46 % and 31 % lower compared with a single IM administration of DMPA-IM (NDA 20-246), respectively.

Table 27. Dose 8/Dose 1 Ratio (ss/sd) Estimates for the AUC and C_{max} of MPA Following Administration of DMPA-IM.

Dose		Accumulation /Linearity		
		Cmaxss/sd	AUCss/sd 0-84	AUCss/sd 0-∞
150 mg	Mean	1.61	1.24	1.04
	Median	1.02	1.16	1.01
	SD	1.02	0.32	0.20
	%CV	63.4	25.8	19.2
	N	9	9	9
	Range			
	95% CI	0.63-2.59	0.99-1.49	0.89-1.19

ss Steady-state
sd Single dose

4.2 Cover Sheet and OCPB Filing/Review Form

APPEARS THIS WAY
ON ORIGINAL

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-584**	**Brand Name**	**Pending**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Medroxyprogesterone acetate injectable suspension**
Medical Division	**DRUDP**	**Drug Class**	**Progestin**
OCPB Reviewer	**Myong-Jin Kim**	**Indication(s)**	**Management of endometriosis-associated pain**
OCPB Team Leader	**Ameeta Parekh**	**Dosage Form**	**Depot Subcutaneous Injection**
		Dosing Regimen	**104 mg/0.65 mL**
Date of Submission	**December 18, 03**	**Route of Administration**	**Subcutaneous Injection**
Estimated Due Date of OCPB Review		**Sponsor**	**Pfizer**
PDUFA Due Date	**October 18, 04**	**Priority Classification**	**Standard**
Division Due Date	**October 1, 04**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	1	1	1	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	1	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	3	3	3	
Phase 3 clinical trial:				
Population Analyses -				

Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	14			
Total Number of Studies				

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included) FDA letter date if applicable
QBR questions (key issues to be considered)	**-SD, MD PK/PD of DMPA-SC -Accumulation of MPA following MD administration -Effect of injection site (anterior thigh vs. abdomen) -Effect of race -Effect of body weight -Dose finding study with Depo-Provera IM formulation**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Myong-Jin Kim, PharmD.**	
Secondary reviewer Signature and Date	**Ameeta Parekh, PhD.**	

CC: NDA 21-584, HFD-850 (L. Lesko, S. Huang), HFD-580 (L. Soule, S. Monroe), HFD-870 (A. Parekh, H. Malinowski, J. Hunt), CDR (B. Murphy)
CP&B Briefing attendees on October 1, 2004: J. Hunt, S. Ortiz, A. Parekh, and L. Soule.

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-584
Compound: Medroxyprogesterone Acetate Injectable Suspension
Sponsor: Pfizer Inc.

Date: February 2, 2004
Reviewer: Myong-Jin Kim

Background:

The sponsor seeks approval of a new, subcutaneous formulation of depot medroxyprogesterone acetate (DMPA) for the indication of endometriosis-associated pain in women [redacted] The recommended dose of DMPA-SC is 104 mg administered by subcutaneous (SC) injection into the anterior thigh or abdomen, once every 3 months. The preparation is presented as a pre-filled, single-use glass syringe, which delivers 104 mg of MPA in 0.65 mL. When administered to women every 3 months, it is proposed to inhibit the secretion of gonadotropins, which in turn, prevents follicular maturation and ovulation, decreases estrogen secretion, and results in endometrial thinning.

Formulation:

	DMPA - SC	Marketed DEPO-PROVERA® IM
Medroxyprogesterone Acetate (MPA)		
Methylparaben		
Propylparaben		
Sodium Chloride		
Polyethylene Glycol		
Polysorbate 80		
Monobasic Sodium Phosphate • 1 H_2O		
Dibasic Sodium Phosphate • 12 H_2O		
Methionine		
Povidone		
Sodium Hydroxide or Hydrochloric Acid		
Water for Injection	QS to	QS to

The dose was determined in Phase I/II dose finding study performed with the currently marketed Depo-Provera IM formulation given subcutaneously. The Phase III pivotal trials were performed with the final formulation and dose/volume of administration.

PK parameters of MPA after a single SC injection of DMPA-SC in healthy women (n=42)

	C_{max} (ng/mL)	T_{max} (day)	$C_{91\ (min)}$ (ng/mL)	AUC_{0-91} (ng·day/mL)	$AUC_{0-\infty}$ (ng·day/mL)	$t_{1/2}$ (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min						
Max						

Healthy Subject PK Studies:

- **Study 265 (US Phase I/II)**: MPA Injectable Sterile Suspension: A PK/PD open-label,

randomized, single-dose, parallel group study after single subcutaneous administration of 50mg, 75mg, 100mg or 150mg dose in women with menstrual ovulatory cycle (n=47, Caucasians).

- The marketed products, Depo-Provera® Contraceptive Injection (150 mg MPA/mL) and Depo-Provera® Sterile Aqueous Suspension (400 mg MPA/mL), were used to produce the subcutaneously administered 50-, 75-, 100-, and 150-mg MPA/0.5 mL dose levels.
- Dose-proportionality, impact of SC injection sites (anterior leg vs. abdomen) on PK/PD profiles.
- The sponsor stated that the relationship between the AUC or the C_{min} and the SC dose of MPA appeared to be linear but the mean C_{max} did not change substantially with increasing dose.
- The sponsor concluded that the 100 mg/0.5 mL was an effective dose given SC every 3 months. Since the SC formulation evaluated in the Phase 3 program was 16% w/v (a concentration of 100 mg MPA/0.625 mL), the injection volume of 0.65 mL yielding 104 mg MPA per injection was chosen.

- **Study 271 (Singapore Phase I)**: A PK/PD single-dose, parallel-group study after a single administration of DMPA-SC in Asian women (n=24) with menstrual-ovulatory cycles
  - The WHO study: an enhanced metabolism and/or clearance of MPA after IM administration of DMPA in Thai women; a faster return of ovarian function in Thai women compared with women from other countries (Dose finding study 265 was done in Caucasian women).
  - The duration of ovulation suppression after DMPA-SC and the PK of DMPA-SC in Asian women were evaluated.
  - The effect of DMPA-SC injection location (anterior leg vs. abdomen) on the PK/PD profiles (*in the proposed label, no effect according to the sponsor*) and whether major Asian ethnic groups exhibit major differences in PK/PD profile of DMPA-SC were evaluated (*no effect according to the sponsor).*
  - The C_{max} was higher in women receiving the injection in the anterior leg relative to the abdomen.

- **Substudy 267**: A study to determine return to ovulation and return to fertility after discontinuation of DMPA-SC following multiple doses. (Phase III 1-year contraception study of DMPA-SC)
  - Steady-state PK data following multiple dose administration.

Healthy Subject PD and PK/PD Study:

- **Study 272 (US Phase I/II)**: A prospective, evaluator-blinded, single-dose, randomized, single-center trial comparing suppression of ovulation, duration of ovulation suppression, and return of ovulation following a single injection of DMPA-SC (104 mg/0.65 mL) or DMPA-IM (150 mg/mL) in 68 subjects (58 evaluable subjects: n=39 DMPA-SC, n=19 DMPA-IM). (The site of injection is not clearly stated)
  - The pharmacokinetics of MPA were determined in subjects enrolled in the DMPA-SC arm.
  - Subgroup analyses for race subgroups (70.7% white, 27.6% black, 1.7 % Asian/Pacific Islander). T_{max} appeared to be longer in black subjects.
  - Subgroup analyses for 3 BMI ranges (18-28 kg/m^2, >28-38 kg/m^2, and >38 kg/m^2). The $AUC_{0\text{-}inf}$ was lower in obese subjects with BMI >38 kg/m^2 (*in the*

proposed label, no dosage adjustment is necessary).

Review Issues:

1. Effect of injection site (anterior thigh vs. abdomen) (Studies 265 and 271).
    a. The proposed label stated that MPA trough concentrations are similar for the two injection locations (C_{min} at Day 91), suggesting that injection site does not negatively affect contraceptive efficacy.
2. Effect of race (Studies 271 and 272)
    a. The proposed label stated that there are no apparent differences in the PK and/or PD of MPA after SC administration of DMPA-SC.
3. Effect of body weight (Study 272)
    a. The proposed label stated that no dosage adjustment is necessary based on body weight. Three BMI groups were evaluated: $\leq$25 kg/m^2, >25-30 kg/m^2, and > 30 kg/m^2.
    b. In the Study 272, 3 BMI ranges were evaluated, 18-28 kg/m^2, >28-38 kg/m^2, and >38 kg/m^2.
4. Accumulation of MPA following MD administration of DMPA-SC.
5. Dose finding study with the Depo-Provera IM formulation.

The to-be-marketed formulation of DMPA-SC is the same as the clinical trial formulation.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II finds that the Human Pharmacokinetics and Bioavailability section for NDA 21-584 is fileable.

_____ _____

Myong-Jin Kim, Pharm.D. Date

_____ _____

Ameeta Parekh, Ph.D., Team Leader Date

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

/s/

Myong-Jin Kim
10/18/04 10:35:43 AM
PHARMACOLOGIST

Ameeta Parekh
10/18/04 10:44:16 AM
BIOPHARMACEUTICS
concur