CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-583

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Memo to File

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA: 21-583

Compound: Medroxyprogesterone Acetate Injectable Suspension

Sponsor: Pfizer Inc.

Date: December 15, 2004

Reviewer: Myong-Jin Kim, Pharm.D.

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 of medroxyprogesterone acetate (MPA) following a subcutaneous (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 document to support that the induction of MPA is more likely with oral administration and less likely with SC administration. The Office of Clinical Pharmacology and Biopharmaceutics agree with this scientific basis and this justification satisfies the Phase IV commitment and no further studies are recommended (see teleconference minutes dated September 22, 2004).

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-583
Brand Name:	Pending
Generic Name:	Medroxyprogesterone Acetate Injectable Suspension
Sponsor:	Pfizer Inc.
Relevant IND(s):	61,388
Date(s) of Submission:	June 30, 2003 October 28, 2003 (SU)
Type of Submission: **Code:**	Original NDA 3S
Formulation: **Strength:**	Subcutaneous Injection 104 mg/0.65 mL
Indication:	Prevention of Pregnancy
Reviewer:	Myong-Jin Kim, Pharm.D.
Team Leader:	Ameeta Parekh, Ph.D.
OCPB Division:	DPE-II
OND Division:	Reproductive & Urologic Drug Products

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1. Executive Summary

The sponsor seeks approval of a depot medroxyprogesterone acetate subcutaneous formulation (DMPA-SC) for the prevention of pregnancy in women of child bearing potential. The recommended dose of DMPA-SC is 104 mg administered by subcutaneous (SC) injection into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks).

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 [150 mg/mL; DMPA-IM] and Depo-Provera® Sterile Aqueous Suspension [400 mg/mL]). Depo-Provera® Contraceptive Injection 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. Provera® is indicated for the treatment of secondary amenorrhea, dysfunctional uterine bleeding, and the prevention of endometrial hyperplasia in women using 0.625 mg of conjugated estrogen. Depo-Provera® Sterile Aqueous Suspension is indicated for the adjunctive and palliative treatment of endometrial or renal carcinoma.

In support of DMPA-SC formulation for use as a contraceptive, the sponsor conducted 3 single dose studies (Studies 265, 271, 272) 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).

Study 265 is a Phase 1/2 dose-finding study in which the PK/PD of MPA were evaluated after SC administration of single doses of 50, 75, 100, or 150 mg per 0.5 mL suspension using the DMPA-IM formulation. The objectives of this study were to characterize the PK of MPA at 4 dose levels, to evaluate dose-proportionality, to determine the lowest effective dose to suppress ovulation, and to evaluate the effect of SC injection sites on the PK/PD profiles in Caucasian women.

Study 271 was conducted in Asian women using the DMPA-SC formulation to determine the PK of MPA and the duration of ovulation suppression, to evaluate effects of SC injection sites on the PK/PD profiles, and to investigate whether women of Asian ethnicity exhibit differences in the PK/PD profiles.

In Study 272, MPA PK was determined and subgroup analyses were performed by race and by body mass index (BMI) to assess the potential effect of intrinsic factors on the PK/PD profiles after DMPA-SC administration in U.S. women. Furthermore, the cumulative rate of return to ovulation at 12 months was assessed after a single dose of DMPA-SC.

In addition to these 3 PK/PD studies, the sponsor submitted the multiple-dose PK data with the 4-Month Safety Update on October 28, 2003 (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 for 2 years. 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 21-583 submitted on June 30th, 2003. The overall Human Pharmacokinetic Section is *acceptable*.

Labeling comments outlined in the labeling section were conveyed to the sponsor on July 15, 2004. As of July 26, 2004, agreement on labeling has not yet been reached between the sponsor and the Agency. On July 23, 2004, the sponsor requested the Agency to issue an approvable action, pending further labeling revisions. An addendum will be added to this review when agreement on labeling is reached.

1.2   Phase IV Commitments

The sponsor was advised to characterize the metabolic pathways of MPA and address the drug interaction potential to appropriately address this information in the label (teleconference on June 23, 2004). As a Phase IV commitment, the sponsor has agreed (July 15, 2004) to undertake an in-vitro metabolism study in accordance with the timelines discussed. Based on the findings from the in-vitro study, an in-vivo confirmatory study may be considered.

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 Study 272. In addition, the potential effects of BMI, race/ethnicity, and the SC injection sites (anterior thigh vs. abdomen) on the PK/PD profiles of MPA were evaluated.

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, ‾‾‾‾ $_{ig}$/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_{0-91} (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						

Multiple-Dose PK
No unexpected accumulation of MPA was observed following multiple SC injections. 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). 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) 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. 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 (abdomen vs. leg), 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 for a consistent contraceptive effect. 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. 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). Consistent with the PK data, overweight/obese subjects tended to return to ovulation sooner compared with healthy/thin subjects following a single dose of DMPA-SC.

Return of Ovulation
The cumulative rate of return to 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. The cumulative rate of ovulation was 1/1 (Asian), 13/13 (black), and 24/25 (white) subjects following a single SC administration of DMPA-SC. Using the 3 BMI categories of = 25 kg/m^2, > 25 to 30 kg/m^2, and > 30 kg/m^2, the cumulative rate of return to ovulation was 19/19, 17/17, and 2/3 subjects, respectively.
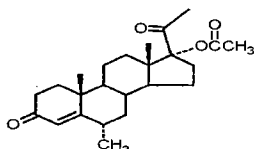
2. Question-Based Review

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	
Powder X-Ray Diffraction	/ / /
Hygroscopicity	Medroxyprogesterone acetate is not hygroscopic

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 buffer, Povidone) (see **General Biopharmaceutics**). Since the active ingredient, MPA, is insoluble in water, both the marketed Depo-Provera 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 at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which in turn, prevents follicular maturation and ovulation and also causes endometrial thinning. These actions produce its contraceptive effect.

What are the proposed indication, dosage and route of administration?
The proposed indication of DMPA-SC is prevention of pregnancy in women of child bearing potential. The recommended dose of DMPA-SC is 104 mg administered by subcutaneous injection into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks).

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?
Ovulation suppression is a surrogate endpoint for prevention of pregnancy. 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.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?
Yes. Blood samples for determination of MPA, progesterone, E_2, 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). Thus, it was important that the proposed dosing regimen for contraceptive indication effectively and consistently maintain MPA concentrations at or above this threshold. As such, 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 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. A dose of 104 mg per 0.65 mL was chosen based on the results of the dose-finding study conducted in women in the U.S (Study 265). The observed ovulation suppression and pharmacokinetic results of the dose-finding study suggest that 104 mg/0.65 mL would be an effective contraceptive dose given SC every 3 months.

Dose of 50-mg DMPA
- Progesterone concentrations were suppressed in 8 of 11 women for = 112 days.
- One woman (Subject No. 42) showed ovulatory progesterone levels ` ¯ ng/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 < 0.20 ng/mL.

Dose of 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.

Dose of 100-mg DMPA
- Progesterone concentrations were suppressed in 11 of 12 women for = 112 days.
- One woman (Subject No. 26) ovulated on Day 70 post-injection. This subject failed efficacy because of an unexpected PK 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 —— ng/mL by Day 49.

Dose of 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.

PK/PD in Asian Women

Figure 1. Mean and Median Concentration-Time Profiles for Progesterone after a Single Dose of DMPA-SC (104 mg/0.65 mL) in Asian Women (Study 271)
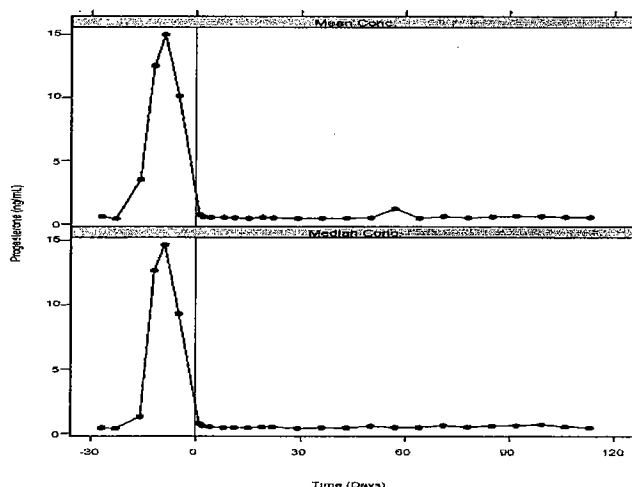
- DMPA-SC was effective in suppressing ovulation in Asian women. No ovulation, based on progesterone, was observed in 23/24 women for at least 112 days post-dosing.

Return of Ovulation

Figure 2. Individual Subject MPA Concentration at Day 91 (C₉₁) vs. Return of Ovulation Based on Serum Progesterone in the DMPA-SC Group (Study 272)

Figure 2. Individual Subject MPA Concentration at Day 91 (C_{91}) vs. Return of Ovulation Based on Serum Progesterone in the DMPA-SC Group (Study 272)

Return of Ovulation (Days) Based on Progesterone
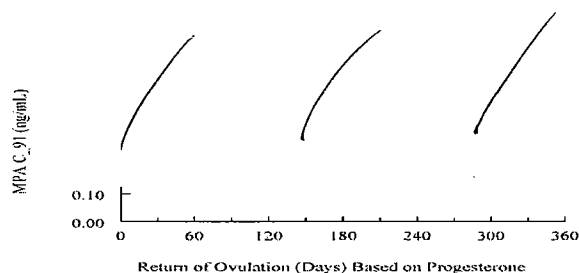
- The correlation coefficient was 0.035 and the coefficient of determination was 0.0012.
- The low coefficient of determination indicates that the C_{91} parameter is not predictive of the return of ovulation following DMPA-SC administration.

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

Time (Days)
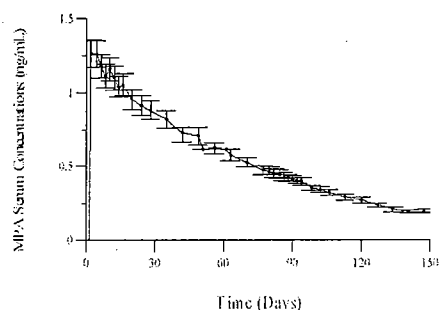
Effect of Injection Site

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 267, 269, and 267 BMD), DMPA-SC was administered into the anterior thigh or abdominal wall. There were no differences in efficacy.

Figure 4. MPA Concentration-Time Profile after a Single DMPA-SC Dose in Asian Women by Injection Site (n=12) (Study 271)
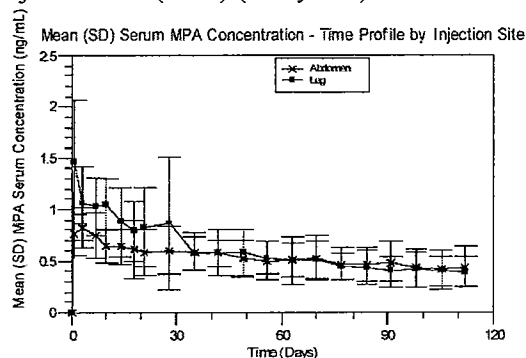

Mean (SD) Serum MPA Concentration - Time Profile by Injection Site

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	
AUC_{0-91}	60.03	65.93			67.75	67.89		0.2530
$AUC_{0-t(last)}$	60.15	66.01			68.17	68.06		0.2399
$AUC_{0-\infty}$	123.75	84.02			112.52	101.44		0.6916
C_{max}	0.943	0.920			1.652	1.775		0.0019
t_{max}	21.9	8.5			4.3	1.0		0.0615
λ_z	0.0100	0.0079			0.0110	0.0110		0.5489
$t_{1/2,z}$	103.7	87.3			80.9	65.9		0.3642
C_{91}	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 5. 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)
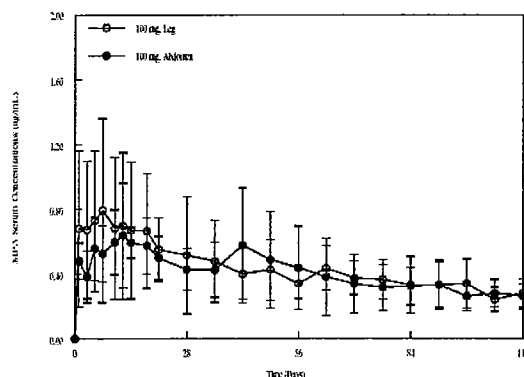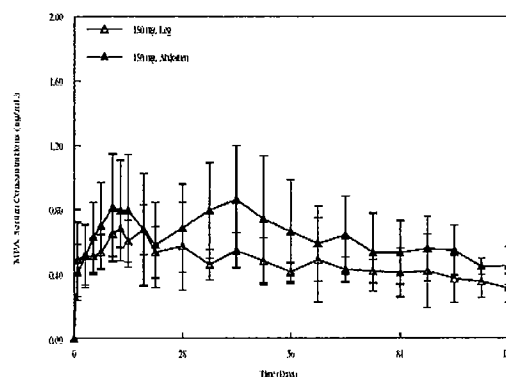
(A) 50-mg
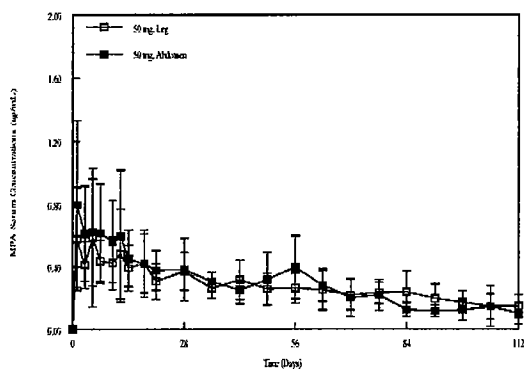
(B) 75-mg
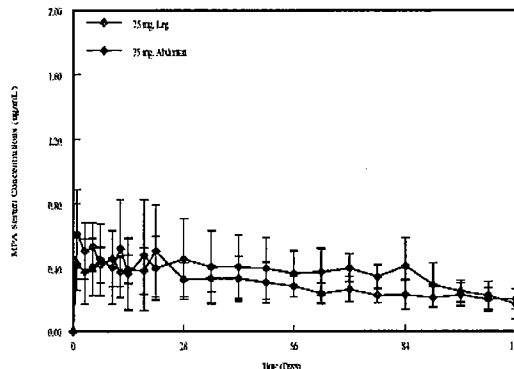
(C) 100-mg

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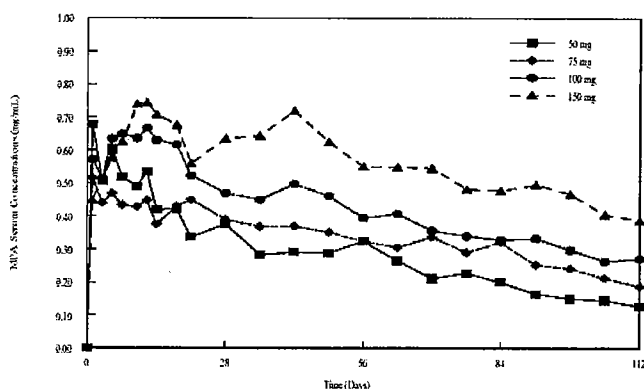

Table 3. Mean (SD) MPA Parameter Estimates after a Single SC Administration of DMPA-IM Formulation (Study 265)

| Parameter	Treatment (mg MPA per 0.5 mL injection)				ANOVA
	50	75	100	150	p-value*
AUC_{0-91} (ng day/mL)	29.2 (6.23)	32.8 (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)	0.8056
$t_{1/2,z}$ (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.
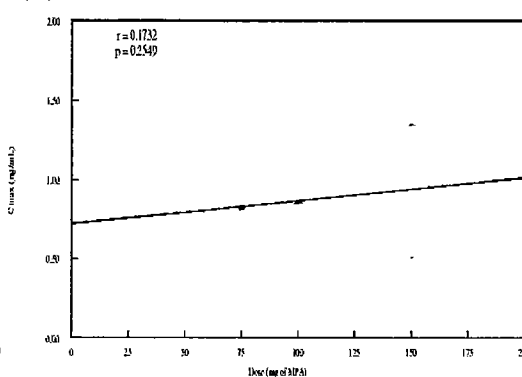* p-value for overall treatment differences by Analysis of Variance (ANOVA).
† Dose-normalized parameters to a 50-mg dose.

Figure 7. Relationship between (A) AUC_{0-inf}, (B) C_{max}, or (C) C_{91} and SC Administration of DMPA-IM Formulation (Study 265)
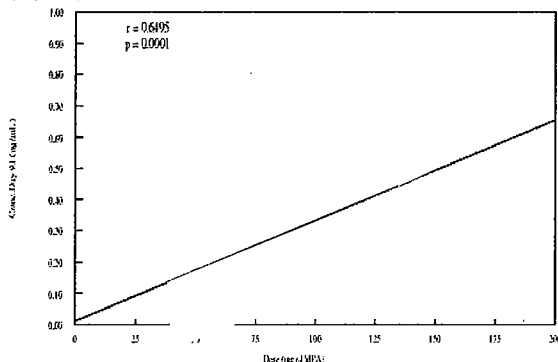
(A) AUC
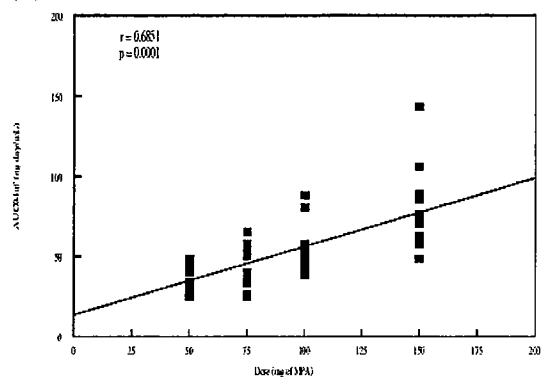
(B) C_{max}

(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 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).

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									
Max									
SD	0.34615	0.72854	0.80469	0.52604	0.52871	0.38986	0.36107	0.35677	0.67458

Figure 8. 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)
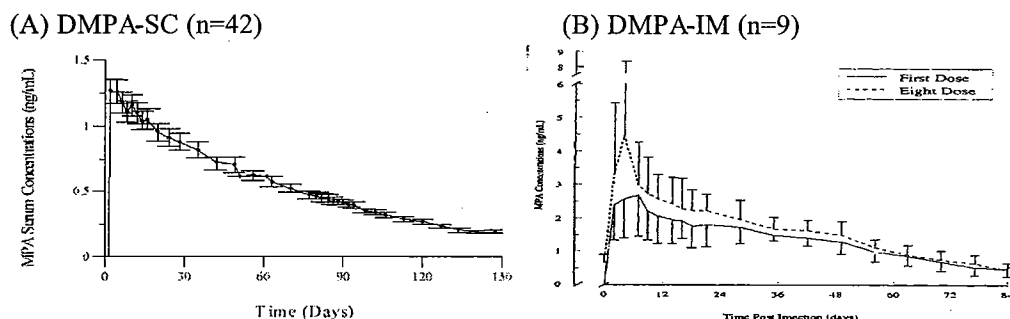
MPA concentration-time profiles after single and multiple IM injections are similar, suggesting that the pharmacokinetics are not influenced by Depo-Provera Contraceptive Injection dosing, and that a single-dose adequately predicts multiple-dose pharmacokinetics 1999 Pharmacia & Upjohn Study Report a0029898).

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	0.83-2.39	0.99-1.49	0.89-1.19

ss Steady-state
sd Single dose
Data from NDA 20,246 (Reviewed by Dr. Ron Kavanagh, PhD, January 8, 2001)

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 $?_z$ 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?

Age
The proposed indication of DMPA-SC is prevention of pregnancy in women of child bearing potential. 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
A PK/PD study conducted by the WHO in women from different countries after IM administration of DMPA-IM appeared to indicate an enhanced metabolism and/or clearance of MPA in Thai women. In addition, the PD results indicated a faster return of ovarian function in Thai women compared with women from other countries.

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 since 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).

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.

Figure 9. MPA Concentration-Time Profile after a Single DMPA-SC Dose in Asian Women (n=24) (Study 271)
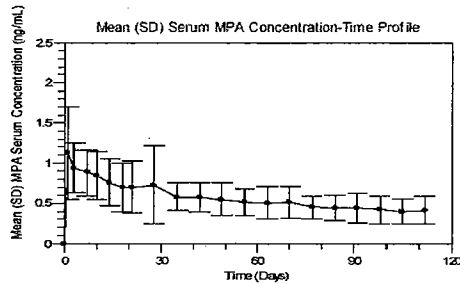
- MPA concentrations were sustained throughout the targeted dosing interval of 91 days indicating that MPA absorption from the SC injection site was prolonged in these Asian women.

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

PARM	N	MEAN	STD	MEDIAN	MIN	MAX
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).

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 = 1)	Black (n = 14)	White (n = 27)	ANOVA p-value
AUC0-91 (ng·day/mL)		62.65	69.58	0.6609
AUC0-t(last) (ng·day/mL)		75.88	83.36	0.6778
AUC0-∞ (ng·day/mL)		86.75	95.83	0.5026
Cmax (ng/mL)		1.377	1.677	0.3201
tmax (day)		16.1	5.3	0.0384
λz		0.0191	0.0197	0.9792
t1/2 (day)		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.

Figure 10. Time to Return of Ovulation Based on Progesterone Concentrations (= 4.7 ng/mL) by Race in Evaluable Subjects (Study 272)
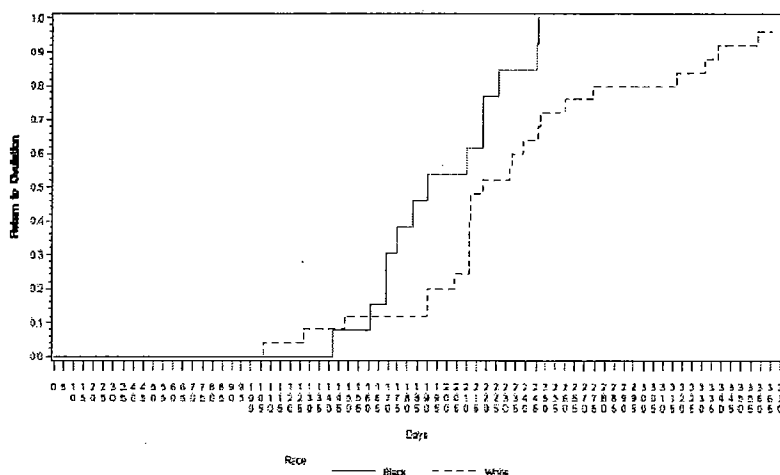

- The cumulative rate of ovulation at the end of 12 months post-injection in evaluable subjects was 97.4 % (38/39) in the DMPA-SC group. The median time of return to ovulation, based on progesterone concentrations = 4.7 ng/mL in evaluable subjects, was 212 days for the DMPA-SC group.
- The cumulative rate of ovulation was 1/1 (Asian), 13/13 (Black), and 24/25 (White) subjects following a single SC administration of DMPA-SC.

Body Mass Index (BMI)

MPA concentrations had tendency to be lower in women with BMI >38 kg/m², but trough concentrations (C_{91}) remained = 0.2 ng/mL for a consistent contraceptive effect. The total MPA exposure (AUC_{inf}) was lower in obese subjects (>38 kg/m²), than healthy or overweight subjects after a single DMPA-SC administration. However, suppression of ovulation was maintained in obese subjects. Consistent with the PK data, overweight/obese subjects tended to return to ovulation sooner compared with healthy/thin subjects following a single dose of DMPA-SC.

The mean BMI of subjects in the Phase 3 trials was 24.6 kg/m². The mean baseline BMI of U.S. subjects and non-U.S. subjects were 27.0 kg/m² and 23.7 kg/m², respectively. There were no no-treatment pregnancies detected in these subjects.

Figure 11. Distribution of Baseline BMI for ITT Group (Phase 3 trials: Studies 267, 269, 267 BMD)
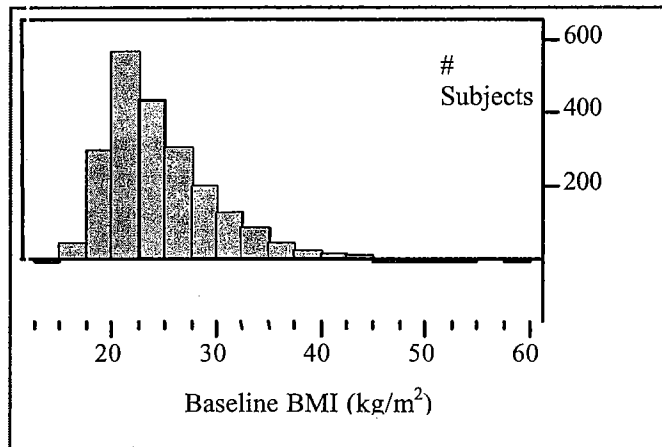

Source: Medical Officer's Review of NDA 21-583

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

PK Parameter	BMI					BMI			
	≤25 (n=13)	>25-30 (n=10)	>30 (n=19)	ANOVA p-value		≤28 (n=19)	>28-38 (n=18)	>38 (n=5)	ANOVA p-value
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}, ?z, and $t_{1/2}$ among the 3 BMI categories. The AUC_{inf} was lower in subjects with a BMI >38 kg/m^2.
- There were no significant differences in the parameter estimates of AUC_{91}, AUC_{last}, C_{max}, ?z, and $t_{1/2}$ among BMI categories used at the time of randomization.
- 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).

Figure 12. Time to Return of Ovulation Based on Progesterone =4.7 ng/mL by BMI in Evaluable
Subjects (Study 272)
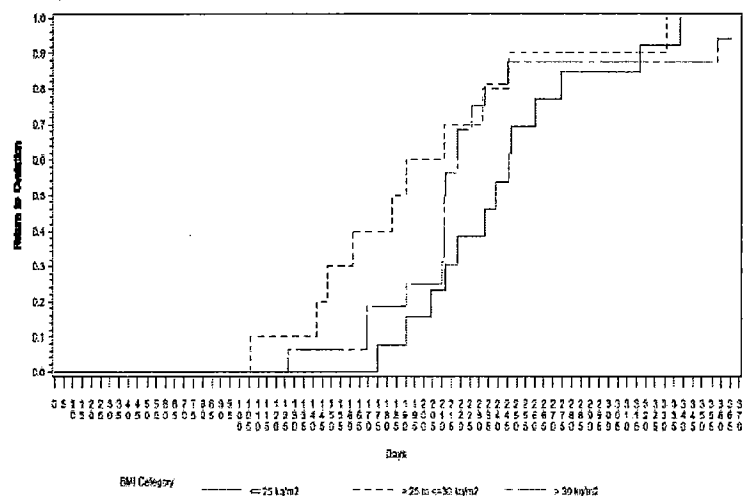
- Using the 3 BMI categories stated in the Dietary Guidelines (=25 kg/m², >25 to 30 kg/m²,
  and >30 kg/m²), the cumulative rate of ovulation was 19/19, 17/17, and 2/3 subjects,
  respectively.

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. In order to ensure that the labeled fill
volume of 0.65 mL can be delivered from the syringe, the finished product is manufactured

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

The sponsor stated that a bridging study was not deemed necessary to link Study 265 findings with
the DMPA-SC (104 mg/0.65 mL) database given minor differences between the formulations.

Table 10. Formulation of the DMPA-SC 104 mg/0.65 mL 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
Polysorbate 80			USP/NF
Monobasic Sodium Phosphate · 1 H₂O			USP
Dibasic sodium Phosphate · 12 H₂O			USP
Methionine			USP
Povidone,			USP
Sodium Hydroxide or Hydrochloric Acid	QS	pH adjustment	USP/NF
Water for injection	QS to		USP

Table 11. Comparison of DMPA-SC and Marketed DMPA-IM Formulations

Substance	DMPA-IM (w/v)	DPMA-SC (w/v)
Drug		
MPA		
Excipients		
Methylparaben		
Propylparaben		
Sodium Chloride		
Polyethylene Glycol 3350		
Polysorbate 80		
Monobasic Sodium Phosphate ·1 H₂O		
Dibasic Sodium Phosphate ·12 H₂O		
Methionine		
Sodium Hydroxide or Hydrochloric Acid*	QS	QS
Water for Injection	QS to	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

All excipients present in the marketed IM formulation are also present in the SC formulation although the quantities are slightly different in some cases in order to accommodate the _____, in comparison with the currently marketed formulation _____ w/v). Some minor modifications were deemed necessary in order to make the product suitable for subcutaneous administration _____

What are the differences between the clinical and the to-be-marketed formulations?
The Phase 3 pivotal trials have been performed with the final formulation and dose/volume of administration. The DMPA-SC lot used in the Phase 3 pivotal trials, as well as the primary registration stability batches, were manufactured on industrial scale at the final commercial manufacturing site (Pharmacia-Puurs, Belgium).

2.6 Analytical

Human serum samples were quantitated for MPA using a sensitive and selective HPLC system that was coupled with a triple quadruple mass spectrometer (LC/MS/MS), _____ This method was developed and validated at _____ . Quantitation of E2, progesterone, LH, and FSH in serum was performed by _____ using an automated chemiluminesence system _____

Calibration standard responses were linear over the range of 0.02 to 5.00 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 0.02 ng/mL. No clinical sample responses exceeded the calibration range. Correlation coefficients were all =0.996. CV% were used to express the precision of the back-calculated CS. The eight CS points had CVs that were =6.93% with mean accuracy between 96.2% and 105%. Inter-day accuracy and precision was further monitored by analysis of three MPA quality control (QC) standards with target concentrations of 0.0500, 1.00 and 4.00 ng/mL. Inter-day precision for the three QC standards was =9.1% with assay accuracy from 97.9% to 104%.
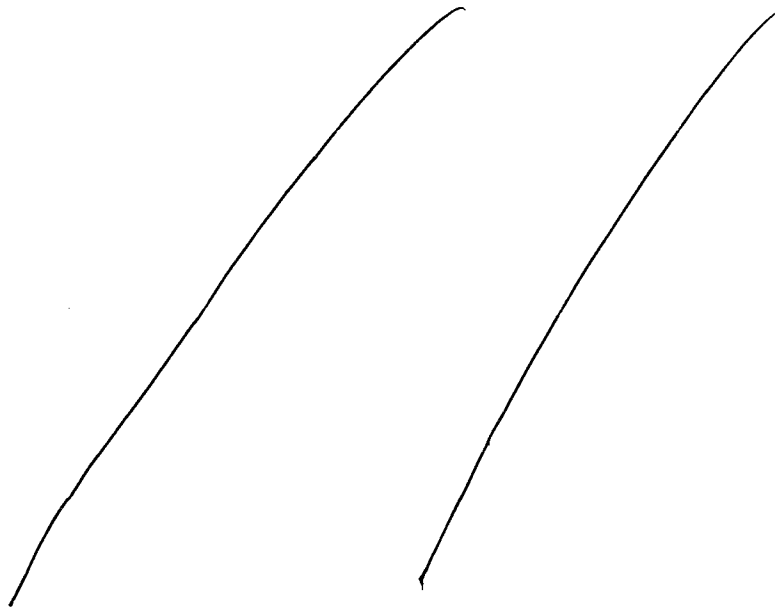
3. **Detailed Labeling Recommendations**

_____ 2 _____ Page(s) Withheld

_____ Trade Secret / Confidential

_____ ✓ _____ Draft Labeling

_____ Deliberative Process

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).

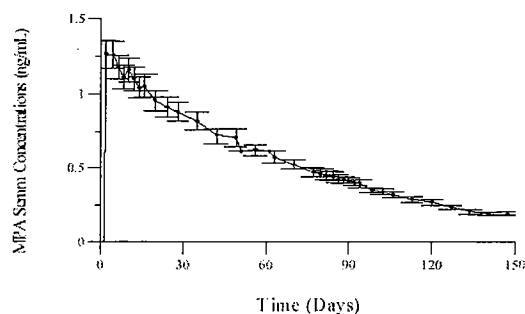Table 12. MPA Pharmacokinetic Parameters after DMPA-SC Administration (n=42)

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)	8.8	13.2	5.0		
λz	0.0195	0.0088	0.0183		
t1/2 (day)	43.2	20.8	37.8		
C91 (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 13. 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)

Time (Days)
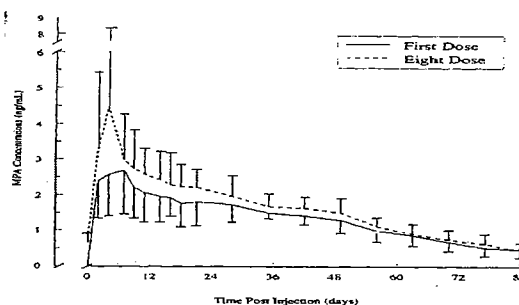
Table 13. MPA Pharmacokinetic Parameters by Race after DMPA-SC Administration

Pharmacokinetic Parameter	Asian (n = 1)	Black (n = 14)	White (n = 27)	ANOVA p-value
AUC0-91 (ng·day/mL)		62.65	69.58	0.6609
AUC0-t(last) (ng·day/mL)		75.88	83.36	0.6778
AUC0-∞ (ng·day/mL)		86.75	95.83	0.5026
Cmax (ng/mL)		1.377	1.677	0.3201
tmax (day)		16.1	5.3	0.0384
λz		0.0191	0.0197	0.9792
t1/2 (day)		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					BMI			
	≤25 (n=13)	>25-30 (n=10)	>30 (n=19)	ANOVA p-value		≤28 (n=19)	>28-38 (n=18)	>38 (n=5)	ANOVA p-value
AUC0-91 (ng·day/mL)	66.50	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
t1/2 (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}, ?z, 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}, ?z, 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 14. Individual Subject MPA Concentration at Day 91 (C91) vs. Return of Ovulation Based on Serum Progesterone in the DMPA-SC Group
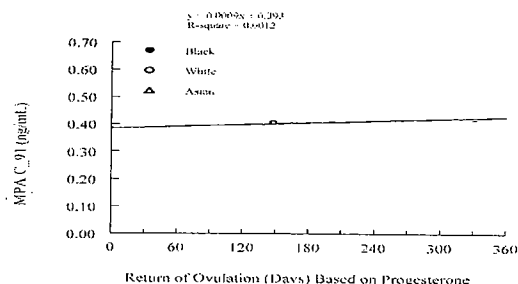
- The correlation coefficient was 0.035 and the coefficient of determination was 0.0012. The low coefficient of determination indicates that the C_{91} parameter is not predictive of the return of ovulation following DMPA-SC administration.

Figure 15. Time to Return of Ovulation Based on Progesterone Concentrations (= 4.7 ng/mL) in Evaluable Subjects
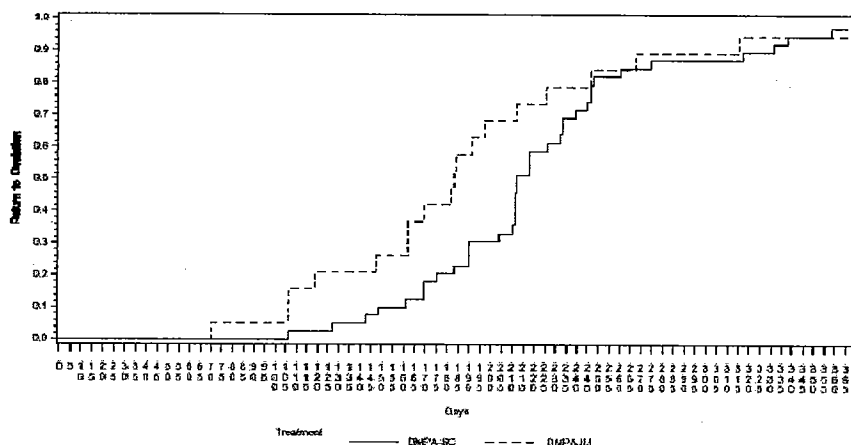
- The cumulative rate of ovulation at the end of 12 months post-injection in evaluable subjects was 97.4 % (38/39) in the DMPA-SC group. The median time of return to ovulation, based on progesterone concentrations = 4.7 ng/mL in evaluable subjects, was 212 days for the DMPA-SC group by Kaplan-Meier analysis.

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 ____ 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 ____ w/v (a concentration of ____ , 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 16. (A) Mean Serum MPA Concentration-Time and (B) Log-Linear Mean Serum MPA Concentration-Time Profiles after a Single DMPA Dose
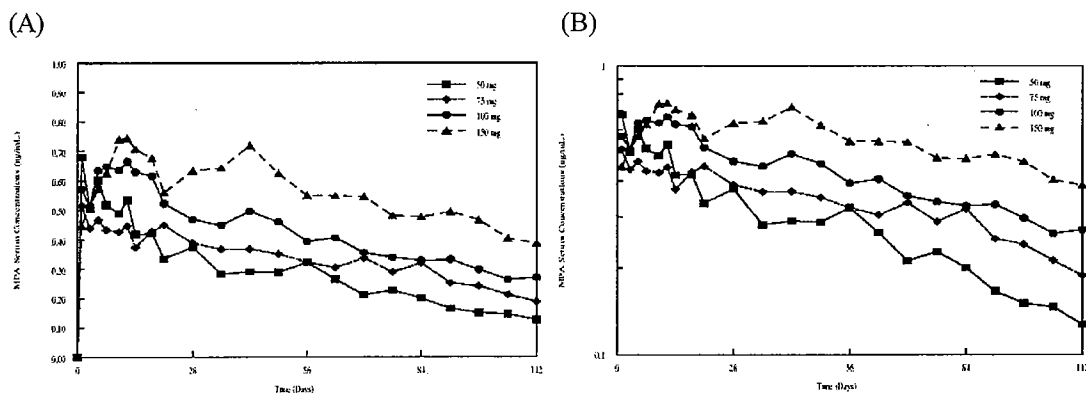
(A)   (B)

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
AUC$_{0-91}$ (ng day/mL)	29.2 (6.23)	32.8 (9.29)	41.5 (13.4)	53.3 (16.4)	.0001	AB, BC
C$_{max}$ (ng/mL)	0.831 (0.387)	0.780 (0.226)	0.889 (0.353)	0.947 (0.277)	.6179	--
C$_{91}$ (ng/mL)	0.174 (0.0822)	0.253 (0.111)	0.332 (0.137)	0.495 (0.215)	.0001	AB, BC
t$_{max}$ (day)	16 (28)	18 (21)	21 (21)	25 (27)	.8058	--
t$_{1/2}$ (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
AUC$_{0-91}$ (ng day/mL)	29.2 (6.23)	21.8 (6.19)	20.8 (6.69)	17.8 (5.46)	.0008	BCD
C$_{max}$ (ng/mL)	0.831 (0.387)	0.520 (0.151)	0.445 (0.177)	0.316 (0.0922)	.0001	BC, CD
C$_{91}$ (ng/mL)	0.174 (0.0822)	0.169 (0.0738)	0.166 (0.0687)	0.165 (0.0718)	.9930	--

* 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 17. Relationship between AUC$_{0-inf}$, C$_{max}$, or C$_{91}$ and DMPA Dose
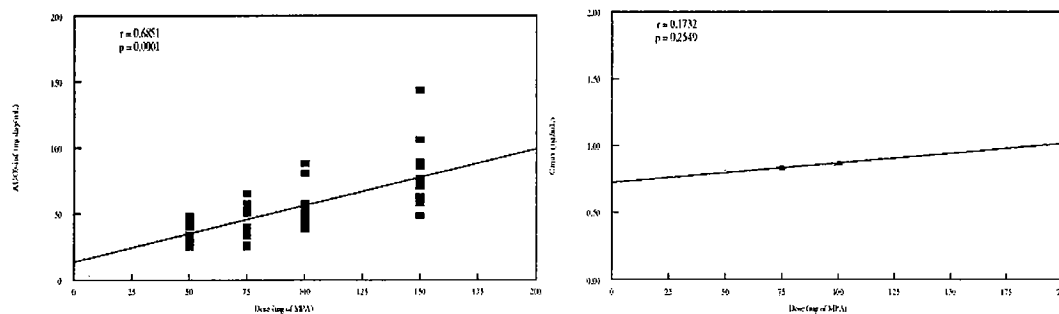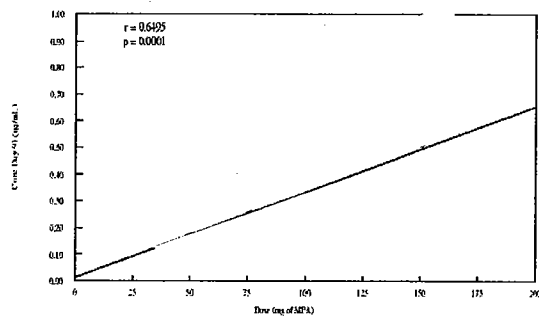
Figure 18. Mean (SD) Serum MPA Concentration-Time Profile after the (A) 50-mg, (B) 75-mg, (C) 100-mg, or (D) 150- mg DMPA Dose by Injection Site

(A) 50-mg
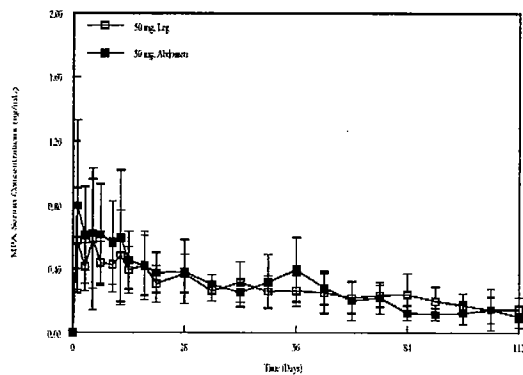
(B) 75-mg
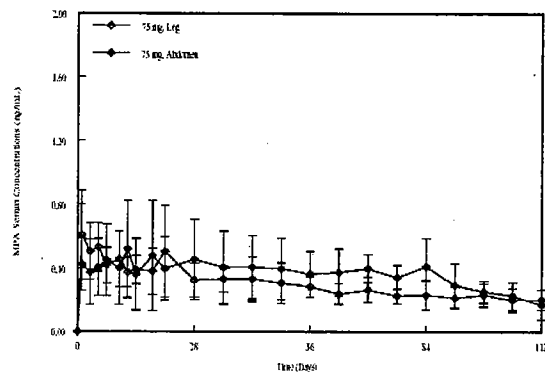
(C) 100-mg
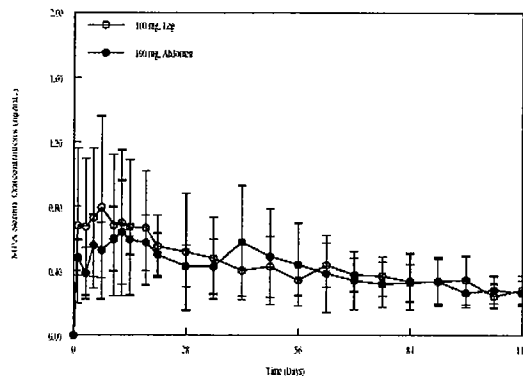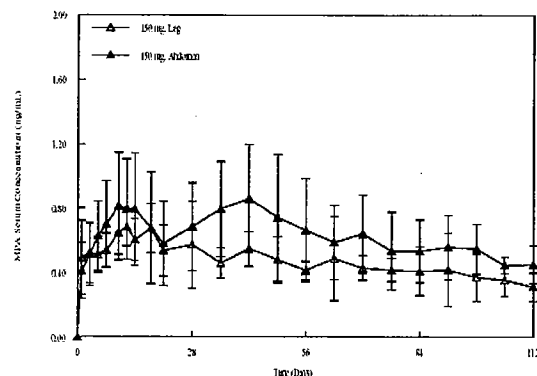
(D) 150-mg

- 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

50-mg DMPA

- Progesterone concentrations were suppressed in 8 of 11 women for = 112 days.
- One woman (Subject No. 42) showed ovulatory progesterone levels — ᵢg/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 ⌐ g/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 ⌐ ng/mL by Day 49.

Figure 19. Composite of Individual Subject Serum MPA Concentration-Time Profiles after the 100-
mg DMPA Dose Including Subject 26
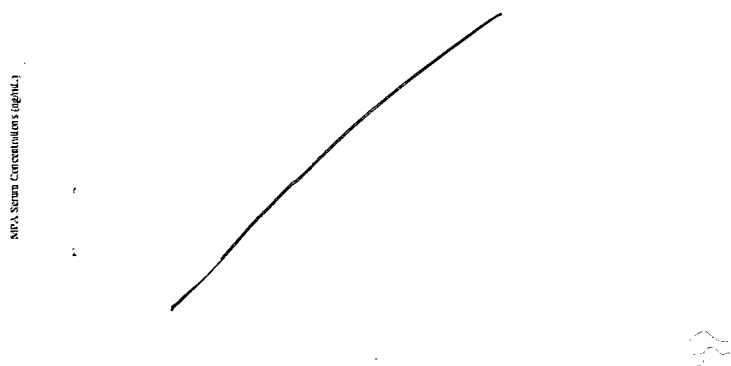
150-mg DMPA
- Serum progesterone concentrations were effectively suppressed in all 11 women completing
  the 112 day time course.
- All women showed MPA C_{91} = 0.2 ng/mL.

*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 20. MPA Concentration-Time Profile after a Single DMPA-SC Dose in Asian Women (n=24)
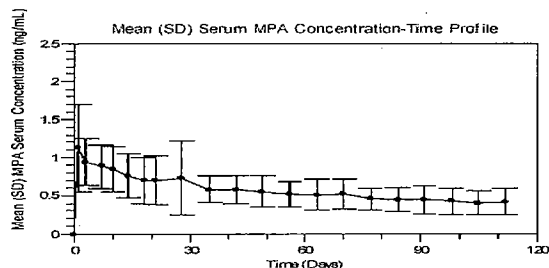
- MPA concentrations of = 0.20 ng/mL were observed for > 91 days in 23 of 24 women after SC administration of DMPA-SC.
- MPA concentrations were sustained throughout the targeted dosing interval of 91 days indicating that MPA absorption from the SC injection site was prolonged in these Asian women.

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

PARM	N	MEAN	STD	MEDIAN	MIN	MAX
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).

Figure 21. MPA Concentration-Time Profile after a Single DMPA-SC Dose in Asian Women by Injection Site (n=12)
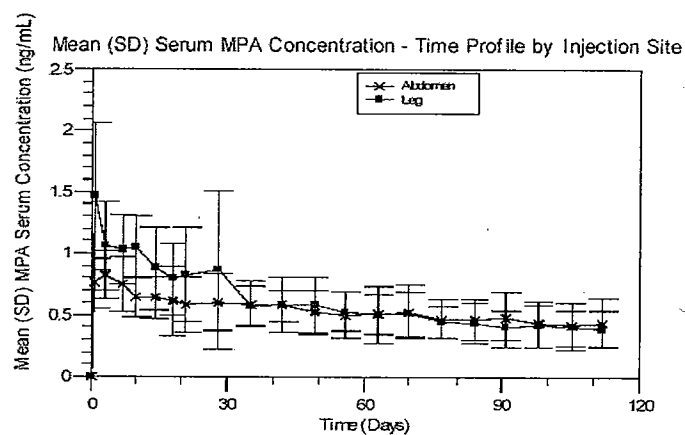
Table 17. PK Parameters of MPA after a Single DMPA-SC in Asian Women by Injection Site

PK Parameter	Abdomen	Leg	t-test p-value
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	0.36420
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

PARM	N	MEAN	STD	MEDIAN	MIN	MAX
AUC0_91	12	60.032	16.3399	65.9336		
AUCON	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

PARM	N	MEAN	STD	MEDIAN	MIN	MAX
AUC0_91	12	67.754	15.8817	67.889		
AUCON	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	1.00		
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

Time (d)	Abdomen	Leg	t-test P-Value
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	0.04030
18	0.60675	0.78758	0.13346
21	0.57942	0.83008	0.05974
28	0.60467	0.86333	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	0.41353	0.39850	0.82443
112	0.44000	0.39558	0.54463

Figure 22. MPA Concentration-Time Profile after a Single DMPA-SC in Asian Women by Ethnicity

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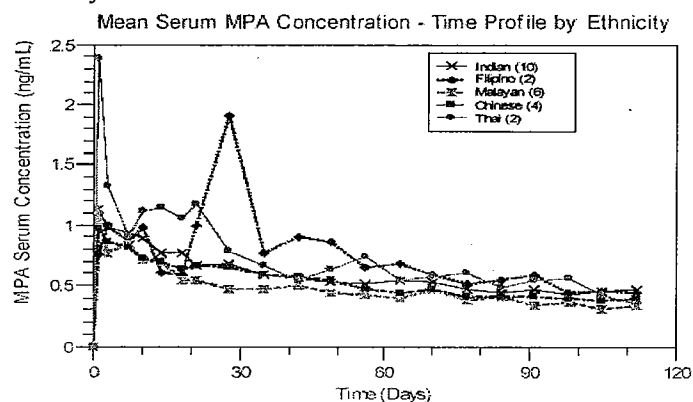
- One Filipino woman (Subject No. 3, leg injection site, 29 years old, BMI of 20) showed a high serum MPA (~2 ng/mL) 28 days after dosing, likely an assay interference.

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

PK Parameter	Chinese (C)	Filipino (F)	Malayan (My)	Thai (th)	Indian (I)	ANOVA p-value
AUCO_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	139.920	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 ⌐ 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 · ⌐ng/mL on Day 50, ⌐ ₁g/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 23. Mean and Median Concentration-Time Profiles for Progesterone after a Single DMPA-SC Dose in Asian Women
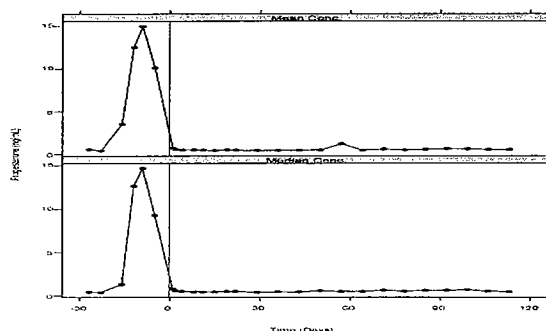
Table 21. Return of Ovarian Function Following a Single Administration of DMPA-SC

Subject	Inj Site	E2[a]		Progesterone[b]		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	----	

[a] E2 ≥ 150 pg/mL
[b] Progesterone levels > 4.7 ng/mL.

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

SUBJECT	CMAX	TMAX	AUC0-91	AUC∞	AUC TOT	LZ	THALF
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							

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 t 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 24. 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
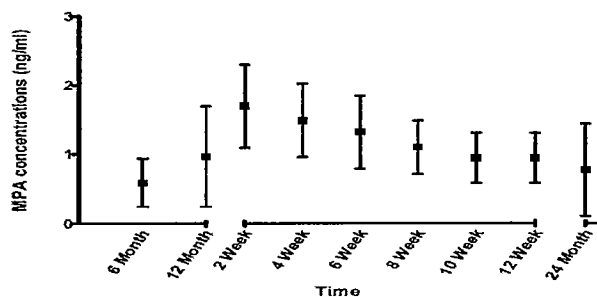
The R value calculated from a mean K value of 0.0195 days^{-1} and a dosing interval of 90 days was 1.21. The observed accumulation based upon the ratio of the trough concentrations observed at 6 months from the larger main protocol dataset (0.67 ng/mL, n=157) and after the single dose administration (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 25. Mean (SD) Serum Concentration-Time Profile of MPA Following the 1ˢᵗ or the 8ᵗʰ IM injection of DPMA-IM (n=9)
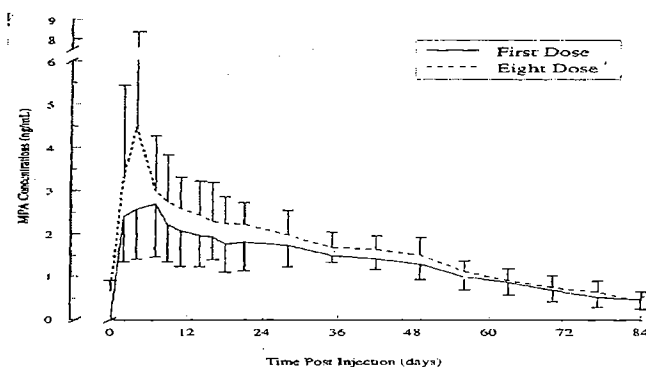
Table 26. Mean (SD) PK Parameters of MPA Following the 1st or the 8th IM Administration of DMPA-IM

| 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	0.83-2.39	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	21-583	Brand Name	
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)	Prevention of Pregnancy
OCPB Team Leader	Ameeta Parekh	Dosage Form	Depot Subcutaneous Injection
		Dosing Regimen	104 mg/0.65 mL
Date of Submission	30-June-03	Route of Administration	Subcutaneous Injection
Estimated Due Date of OCPB Review		Sponsor	Pfizer
PDUFA Due Date	30-June-04	Priority Classification	Standard
Division Due Date	10-June-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			
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	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:	1			
Phase 3 clinical trial:	1			
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 21-583, HFD-850 (L. Lesko, S. Huang), HFD-580 (L. Furlong, S. Monroe), HFD-870 (A. Parekh, H. Malinowski, J. Hunt), CDR (B. Murphy)
CP&B Briefing attendees on May 26, 2004: Dr. Lesley Furlong, John Hunt, Dr. Leslie Kenna, Dr. John Lazor, Dr. Henry Malinowski, Dr. Stephan Ortiz, Dr. Ameeta Parekh, and Charlene Williamson.

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-583
Compound: Medroxyprogesterone Acetate Injectable Suspension
Sponsor: Pharmacia and Upjohn

Date: August 12, 2003
Reviewer: Myong-Jin Kim

Background:

Depot medroxyprogesterone acetate (MPA) subcutaneous injection (DMPA-SC) is indicated for the prevention of pregnancy in women of child bearing potential. DMPA-SC is a new formulation of MPA injectable suspension administered at a lower dose and new route of administration, as compared to the currently marketed Depo-Provera® Contraceptive Injection. 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. When administered to women every 3 months (12 to 13 weeks, not to exceed 14 weeks), it is proposed to inhibit the secretion of gonadotropins which in turn prevents follicular maturation and ovulation.

Formulation:

	DMPA - SC	Marketed DEPO-PROVERA® IM
Medroxyprogesterone Acetate (MPA)		
Methylparaben		
Propylparaben		
Sodium Chloride		
Polyethylene Glycol 3350		
Polysorbate 80		
Monobasic Sodium Phosphate • 1 H2O		
Dibasic Sodium Phosphate • 12 H2O		
Methionine		-
Povidone		-
Sodium Hydroxide or Hydrochloric Acid	QS	QS
Water for Injection	QS to ⁄ mL	QS to ⁄ mL

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. The DMPA-SC lot used in the Phase 3 pivotal trials and the primary registration stability batches were manufactured on industrial scale at the final commercial manufacturing site (Pharmacia-Puurs, Belgium).

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						

<u>Healthy Subject PK Studies:</u>

- **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).
  - o 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.
  - o Dose-proportionality, impact of SC injection sites (anterior leg vs. abdomen) on PK/PD profiles.
  - o 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.
  - o The sponsor concluded that the ⌐ ⎯ ⌐ was an effective dose given SC every 3 months. Since the SC formulation evaluated in the Phase 3 program was ⎯ w/v (a concentration of ⎯), 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
  - o 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).
  - o The duration of ovulation suppression after DMPA-SC and the PK of DMPA-SC in Asian women were evaluated.
  - o The effect of DMPA-SC injection location (anterior leg vs. abdomen) on the PK/PD profiles ⌐ ⎯ and whether major Asian ethnic groups exhibit major differences in PK/PD profile of DMPA-SC were evaluated · ⎯
  - o The C_{max} was higher in women receiving the injection in the anterior leg relative to the abdomen.

- **Substudy 267**: On-going 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)
  - o Steady-state PK data following multiple dose administration will be submitted in a 4-month Safety Update.

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)
  - o The pharmacokinetics of MPA were determined in subjects enrolled in the DMPA-SC arm.

o 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.
o Subgroup analyses for 3 BMI ranges (18-28 kg/m^2, >28-38 kg/m^2, and >38 kg/m^2). The AUC_{0-inf} was lower in obese subjects with BMI >38 kg/m^2

Review Issues:
1. Effect of injection site (anterior thigh vs. abdomen) (Studies 265 and 271).
   a. The proposed label stated

2. Effect of race (Studies 271 and 272)
   a. The proposed label stated

3. Effect of body weight (Study 272)
   a. The proposed label stated
      —.. Three BMI groups were evaluated: =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 find that the Human Pharmacokinetics and Bioavailability section for NDA 21-583 is fileable.

_____   _____
Myong-Jin Kim, Pharm.D.   Date

_____   _____
Ameeta Parekh, Ph.D., Team Leader   Date

/s/

Myong-Jin Kim
7/26/04 04:17:48 PM
PHARMACOLOGIST

Ameeta Parekh
7/26/04 04:39:39 PM
BIOPHARMACEUTICS
I concur