CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-778

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

04/05/05

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-778	Submission Dates: 06-29-2004, 01-27-2005, 02-17-2005, 02-21-2005
Brand Name	Megace ES™
Generic Name	Megestrol acetate oral suspension [redacted]
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Endocrine and Metabolic Drug Products (HFD-510)
Sponsor	Par Pharmaceutical, Inc.
Relevant IND(s)	65,178
Submission Type; Code	505 (b) (2), 1S
Formulation; Strength(s)	[redacted] (125 mg/mL?)
Dosing regimen	[redacted] (5mL/day).
Indication	Treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

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1 Executive Summary

Par Pharmaceutical, Inc. submitted a 505 (b) (2) NDA for marketing of Megace ES™ (Megestrol acetate oral suspension ([redacted]). A total of 9 studies were submitted, 4 of which were preliminary studies for formulation development and 2 in vitro drug metabolism studies.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the information provided in the original NDA 21-778 for Megace ES™ in the section of human pharmacokinetics and biopharmaceutics. OCPB has found the application acceptable provided that the sponsor agrees with the following Agency's recommendations

(1) The Agency recommends the strength 125 mg/mL (625 mg/5mL) be approved for the marketing drug product.

(2) Dissolution specifications as follows:

Apparatus	**USP Apparatus II (paddles)**
RPM	25
Time	10 minutes
Q	NLT [redacted] (Q) in 10 minutes
Volume	900 mL
Bath Temperature	37°C
Sample introduction amount	5 mL (one unit dose)
Medium	1.0% Sodium Lauryl Sulfate in water

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

• Relative bioavailability of Megestrol acetate to the reference drug product, Megace®:

The sponsor conducted a pivotal single-dose, four-way, comparative bioavailability study in healthy subjects to compare the rate and extent of absorption of three strength formulations of megestrol acetate oral suspension NCD (575 mg/5mL [115 mg/mL], 625 mg/5mL [125 mg/mL] and 675 mg/5mL [135 mg/mL]) versus Megace® (megestrol acetate oral suspension 800 mg/20mL [40 mg/mL]), administered under fed conditions. Bioequivalence analysis indicates that the lower limits of the 90% confidence intervals for AUC_{0-t} and AUC_{0-inf} for the strength 115 mg/mL were slightly below the [redacted] respectively). The two higher strengths of megestrol acetate oral

suspension NCD (125mg/mL and 135 mg/mL) are bioequivalent to Megace® 800 mg/20mL. In an IND meeting with the sponsor in 2003, the sponsor informed the Agency that megestrol NCD formulation may not be able to meet both Cmax and AUC criteria for bioequivalence in comparison with Megace® based on their preliminary studies and the Agency agreed with the sponsor that they may use Cmax as the primary endpoint and AUC as the secondary endpoint to establish equivalence if that is the case. Since then, the sponsor has focused on the strength of [redacted] for their drug development program though they have been keeping two additional strengths, [redacted] in their drug programs.

- **Food effect:**

Pharmacokinetic results showed that the administration of megestrol acetate oral suspension NCD with food resulted in higher plasma megestrol acetate concentrations. The geometric mean ratio for Cmax was 154% and those for AUC0-t and AUC∞ were 139% and 141%, respectively, indicating a significant effect of food on absorption. However, the food effect on bioavailability is much smaller from this NCD formulation than that from Megace® formulation which has shown that food may increase Megace® Cmax as much as 8 fold in comparison with the fasting condition.

- **Drug interaction:**

Megestrol acetate, given as 675 mg (5 ml X 135 mg/mL) once daily from Days 2 to 15, reduced the Cmax and AUC on Day 15 of Indinavir, given as 800 mg once daily, by 32% and 21%, respectively in healthy male subjects.

- **In vitro drug interactions:**

From an in vitro human liver microsomal study, megestrol acetate exhibited a moderate inhibitor of 2C9, 2C19 and a mild inhibitor of 2A6, and 2D6 activities, and a stimulator of CYP1A2 and 2E1 activities. Megestrol at 0.25, 2.5, and 25 μM did not induce CYP1A2, CYP2C9, and CYP3A4 activity in cryopreserved human hepatocytes isolated from the three donors.

- **Analytical assay:**

For the quantitation of plasma megestrol acetate concentrations, high performance liquid chromatographic method with tandem mass detection (LC/MS/MS) was developed and validated. The method used in pivotal bioequivalence study indicated that the sensitivity range is from [redacted] ng/mL. The lowest validated limit of quantitation (LLOD) for megestrol is 2.00 ng/mL.

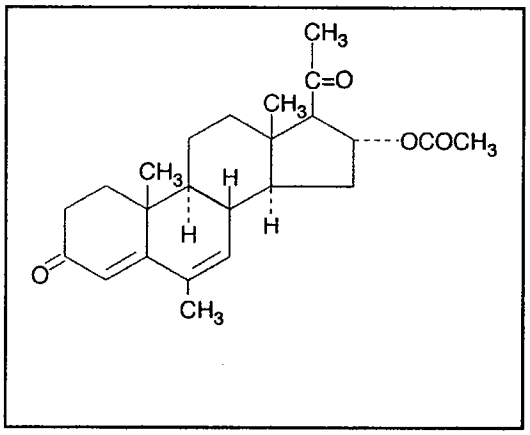
2. QUESTION BASED REVIEW (QBR)

2.1 GENERAL ATTRIBUTES OF THE DRUG

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance?

Megestrol acetate oral suspension contains megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone in nanocrystal form. Megestrol acetate is a white, crystalline solid chemically designated as 17-Hydroxy-6-methylpregna-4, 6-diene-3,20-dione acetate. Solubility at 37° C in water is 2 μg per mL, solubility in plasma is 24 μg per mL. Its molecular weight is 384.52.

The chemical formula is $C_{24}H_{32}O_4$ and the structural formula is represented as follows:



2.1.2 What are the highlights of the formulation of drug product?

The sponsor developed a total of [redacted] different strengths, of which three strengths were used in a pivotal bioequivalence study. These different strengths were made from the same amounts of active ingredients, dispersants or stabilizers, but different amounts of buffers, water and different final volumes to adjust the final concentrations of oral suspensions. Megestrol acetate oral suspension NCD is supplied in [redacted] cap. The composition of formulation is summarized in Table 1.

NanoCrystal™ technology is a formulation and manufacturing approach to enhancing the performance of poorly water-soluble drugs in which the drug particles are [redacted]

[redacted]

[redacted] drug formulations have substantially increased surface area per unit mass relative to micronized drug particles. As a result, drug [redacted] have substantially increased rates of dissolution. For orally administered products in which absorption is dissolution rate-limited, [redacted] technology can improve overall bioavailability, increase the rate of absorption, and decrease variability that is associated with food effects.

Table 1. Composition of Megestrol acetate oral suspensions NCD for three different strengths

STRENGTH (mg/mL)	Function	115 mg/mL	125 mg/mL	135 mg/mL
Density (g/mL)		1.04 g/mL	1.04 g/mL	1.04 g/mL
Final Amounts		Grams	Grams	Grams
Megestrol Acetate USP	Active ingredient			
Hydroxypropyl methylcellulose USP				
Docusate sodium USP				
Sodium Benzoate NF				
Sodium Citrate USP (Dihydrate)				
Citric acid USP (Monohydrate)				
Sucrose NF				
Natural & Artificial Lemon Flavor				
Artificial Lime Flavor				
Purified water USP				
Total Grams				
Total Volume				

[redacted]

2.1.3 What is the proposed mechanism of drug action and the therapeutic indications?

Several investigators have reported on the appetite enhancing property of megestrol acetate and its possible use in cachexia. The precise mechanism by which megestrol acetate produces effects in anorexia and cachexia is unknown at the present time.

Megace ES™ (megestrol acetate) oral suspension is indicated for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS). Megace ES™ can be administered with or without food.

2.1.4 What is the proposed dosage and route of administration?

The recommended adult initial dose of megestrol acetate oral suspension NCD is 575 mg/day (5mL/day). Shake container well before using. In clinical trials evaluating different dose schedules, daily doses of 400 and 800 mg/day of Megace® (800 mg equivalent to 575 mg/5 mL of NCD formulation) were found to be clinically effective.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What is bioavailability of Megestrol acetate oral suspension NCD relative to Megace® under fed condition after a single dose? Which strength should we choose for the final marketing drug product?

The sponsor conducted a pivotal single-dose, four-way, comparative bioavailability study in healthy subjects to compare the rate and extent of absorption of three strength formulations of megestrol acetate oral suspension NCD (575 mg/5mL [115 mg/mL], 625 mg/5mL [125 mg/mL] and 675 mg/5mL [135 mg/mL]) versus Megace® (megestrol acetate oral suspension 800 mg/20mL [40 mg/mL]), administered under fed conditions (Study 30421) in healthy male subjects. Subjects received a single dose of the study drugs in each of the 4 treatment periods according to a crossover design. Doses were administered after a 10-hour, overnight fast and within 30 minutes after a standard high-fat breakfast of approximately 1000 calories. A total of 42 healthy, adult male subjects signed the study-specific informed consent form. Of these subjects, 38 were dosed and were considered to have enrolled in the study; 33 subjects completed the study. Per the study protocol, PK data from 33 subjects were analyzed. Results are shown in the Figure 1 and the pharmacokinetic parameters are summarized in Table 2.

Figure 1. Mean plasma concentrations of megestrol acetate after oral administration of 575 mg, 625 mg, and 675 mg of megestrol acetate oral suspension NCD and 800 mg of Megace® suspension to healthy volunteers under fed conditions

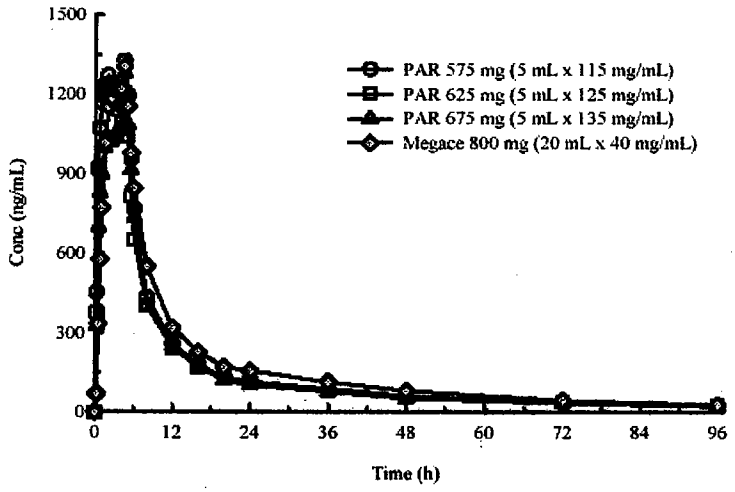


Table 2. Comparison of pharmacokinetic parameters after oral administration of 575 mg, 625 mg, and 675 mg of megestrol acetate oral suspension NCD and 800 mg of Megace® suspension to healthy volunteers under fed conditions (N=33)

Parameters	Test-1 [Megestrol Acetate 575 mg/5mL (A)] Mean ± SD	Reference [Megace 40 mg/mL (B)] Mean ± SD
AUC_{0-t} (ng•h/mL)	13657.52 ± 3900.50	16896.21± 4942.51
$AUC_{0-\infty}$ (ng•h/mL)	14746.46±4453.99	18274.06±5623.07
Cmax (ng/mL)	1420.73±420.79	1400.66±350.57
Tmax (h)	3.75±1.57	3.88±1.02
K_{el}	0.0224±0.0062	0.0238±0.0054
$T_{1/2\,el}$ (h)	32.85±7.46	30.53±6.66

Parameters	Test-2 [Megestrol Acetate 625 mg/5mL (C)] Mean ± SD	Test-3 [Megestrol Acetate 675 mg/5mL (D)] Mean ± SD
AUC_{0-t} (ng•h/mL)	14685.42 ± 4847.83	15324.17± 4526.37
$AUC_{0-\infty}$ (ng•h/mL)	16084.59±5566.01	16739.06±5432.83
Cmax (ng/mL)	1516.79±389.01	1645.74±455.71
Tmax (h)	2.52±1.60	3.13±1.64
K_{el}	0.0211±0.0055	0.0211±0.0054
$T_{1/2\,el}$ (h)	34.74±7.81	34.81±8.10

The geometric mean ratios and 90% confidence intervals for Cmax and AUC between megestrol acetate oral suspension NCD and Megace® are summarized in Table 3.

Table 3. Treatment comparisons

Parameter	Ratio (%)	90% CI
Megestrol acetate oral suspension NCD 575 mg/5mL (115 mg/mL) (A) vs. Megace® 800 mg (40 mg/mL) (B)		
Cmax	100.62	94.10 - 107.60
AUC_{0-t}	81.06	**78.19 - 84.04**
$AUC_{0-\infty}$	80.93	**77.96 - 84.02**
Megestrol acetate oral suspension NCD 625 mg/5mL (125 mg/mL) (C) vs. Megace® 800 mg (40 mg/mL) (B)		
Cmax	**108.18**	**101.17 - 115.69**
AUC_{0-t}	**86.30**	**83.25 - 89.47**
$AUC_{0-\infty}$	**87.34**	**84.13 - 90.67**
Megestrol acetate oral suspension NCD 675 mg/5mL (135 mg/mL) (D) vs. Megace® 800 mg (40 mg/mL) (B)		
Cmax	116.72	109.15-124.82
AUC_{0-t}	90.63	87.42-93.96
$AUC_{0-\infty}$	91.31	87.95-94.79

The lower limits of the 90% confidence intervals for AUC0-t and AUC0-inf for the 115 mg/mL were slightly below the [redacted] The two higher strengths of megestrol acetate oral suspension NCD (125mg/mL and 135 mg/mL) are

bioequivalent to Megace® 800 mg/20mL, but the point estimates of Cmax and AUC for 125mg/mL is closer to Megace® than 135 mg/mL.

In an IND meeting with the sponsor in 2003, the sponsor presented the Agency that megestrol NCD formulation may not be able to meet both Cmax and AUC criteria for bioequivalence in comparison with Megace® based on their preliminary studies and the Agency agreed with the sponsor that they might use Cmax as the primary endpoint and AUC as the secondary endpoint to establish equivalence if AUC is not substantially higher than the reference drug product. Otherwise, a clinical safety study may be required. The sponsor did preliminary pharmacokinetic studies ranging from 150 mg dose up to 675 mg dose under fed conditions and demonstrated they were within a linear range from which the sponsor plotted against the Megace® pharmacokinetic data and determined the best corresponding dose to Megace® 800 mg. The sponsor has been focused on the strength of 115 mg/mL for their drug development program though they have been keeping 2 additional strengths, 125 mg/mL and 135 mg/mL in their drug programs. However, based on this final, pivotal bioequivalence study, the two higher strengths, 125 mg/mL and 135 mg/mL meet the 90% CI criteria for bioequivalence. Between these two higher strengths, 125 mg/mL is closer to Megace® than 135 mg/mL in terms of the point estimate of AUC (86%). This reviewer recommends the strength 125 mg/mL (625 mg/5mL) be approved for the marketing drug product.

2.2.2 What is the effect of food on the bioavailability of megestrol acetate oral suspension?

The sponsor conducted a randomized, single-dose, single-center, open-label, 2-way crossover bioavailability study under fasted and fed conditions to evaluate the food effect on the bioavailability of megestrol acetate oral suspension NCD (Study 30422). The highest strength 135 mg/mL formulation the sponsor developed was used in the study. 36 subjects received a single dose of the study drug in each of the 2 treatment periods according to a crossover design: 675 mg (5 mL x 135 mg/mL) under fasting conditions, and 675 mg (5 mL x 135 mg/mL) under fed conditions. The treatment phases were separated by a washout period of 14 days.

Pharmacokinetic results showed that the administration of megestrol acetate oral suspension NCD with food resulted in higher plasma megestrol acetate concentrations (Figure 2 and Table 4) and higher mean values for Cmax, AUC0-t, and AUC0-∞. The geometric mean ratio for Cmax was 154% and those for AUC0-t and AUC∞ were 139% and 141%, respectively, and the upper limits of the 90% confidence intervals were >125% (Table 5), indicating a significant effect of food on absorption.

Figure 2. Mean plasma concentrations of megestrol acetate after oral administration of 675 mg of megestrol acetate oral suspension NCD to healthy volunteers under fasted and fed conditions

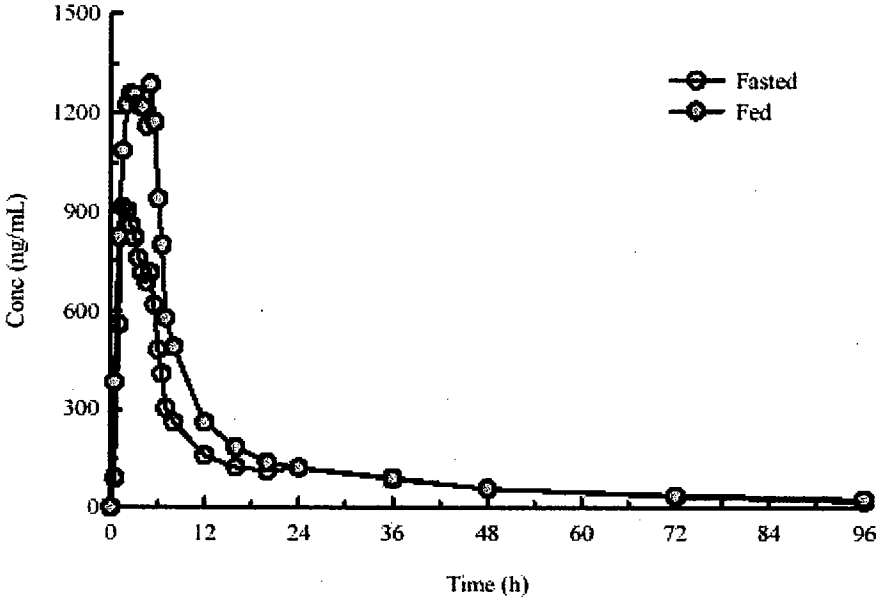


Table 4. Pharmacokinetic parameters after oral administration of 675 mg of megestrol acetate oral suspension NCD in fasting and fed conditions (N=34)

Parameters	Megestrol Acetate (Fasting condition) Mean ± SD	Megestrol Acetate (Fed condition) Mean ± SD
AUC_{0-t} (ng·h/mL)	10977.52 ± 3473.63	15403.06 ± 5436.98
$AUC_{0-\infty}$ (ng·h/mL)	11878.79 ± 4109.82	17029.04 ± 6676.92
Cmax (ng/mL)	1043.53 ± 268.06	1615.85 ± 431.16
Tmax (h)	1.96 ± 1.41	2.76 ± 1.56
K_{el}	0.0267 ± 0.0078	0.0227 ± 0.0084
$T_{1/2el}$ (h)	27.97 ± 7.32	34.89 ± 13.81

Table 5. Megestrol acetate (fed condition) (B) vs Megestrol acetate (Fasting condition) (A)

Parameter	Ratio	
	Estimate	90% Confidence Interval
AUC_{0-t}	139.19	132.57 – 146.15
$AUC_{0-\infty}$	141.44	134.11 – 149.17
Cmax	154.15	142.47 – 166.78

High-fat, high-caloric meal increases AUC and Cmax of megestrol acetate oral suspension NCD by approximately 40% and 54%, respectively. This reviewer recognized that the food effect on bioavailability is significantly reduced by this new

NCD formulation in comparison with the reference Megace® formulation. In an early study (Study 30146), the sponsor compared 375 mg megestrol acetate oral suspension (the strength 75 mg/mL) with 800 mg Megace® (20 ml x 40 mg/mL) under fasting condition. In Study 30147, the sponsor compared 375 mg megestrol acetate oral suspension (5 ml x 75 mg/mL) with 800 mg Megace® (20 ml x 40 mg/mL) under fed condition. These study results are shown in Figure 3 and Figure 4.

Figure 3. Mean plasma concentrations of megestrol acetate after oral administration of 375 mg of megestrol acetate oral suspension NCD and 800 mg of Megace® suspension to healthy volunteers under fasted conditions

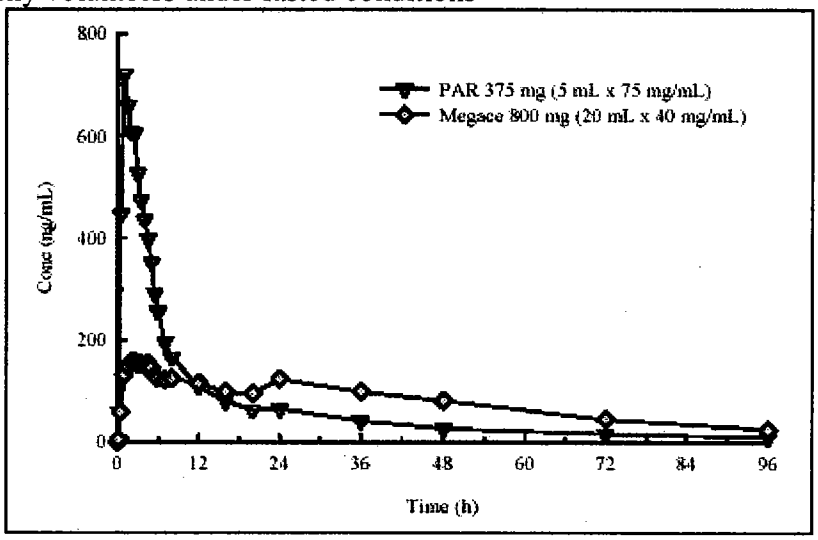
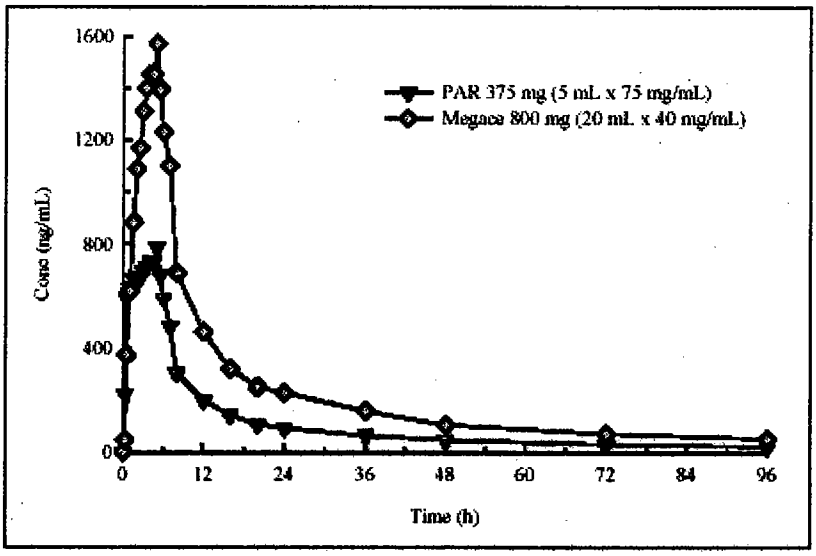


Figure 4. Mean plasma concentrations of megestrol acetate after oral administration of 375 mg of megestrol acetate oral suspension NCD and 800 mg of Megace® suspension to healthy volunteers under fed conditions



Cross study comparisons show that food may increase Megace® Cmax as much as 8 fold in comparison with the fasting condition, whereas Megestrol acetate oral suspension NCD has shown 40% increase in its Cmax with food.

2.2.3 Dose Megestrol acetate oral suspension have effect on Indinavir pharmacokinetics?

The sponsor conducted a multiple dose, open-label, crossover drug interaction study to evaluate the potential effect of megestrol acetate given as 675 mg (5 ml X 135 mg/mL) once daily from Days 2 to 15 on the pharmacokinetics of indinavir, administered as 2 X 400 mg capsules (for a total dose of 800 mg) once daily on Days 1 and 15 in 28 healthy male subjects. The pharmacokinetic results are summarized in Figure 5 and Table 6. The ratios between Day 15 and Day 1 for Indinavir pharmacokinetic parameters are summarized in Table 7.

Figure 5. The effect of Megestrol acetate (675 mg) on Indinavir (800 mg) pharmacokinetics

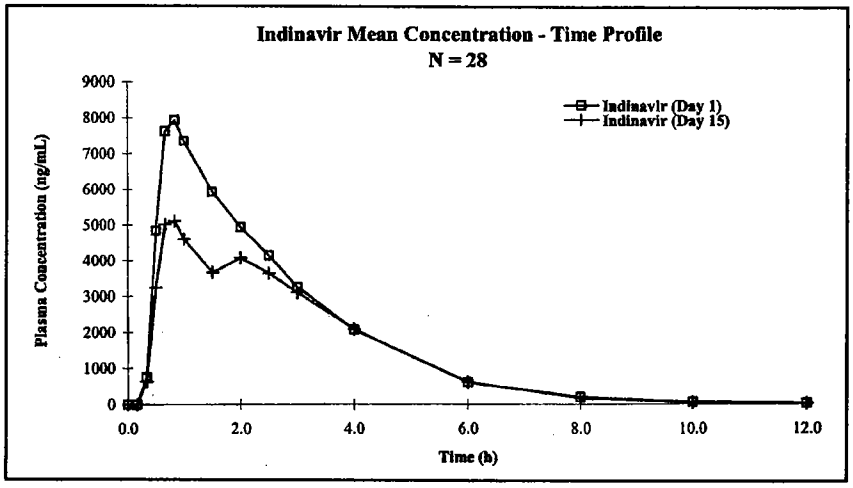


Table 6. Pharmacokinetic parameters of Indinavir before and after megestrol acetate

Parameters	Indinavir (Day 1) (Mean ± SD)	Indinavir (Day 15) (Mean ± SD)
$AUC_{0\text{-}8}$ (ngh/mL)	20778.58 ± 6059.66	16740.40 ± 5910.99
AUC_{∞} (ngh/mL)	20856.64 ± 6064.99	16810.98 ± 5918.94
Cmax (ng/mL)	8491.15 ± 2127.58	5913.44 ± 2112.83
Tmax (h)	0.881 ± 0.360	1.13 ± 0.72
K_{el}	0.5073 ± 0.0679	0.5513 ± 0.0627
$T_{1/2el}$ (h)	1.39 ± 0.19	1.27 ± 0.15

Table 7. Indinavir (Day 15) vs Indinavir (Day 1)

Parameter	Ratio	
	Estimate	90% Confidence Interval
AUC $_{0-t}$	78.73%	70.67 – 87.71
AUC $_{0-\infty}$	78.78%	70.74 – 87.73
Cmax	67.64%	59.22 – 77.25

Megestrol acetate reduced Indinavir Cmax and AUC by 32% and 21%, respectively. Based on these in vivo drug interaction study results, we can conclude that megestrol acetate may have induced enzymes that metabolized Indinavir.

2.2.4 What is the effect of megestrol acetate oral suspension on drug metabolism enzymes from in vitro studies?

The sponsor conducted in vitro studies to determine the inhibitory potential of megestrol on the activities o CYP1A2, 1A6, 2C9, 2C19, 2D6, 2E1 and 3A4 in human microsomes (Table 8). Microsomes were incubated in the presence of megestrol acetate concentrations from 0.385 μg/mL to 19.2 μg/mL with selective substrates for each CYP enzyme, each containing 0.1% methanol. The highest tested megestrol concentration was 50 μM instead of 100 μM because the 1000X megestrol (100 μM) was not soluble in methanol. Ketoconazole in a concentration of 0.1 μM in 0.1 methanol was used as a positive control. The test system was considered responsive if the mean activity of CYP3A4 in the positive control samples treated with ketoconazole was ≤ 50% of that in the control samples. Microsomes were prepared and pooled from at least ten human donors.

Table 8. In vitro inhibitory drug metabolism experiments

CYP	Selective substrate	Substrate concentration
CYP1A2	Phenacetin O-Deethylation	150 μM
CYP2A6	Coumarin 7-Hydroxylation	8 μM
CYP2C9	Tolbutamide Methyl-Hydroxylation	250 μM
CYP2C19	S-mephenyton 4'-Hydroxylation	50 μM
CYP2D6	Dextromethorphan O-Demethylation	72 μM
CYP2E1	Chlorzoxazone 6-hydroxylation	50 μM
CYP3A4	Testosterone 6β-hydroxylation	100 μM

Megestrol acetate at clinical concentrations (a peak concentration of approximately 1.5 μg/mL) is a moderate inhibitor of 2C9, 2C19 and a mild inhibitor of 2A6, and 2D6 activities, and a stimulator of CYP1A2 and 2E1 activities (Table 9)..

Table 9. Percent of control activity of CYP enzymes in the presence of megestrol

Megestrol (μM)	Percent of Control (%)						
	1A2	2A6	2C9	2C19	2D6	2E1	3A4
1	105	100	100	129	94.5	113	104
10	138	90.9	80.3	86.3	90.3	152	95.7
50	145	86.1	**65.4**	**67.0**	84.5	182	93.2

The sponsor also conducted in vitro studies to determine the induction potential of megestrol on the activities o CYP1A2, 2C9, and 3A4 in human Cryopreserved human hepatocytes (Table 10). Hepatocytes were incubated with megestrol for 2 days, after a selective substrate for each CYP enzyme was added. The formation of the selective metabolite from its substrate was measured by spectrophotometry or HPLC. Megestrol at 0.25, 2.5 and 25 μM did not induce CYP1A2, CYP2C9 and CYP3A4 activity in cryopreserved human hepatocytes isolated from these three donors.

Table 10. In vitro induction drug metabolism experiments

CYP	Selective substrate	Substrate concentration
CYP1A2	Ethoxyresoruin O-Deethylation	2 μM
CYP2C9	Tolbutamide Methyl-Hydroxylation	50 μM
CYP3A4	Testosterone 6β-hydroxylation	125 μM

Only hepatocytes preparations with ≥70% viability were used in this study. Omeprazole and rifampin, selective inducers of CYP1A2 and CYP3A4, respectively, were added to hepatocyte incubations with 1% acetonitrile to verify that the test system was responsive to inducers. The final concentrations of omeprazole and rifampin in the incubation systems were 50 μM and 25 μM, respectively.

Three donors' livers were used. The donors were Lot No. [redacted] (46 yrs old Caucasian male died of head trauma), Lot No. [redacted] (39 yrs old Hispanic male died of head trauma), Lot No. 130 (2 yrs old female died of anoxia). Donors had normal urinalyses and blood chemistries and no history of alcohol, tobacco or drug use. No chronic medications were listed.

The sponsor concluded that megestrol at 0.25, 2.5, and 25 μM did not induce CYP3A4 (Table 11), CYP1A2 (Table 12), and CYP2C9 (Table 13) activity in cryopreserved human hepatocytes isolated from these three donors. However, this reviewer noticed that for CYP3A4 and CYP1A2, at least one donor did show that there was no change after megestrol incubation though some results revealed that the formation of metabolites were below the lowest point in the standard curve, which is not reliable for the observed values. For CYP2C9, the results are not reliable since there were no positive controls and both vehicle controls and samples with megestrol generated the product below the lowest point in the standard curve range. In these in vitro studies, samples sizes are very small and not all samples worked well. A solid conclusion can not be drawn. In addition, the in vivo drug interaction study with indinavir has shown that megestrol reduced the Cmax and AUC of indinavir by 32% and 21%, most likely due to enzyme induction.

Table 11. CYP 3A4 activity in cryopreserved hepatocytes following incubation with rifampin and megestrol

Agent	Lot. No. [redacted]		Lot. No. [redacted]		Lot. No. 130	
	Pmol/min/million cells	% of control	Pmol/min/million cells	% of control	Pmol/min/million cells	% of control
Control	10.0 ± 1.81	100	6.81 ± 0.390	100	12.1 ± 0.863	100
Rifampin 25 µM	121 ± 17.8	1,214	14.7 ± 2.98	216	143 ± 16.4	1,185
Control	14.2 ± 0.861	100	6.79 ± 0.390	100	7.99 ± 0.564	100
Megestrol						
0.25 µM	10.8 ± 0.447	76.3	4.42 ± 0.236	65.1	6.16 ± 0.553	77.1
2.5 µM	6.96 ± 1.28	48.9	*<2.86 ± 0.00	<42.1	*<2.86 ± 0.000	<35.8
25 µM	*<2.86 ± 0.00	<20.1	*<2.86 ± 0.00	<42.1	*<2.86 ± 0.000	<35.8

*The observed analyzed value is below the lowest concentration on the standard curve.

Table 12. CYP 1A2 activity in cryopreserved hepatocytes following incubation with omeprazole and megestrol

Agent	Lot. No. [redacted]		Lot. No. [redacted]		Lot. No. 130	
	Pmol/min/million cells	% of control	Pmol/min/million cells	% of control	Pmol/min/million cells	% of control
Control	0.0676 ± 0.0238	100	*<0.0457 ± 0.000	100	0.103 ± 0.0199	100
Omeprazole 50 µM	2.63 ± 0.526	3,894	0.571 ± 0.0563	>1,250	7.31 ± 0.371	7,083
Control	*<0.0457 ± 0.000	100	*<0.0457 ± 0.000	100	0.129 ± 0.0313	100
Megestrol						
0.25 µM	*<0.0457 ± 0.000	100	*<0.0457 ± 0.000	100	0.129 ± 0.0247	100
2.5 µM	*<0.0457 ± 0.000	100	*<0.0457 ± 0.000	100	0.125 ± 0.0320	97.6
25 µM	*<0.0457 ± 0.000	100	*<0.0457 ± 0.000	100	*<0.0651 ± 0.0309	<50.6

*The observed analyzed value is below the lowest concentration on the standard curve.

Table 13. CYP 2C9 activity in cryopreserved hepatocytes following incubation with megestrol

Agent	Lot. No. [redacted]		Lot. No. [redacted]		Lot. No. 130	
	Pmol/min/million cells	% of control	Pmol/min/million cells	% of control	Pmol/min/million cells	% of control
Control	*<2.24 ± 0.000	100	<2.24 ± 0.000	100	<2.30 ± 0.0548	100
Megestrol						
0.25 µM	*<2.24 ± 0.000	100	<2.24 ± 0.000	100	<2.24 ± 0.000	97.5
2.5 µM	*<2.24 ± 0.000	100	<2.24 ± 0.000	100	<2.24 ± 0.000	97.5
25 µM	*<2.24 ± 0.000	100	<2.24 ± 0.000	100	<2.24 ± 0.000	97.5

*The observed analyzed value is below the lowest concentration on the standard curve.

2.3 General Biopharmaceutics

2.3.1 What are the dissolution method and specification for megestrol acetate oral suspension NCD?

Megestrol acetate is generally insoluble in aqueous media. A dissolution test in a compendial apparatus utilizes a surfactant based modifier in an aqueous system to assist solubilization of active ingredient (Table 14).

Table 14. The effect of surfactant sodium lauryl sulfate on megestrol dissolution using the highest potency finished dosage form 135 mg/mL

Test	% surfactant	mL of oral suspension added	Result
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Sodium lauryl sulfate (SLS) was chosen as a surfactant. The amount of megestrol acetate that can be dissolved in a given volume is proportional to the SLS concentrations in the dissolution medium. Table 15 below shows the solubility of megestrol acetate in SLS media.

Table 15. saturated megestrol in different sodium lauryl sulfate concentrations

Test	% surfactant	Maximum mg/900 mL of Meestro Acetate dissolved
1		
2		
3		
4		

A plot of maximum megestrol acetate concentration for a given concentration of SLS % in water is shown in Figure 6.

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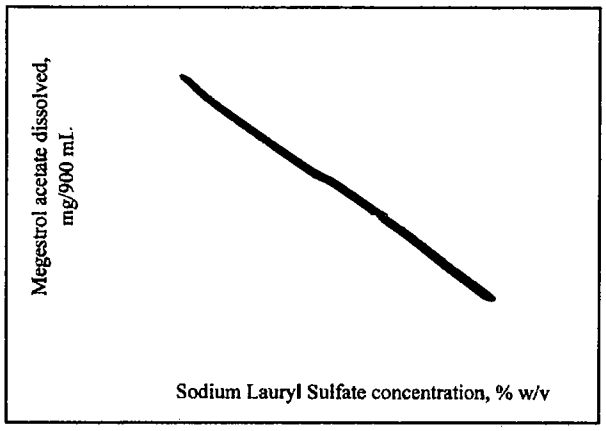
Figure 6. Maximum Megestrol Acetate Solubility in Sodium Lauryl Sulfate Aqueous solutions



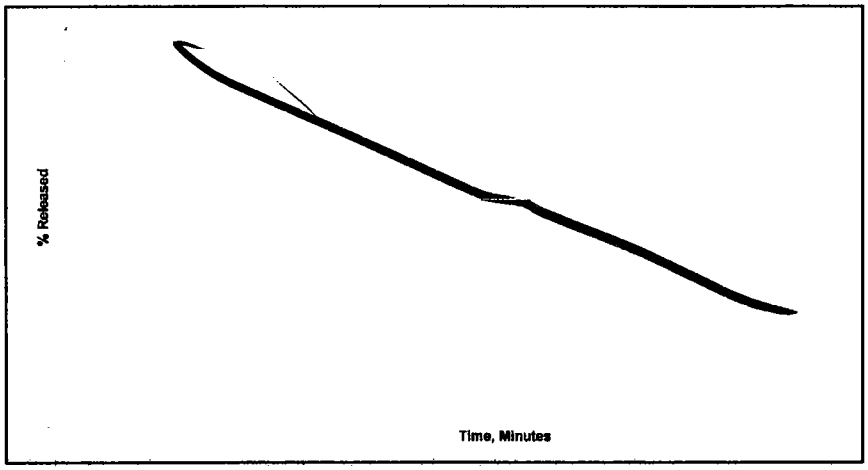
The dissolution parameters of the current USP for Megestrol Acetate Oral Suspension are listed in Table 16.

Table 16. Current USP Conditions for Megace® Suspension

Apparatus	**USP Apparatus II (paddles)**
RPM	50
Time	20 minutes
Q	(Q) in 20 minutes
Volume	900 mL
Bath Temperature	37°C
Sample introduction amount	10 mL (1/2 unit dose)
Medium	0.5 % Sodium Lauryl Sulfate in water

The sponsor presented the dissolution data in two different RPM conditions: 25 rpm and 50 rpm in 1% SLS (Figure 7)

Figure 7. Megestrol Acetate Oral Suspension (NCD), 115 mg/mL, Dissolution Profile in Sodium Lauryl Sulfate (SLS) in water, apparatus II, 900 ml @ 25 rpm and 50 rpm



Based on the results presented by the sponsor, we recommend the following dissolution method and specifications (Table 17):

Table 17. Recommended dissolution method and specifications for megestrol acetate Oral suspension NCD

Apparatus	**USP Apparatus II (paddles)**
RPM	25
Time	10 minutes
Q	NLT [redacted] (Q) in 10 minutes
Volume	900 mL
Bath Temperature	37°C
Sample introduction amount	5 mL (one unit dose)
Medium	1.0% Sodium Lauryl Sulfate in water

2.4 Analytical Section

2.4.1 What is the property of analytical method?

For the quantitation of plasma megestrol acetate concentrations, high performance liquid chromatographic method with tandem mass detection (LC/MS/MS) was developed and validated. The method used in pivotal bioequivalence study indicated that the calibration curve ranged from . [redacted] ng/mL. The lowest validated limit of quantitation (LLOD) for megestrol is 2.00 ng/mL. Inter- and intraday variabilities are summarized in Table 18.

Table 18. Variability of LC/MS/MS assay for megestrol in human plasma

Between-run accuracy
Between-run precision
Within-run accuracy
Within-run precision
Recovery rate
Dilution integrity accuracy
Dilution integrity precision

3. DETAILED LABELING RECOMMENDATIONS

Labeling comments will be made in an addendum to the review.

4. Appendices:

4.1 Proposed Package Insert (separate file)

4.2 Individual Study Review (see Addenndum as a separate file)

4.3 OCPB Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-778	Brand Name	Not available
OCPB Division (I, II, III)	DPE II	Generic Name	Megestrol Acetate Oral Suspension [redacted]
Medical Division	HFD-510	Drug Class	Synthetic progesterone derivative
OCPB Reviewer	Xiaoxiong (Jim) Wei	Indication(s)	Cachexia
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Suspension
		Dosing Regimen	[redacted] mL QD
Date of Submission	06-29-2003	Route of Administration	PO
Estimated Due Date of OCPB Review	02-01-05	Sponsor	Par Pharmaceutical
PDUFA Due Date	04-29-05	Priority Classification	S1
Division Due Date	02-10-05		

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			Table of contents for electronically submitted section was not sufficient to locate information
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:	X	(8)		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:		1		
In-vitro:	X	2		
Subpopulation studies -				
ethnicity:				
gender:				Only male subjects enrolled
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		5		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:		1		
Dissolution:				Not established
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		9		

Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	**Yes**			
Comments sent to firm?	**Yes**	1) Please provide a table of contents for electronically submitted study reports and data 2) A dissolution test is required for suspension drug products. The dissolution method should be developed and optimized by using three different conditions with three different lots. Mild dissolution conditions (e.g., a paddle speed of 25 rpm) should be considered.		

Briefing in Content:

Par Pharmaceutical submitted a NDA under 505 b (2) application to market Megestrol Acetate Oral Suspension [redacted] Megestrol acetate is currently approved as a 40 mg/mL oral suspension (Bristol-Myers Squibb) under the brand name Megace®. The sponsor holds an approved ANDA (No. 75-671) for Megestrol Acetate Suspension 40 mg/mL and generic formulations are also available from other companies.

Studies with Megace® in humans have shown that there is a positive food effect on the extent and rate of absorption of megestrol acetate. [redacted] NanoCrystal drug formulations have substantially increased surface area per unit mass relative to micronized drug particles. This increased surface area of the nanoparticles provides an increase in the bioavailability of megestrol and a decrease in variability between fed and fasted conditions.

The sponsor submitted five pilot and one pivotal relative BA/BE studies to compare Megestrol Oral Suspension NCD to the reference drug Megace®. The sponsor also submitted one food effect study, one drug interaction study between Megestrol and indinavir and two in vitro drug metabolism studies.

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/s/

Xiao-xiong Wei
4/5/05 01:46:42 PM
BIOPHARMACEUTICS

Hae-Young Ahn
4/5/05 06:07:55 PM
BIOPHARMACEUTICS

04/12/05

Addenndum
4.2 Individual Study Review

NDA: 21-778 (N-000)
Drug name: Megace ES™ (Megestrol acetate oral suspension [redacted])
Indication: Treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).
Submission date: 06-27-2004
Reviewer: Xiaoxiong (Jim) Wei
Team Leader: Hae-Young Ahn
OCPB: DPE2
OND: DMEDP (Division of Metabolic and Endocrine Drug Products, HFD-510)

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3	30054	Drug Interaction Study to Evaluate the Effect of Megestrol Acetate Oral Suspension on Indinavir Pharmacokinetics in Healthy Subjects	7
4	30146	Randomized, 2-Way Crossover, Comparative Bioavailability Study of Megestrol Acetate 75 mg/mL Oral Suspension and Megace® 40 mg/mL Oral Suspension and Administered as 1 X 5 mL (375 mg) or 1 X 20 mL (800 mg) of Oral Suspension in Healthy Subjects Under Fasting Conditions	13
5	30147	Randomized, 2-Way Crossover, Comparative Bioavailability Study of Megestrol Acetate 75 mg/mL Oral Suspension and Megace® 40 mg/mL Oral Suspension and Administered as 1 X 5 mL (375 mg) or 1 X 20 mL (800 mg) of Oral Suspension in Healthy Subjects Under Fed Conditions	24
6	272-1052 -01	Determination of the Inhibitory Potential of Megestrol on the Activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in Human Liver Microsomes	30
7	272-1053 -02	Determination of the Induction Potential of Megestrol on the Activities of CYPIA2, CYP2C9, and CYP3A4 in Cryopreserved Human Hepatocytes	40

Study 30421

Title
Four-Way, Comparative Bioavailability Study of Three Different Formulations of Megestrol Acetate Oral Suspension and Megace® 40 mg/mL Oral Suspension Administered in Healthy Subjects Under Fed Conditions

Methods
The purpose of Study 30421 was to compare the rate and extent of absorption of three doses of megestrol acetate oral suspension NCD (575 mg [115 mg/mL], 625 mg [125 mg/mL] and 675 mg [135 mg/mL]) versus Megace® (megestrol acetate oral suspension 800 mg[40 mg/mL]), administered under fed conditions.

This was a single-center, single-dose, open-label, 4-way bioavailability study conducted under fed conditions at [redacted] Subjects received a single dose of the following study drugs in each of the 4 treatment periods according to a crossover design:

– Treatment Period 1: 575 mg (5 mL x 115 mg/mL) megestrol acetate oral suspension NCD,
– Treatment Period 2: 800 mg (20 mL x 40 mg/mL) Megace®,
– Treatment Period 3: 625 mg (5 mL x 125 mg/mL) megestrol acetate oral suspension NCD, and
– Treatment Period 4: 675 mg (5 mL x 135 mg/mL) megestrol acetate oral suspension NCD.

The single oral doses were separated by a 14-day washout period.

Doses were administered after a 10-hour, overnight fast and within 30 minutes after a standard high-fat breakfast of approximately 1000 calories. For each treatment period, subjects were confined to the research facility from at least 11 hours prior to drug administration until after the 24-hour post-dose blood draw. Blood samples for measurement of megestrol acetate were collected for 96 hours after dosing and the resultant plasma analyzed for megestrol acetate using an LC/MS/MS method with an LOQ of 5 ng/mL. Clinical laboratory tests were performed at screening, at entry into Treatment Periods 3 and 4 (hematology only), and at end of study. There were no protocol deviations that were judged to affect the results and conclusions of the study.

A total of 42 healthy, adult male subjects signed the study-specific informed consent form. Of these subjects, 38 were dosed and were considered to have enrolled in the study; 33 subjects completed the study. Per the study protocol, PK data from 33 subjects were analyzed. Five subjects withdrew from the study prior to completion. Two subjects (Nos. 11 and 14) withdrew from the study due to professional obligations and 3 subjects were withdrawn due to an AE (Nos. 20, 33, and 34). Subject No. 20 was withdrawn after Treatment Period 3 due to vomiting within 8 hours after receiving 625 mg (125 mg/mL) megestrol acetate oral suspension NCD, Subject No. 33 was withdrawn prior to Treatment Period 3 drug administration due to clinically significant low platelet count 14 days after receiving Megace® and Subject No. 34 was withdrawn after Treatment Period 4 drug administration due to vomiting within 8 hours after receiving 675 mg (135 mg/mL) megestrol acetate oral suspension NCD.

At screening, the mean age of the subjects was 32 years (range 21-59), mean body mass index was 24.9 kg/m2 (range 21.4-29.5), mean weight was 77.5 kg (range 59.9-98.9), and mean height was 176.2 cm (range 159.5-191.5). The majority of subjects enrolled were Caucasian (95%, 36/38), 3% (1/38) were Black, and 3% (1/38) were American Hispanic.

Pharmacokinetic Results
As illustrated in Figure 1, mean plasma megestrol concentrations were close after administration of 575, 625, and 675 mg megestrol acetate oral suspension NCD and Megace® 800 mg oral suspension, as were mean values for Cmax, AUC0-t, and AUC0-inf.

The lower limits of the 90% confidence intervals for AUC0-t and AUC0-inf were slightly below the 80% – 125% window for the 575 mg but within the window for the other two strengths of megestrol acetate oral suspension NCD relative to Megace® (Table 1), indicating an extent of absorption that was not greater than Megace®. The geometric mean ratios for Cmax ranged from 100.62% for the 575 mg NCD suspension to 116.72% for the 675 mg suspension and the 90% confidence limits for all three strengths were within the 80% – 125% window (Table 2). These results indicate that 575 mg megestrol acetate oral suspension NCD provides a Cmax that is equivalent to that of Megace® under fed conditions with an AUC that fails to meet BE criteria.

Figure 1. Mean plasma concentrations of megestrol acetate after oral administration of 575 mg, 625 mg, and 675 mg of megestrol acetate oral suspension NCD and 800 mg of Megace® suspension to healthy volunteers under fed conditions

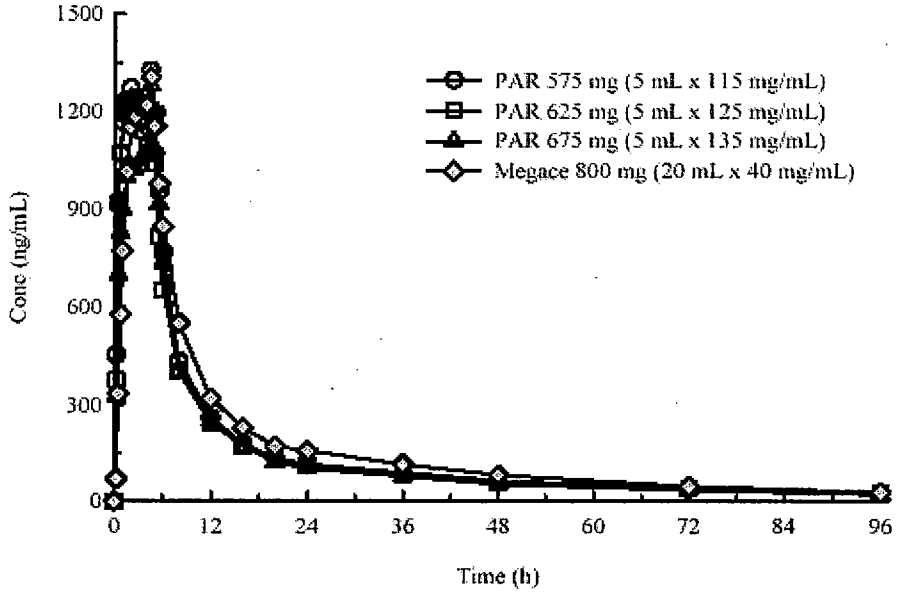

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Table 1. Comparison of pharmacokinetic parameters after oral administration of 575 mg, 625 mg, and 675 mg of megestrol acetate oral suspension NCD and 800 mg of Megace® suspension to healthy volunteers under fed conditions (N=33)

Parameters	Test-1 [Megestrol Acetate 575 mg/5mL (A)] Mean ± SD	Reference [Megace 40 mg/mL (B)] Mean ± SD
AUC_{0-t} (ng•h/mL)	13657.52 ± 3900.50	16896.21± 4942.51
$AUC_{0-\infty}$ (ng•h/mL)	14746.46±4453.99	18274.06±5623.07
Cmax (ng/mL)	1420.73±420.79	1400.66±350.57
Tmax (h)	3.75±1.57	3.88±1.02
K_{el}	0.0224±0.0062	0.0238±0.0054
$T_{1/2\ el}$ (h)	32.85±7.46	30.53±6.66
Parameters	**Test-2 [Megestrol Acetate 625 mg/5mL (C)] Mean ± SD**	**Test-3 [Megestrol Acetate 675 mg/5mL (D)] Mean ± SD**
AUC_{0-t} (ng•h/mL)	14685.42 ± 4847.83	15324.17± 4526.37
$AUC_{0-\infty}$ (ng•h/mL)	16084.59±5566.01	16739.06±5432.83
Cmax (ng/mL)	1516.79±389.01	1645.74±455.71
Tmax (h)	2.52±1.60	3.13±1.64
K_{el}	0.0211±0.0055	0.0211±0.0054
$T_{1/2\ el}$ (h)	34.74±7.81	34.81±8.10

Table 2. Treatment comparisons

Parameter	Ratio (%)	90% CI
Megestrol acetate oral suspension NCD 575 mg/5mL (115 mg/mL) (A) vs. Megace® 800 mg (40 mg/mL) (B)		
Cmax	100.62	94.10 - 107.60
AUC_{0-t}	81.06	78.19 - 84.04
$AUC_{0-\infty}$	80.93	77.96 - 84.02
Megestrol acetate oral suspension NCD 625 mg/5mL (115 mg/mL) (C) vs. Megace® 800 mg (40 mg/mL) (B)		
Cmax	**108.18**	**101.17 - 115.69**
AUC_{0-t}	**86.30**	**83.25 - 89.47**
$AUC_{0-\infty}$	**87.34**	**84.13 - 90.67**
Megestrol acetate oral suspension NCD 675 mg/5mL (115 mg/mL) (D) vs. Megace® 800 mg (40 mg/mL) (B)		
Cmax	116.72	109.15-124.82
AUC_{0-t}	90.63	87.42-93.96
$AUC_{0-\infty}$	91.31	87.95-94.79

Conclusion:

These results indicate that 575 mg megestrol acetate oral suspension NCD provides a Cmax that is equivalent to that of Megace® under fed conditions with an AUC that fails to meet BE criteria. However, both 625 mg and 675 mg megestrol acetate oral suspension NCD meet 90% confidence intervals for bioequivalence criteria.

Reviewer's comments:

This pivotal BE study demonstrated that two higher strengths (625 mg/5mL and 675 mg/5mL) are bioequivalent to Megace® 800 mg/20mL. In a IND meeting with the sponsor in 2003, the

sponsor presented the Agency that megestrol NCD formulation may not be able to meet both Cmax and AUC criteria for bioequivalence in comparison with Megace® based on their preliminary studies and the Agency agreed with the sponsor that they may use Cmax as the primary endpoint and AUC for the secondary endpoint to establish equivalence if AUC is not substantially higher than the reference drug product. Otherwise, a clinical safety study may be required. [redacted] However, based on this final, pivotal bioequivalence study, the two higher strengths, 125 mg/mL and 135 mg/mL actually passed the 90% CI criteria for bioequivalence. The strength 125 mg/mL is closer to the reference Megace® than the strength 15mg/mL in terms of the relative bioavailability to Megace®.

Study 30422
Title
Randomized, 2-Way Crossover, Food Effect Comparative Bioavailability Study of Megestrol Acetate 675 mg/5 mL Oral Suspension Administered as 1 x 5 mL (675 mg) Oral Suspension in Healthy Subjects Under Fasting and Fed Conditions.

Treatment: A (fasting) and B (fed])

Unit dose: 675 mg/5 mL

Regimen: oral suspension/oral
Single dose of 1 x 5 mL (675 mg) oral suspension per subject in assonance with the randomization scheme

Batch No.: 40968

Methods
The purpose of Study 30422 was to compare the rate and extent of absorption of megestrol acetate oral suspension NCD 135 mg/mL, administered as 1 x 5 mL (675 mg) under fasting and fed conditions.

This was a randomized, single-dose, single-center, open-label, 2-way crossover bioavailability study conducted under fasted and fed conditions

Subjects received a single dose of the following study drugs in each of the 2 treatment periods according to a crossover design:
- 675 mg (5 mL x 135 mg/mL) megestrol acetate oral suspension NCD under fasting conditions,
- 675 mg (5 mL x 135 mg/mL) megestrol acetate oral suspension NCD under fed conditions.

The single oral doses were separated by a 14-day washout period.

Doses were administered after a 10-hour overnight fast. For each treatment period, subjects were confined to the research facility from at least 11 hours prior to drug administration until after the 24-hour post-dose blood draw. Blood samples for measurement of megestrol acetate were collected for 96 hours after dosing and the resultant plasma analyzed for megestrol acetate using an LC/MS/MS method with a LOQ of 2 ng/mL. Clinical laboratory tests were performed at screening and at end of study.

There were no protocol deviations that were judged to affect the results and conclusions of the study.

A total of 43 healthy, adult male subjects signed the study-specific informed consent form. Of these subjects, 36 were dosed and were considered to have enrolled in the study; all the enrolled subjects completed the study. Per the study protocol, PK data from 34 subjects were analyzed.

At screening, the mean age of the subjects was 36 years (range 21-55), mean body mass index was 25.2 kg/m2 (range 19.4-29.9), mean weight was 78.6 kg (range 57.0-108.7), and mean height was 176.4 cm (range 159.0-194.5). The majority of subjects enrolled were Caucasian (94%, 34/36), 3% (1/36) were Black, and 3% (1/36) were American Hispanic.

Diagnosis and main criteria for inclusion:

Subjects had to be healthy adult mate subjects, aged IS and older; body mass indices below 30 kg'm2. All subjects had to meet the inclusion and exclusion criteria described in the protocol and were judged eligible for enrolment in this study, based on medical and medication histories, demographic data (including sex, age, race, body weight [kg], height [cm] and BMI [kg/rn2]), vital signs. 12 lead ECG, physical examination, a urine drug screen, and clinical laboratory tests (hematology, biochemistry, urinalysis, HIV and hepatitis C [HCV] antibodies, and hepatitis B antigen [HBsAg]),

Duration of treatment: A single oral dose of megestrol acetate as x 5 mL (675 mg) oral suspension was administered under fasting and fed conditions, in each study period. The treatment phases were separated by a washout period of 14 days.

Blood sampling points: Blood samples were drawn into blood collection tubes containing EDTA K3 prior to drug administration and 0.250, 0.500, 10), 1.50, 2.00, 2.50. 3.00, 3.50, 4.00, 4.50, 500, 5.50, 6.00, 7.00, 8.00, 12.0, 16.0, 20.0, 24.0, 36.0, 48.0, 72.0, and 960 hours post-dose in each period.

Criteria for evaluation:

Pharmacokinetics: AUC0-t, AUC0-inf, Cmax, Tmax, Kel and T1/2 el,

Primary Parameters: AUC0-t, AUC0-inf, Cmax

Secondary parameters: Tmax, Kel and T1/2 el,

Statistical Methods:

Pharmacokinetics

* Parametric ANOVA on AUC0-t, AUC0-inf, Cmax, Tmax, Kel and T1/2 el; geometric confidence intervals for AUC0-t, AUC0-inf, Cmax.

* Covariates in the ANOVA model: Sequence, Subject within Sequence, Period and Treatment.

* Ln-transformed parameters: AUC0-t, AUC0-inf and Cmax.

Assessment of food effect for the test formulation:
* 90% geometric confidence interval of the ratio (B/A) of least-squares means from the ANOVA of the ln-transformed AUC0-t, AUC0-inf and Cmax should be within 80.00% to 12500%;

Pharmacokinetic Results
Administration of megestrol acetate oral suspension NCD with food resulted in higher plasma megestrol acetate concentrations (Figure 15) and higher mean values for Cmax, AUC0-t, and AUC0-∞. The geometric mean ratio for Cmax was 154% and those for AUC0-t and AUC∞ were 139% and 141%, respectively, and the upper limits of the 90% confidence intervals were >125% (Table 7), indicating a significant effect of food on absorption.

Comparison of two lots of Megace∨ under fasted and fed conditions [Lot #1J48579, Studies 02097 (fasted) and 02098 (fed); Lot #1K52545, Studies 30146 (fasted) and 30147 (fed); demonstrates an ~800% increase in Cmax and ~250% increase in AUC∞. Consequently, the effect of food on megestrol acetate oral suspension NCD was substantially less than the effect on Megace®.

Figure. Mean plasma concentrations of megestrol acetate after oral administration of 675 mg of megestrol acetate oral suspension NCD to healthy volunteers under fasted and fed conditions

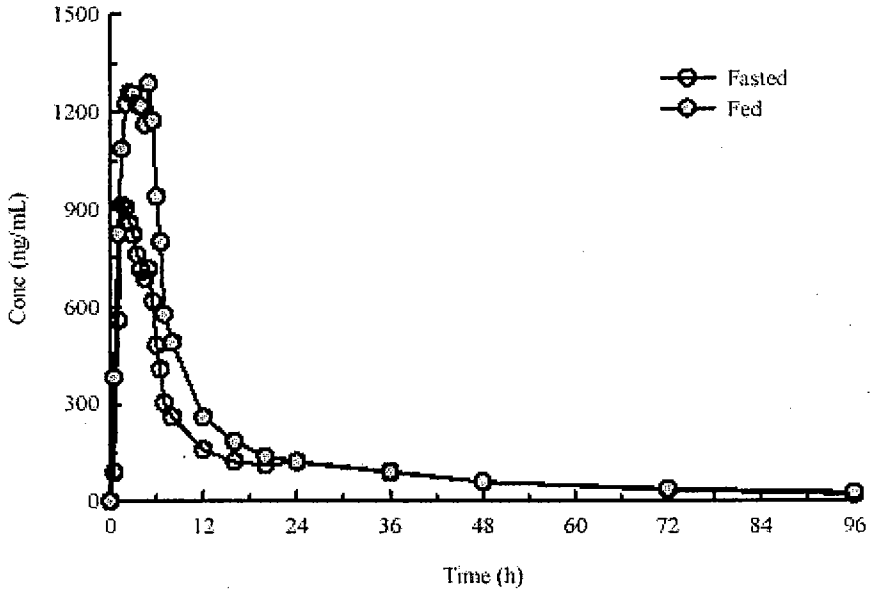

Table. Pharmacokinetic parameters after oral administration of 675 mg of megestrol acetate oral suspension NCD in fasting and fed conditions (N=34)

Parameters	Megestrol Acetate (Fasting condition) Mean ± SD	Megestrol Acetate (Fed condition) Mean ± SD
AUC_{0-t} (ng·h/mL)	10977.52 ± 3473.63	15403.06 ± 5436.98
$AUC_{0-\infty}$ (ng·h/mL)	11878.79 ± 4109.82	17029.04 ± 6676.92
Cmax (ng/mL)	1043.53 ± 268.06	1615.85 ± 431.16
Tmax (h)	1.96 ± 1.41	2.76 ± 1.56
K_{el}	0.0267 ± 0.0078	0.0227 ± 0.0084
$T_{1/2\,el}$ (h)	27.97 ± 7.32	34.89 ± 13.81

Table. Megestrol acetate (fed condition) (B) vs Megestrol acetate (Fasting condition) (A)

Parameter	Ratio	
	Estimate	90% Confidence Interval
AUC_{0-t}	139.19	132.57 – 146.15
$AUC_{0-\infty}$	141.44	134.11 – 149.17
Cmax	154.15	142.47 – 166.78

Conclusion:
Results from the study suggest that food has effect on bioavailability of megestrol acetate oral suspension. It can be concluded that a high-fat, high-caloric meal increases AUC and Cmax by approximately 40% and 54%, respectively and delays Tmax by approximately 1 hour.

Reviewer's comments:
We agree with the sponsor that high-fat, high-caloric meal increases AUC and Cmax of megestrol acetate oral suspension NCD by approximately 40% and 54%, respectively.

Study 30054

Title: Drug Interaction Study to Evaluate the Effect of Megestrol Acetate Oral Suspension on Indinavir Pharmacokinetics in Healthy Subjects

Objective: The objective of this drug interaction study was to evaluate the potential effect of megestrol acetate administered as 5 mL x 135 mg/mL oral suspension (for a total dose of 67S mg) once daily from Days 2 to ~5 on the pharmacokinetics of indinavir, administered as 2 x 400mg capsules (for a total dose of 800 mg) once daily on Days 1 and 15.

Study design:
This was a single center, Phase I, openlabel, multiple-dose, l-sequence crossover drug interaction study. Subjects were confined to the [redacted] from at least 10 hours prior to drug administration on Day 1 until at least 4 hours after drug administration on Day 2, from at least 1 hour prior until at east I hour after thug administration art Days 3 to 14, and from at least 10 hours prior to drug administration on Day 15 until after the 24-hour post 15th-dose blood draw.

Subjects:
Enrolled and randomized: 30
Drop-outs: 0
Withdrawals: 2
Completed: 28
Data set for safety analysis; 30
Data set for statistical analysis: 28

Diagnosis and main criteria for inclusion:
Subjects had to be healthy male, non-smokers, age4 between 18 and 45 years of age; body mass indices below 30.0 kg/m^2. All subjects had to meet the inclusion and exclusion criteria described in the protocol and were judged eligible for enrolment in this study, based on medical and medication histories, demographic data (including so; age, race, body weight, vital sign 12-lead ECG, physical examination, a urine drug screen, and clinical laboratory tests (hematology. biochemistry, urinalysis, HIV and hepatitis C [HCV] antibodies, and hepatitis B antigen.

Unit Dose: A: 135 mg/mL oral suspension; B: 400 mg Capsule.

Duration of treatment: An oral dose of megestrol acetate was administered as 5 mL x 135mg/mL oral suspension (for a total dose of 675 mg) once daily from Day 2 to 15 and an oral dose of Indinavir was administered as 2 x 400 ng capsules (for a total dose of 800 mg) once daily on Days 1 and 15.

Blood sampling points: Blood samples were collected prior to 4mg administration and 0.167, 0333, 0500, 0.667, 0.833, 1,00, 1.50. 2.00, 250, 3.00, 4.00, 6.00, 8.00, 10.0, 12.0 16.0, and approximately 24.0 hours post-dose on Days 1 and 15.

Criteria for evaluation:

Pharmacokinetics:

AUC0-t, AUC0-inf, Cmax, Tmax, Kel, T1/2 el, and V/F.

Primary parameters:

AUC0-t, AUC0-inf, Cmax

Statistical Methods:

Pharmacokinetics:

* Parametric ANOVA on AUC0-t. AUC0-inf, Cmax, Tmax,, Kel and T1/2 el; geometric confidence intervals for AUC0-t, AUQ0-inf, and Cmax.

* Covariates in the ANOVA model: Subject and Treatment.

* Ln-transformed parameters: AUC0-t. AUC0-inf, Cmax.

Criteria for interaction effect:
* If the ratio and 90% geometric confidence interval of the ratio (Day 15/Day 1) of least-squares means from the ANOVA of the Ln-transformed AUC0-t, AUC0-inf, Cmax are within 80% to 125%, this will indicate that megestrol acetate has no effect on indinavir pharmacokinetics.

Results:
There was a decrease in the mean plasma concentrations of indinavir after 14 days of dosing with megestrol acetate oral suspension NCD, as were mean values for Cmax, AUC0-t, and AUC0-inf. Although there appeared to be a low probability of inhibition based on the in vitro study, there was an ~24% decrease in the extent of exposure (AUC0-t) and an ~32% decrease in the rate of exposure (Cmax) and the 90% confidence intervals for the geometric mean ratios fell below the 80% ~ 125% window. This indicates, based on the current FDA Guidance, that there is a significant drug interaction between the product megestrol acetate and indinavir. These results were obtained with a higher dose of the NCD product (675 mg) than that which will be marketed (575 mg). This type of interaction is not thought to be limited to the NCD formulation, but is likely representative of interactions between these classes of compounds. Any variation from the reference listed drug labeling should apply to all products containing megestrol acetate.

Figure. Mean plasma concentrations of indinavir after oral administration of 800 mg alone and after administration of megestrol acetate oral suspension NCD 675 mg daily x 14 days to healthy volunteers

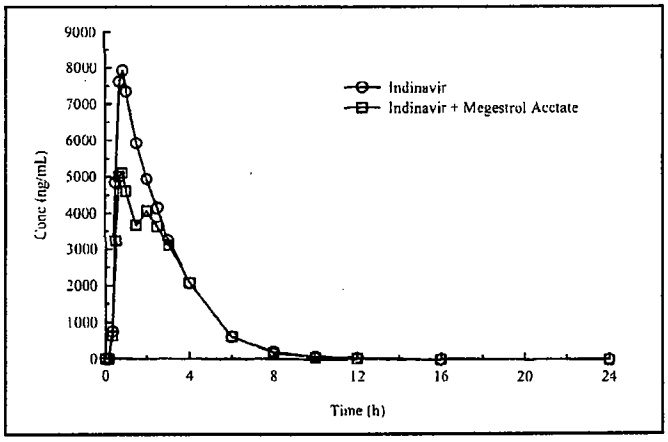

Table. Pharmacokinetic parameters of Indinavir before and after megestrol acetate

Parameters	Indinavir (Day 1) (Mean ± SD)	Indinavir (Day 15) (Mean ± SD)
AUC_{0-t} (ng•h/mL)	20778.58 ± 6059.66	16740.40 ± 5910.99
$AUC_{0-\infty}$ (ng•h/mL)	20856.64 ± 6064.99	16810.98 ± 5918.94
Cmax (ng/mL)	8491.15 ± 2127.58	5913.44 ± 2112.83
Tmax (h)	0.881 ± 0.360	1.13 ± 0.72
K_{el}	0.5073 ± 0.0679	0.5513 ± 0.0627
$T_{1/2,el}$ (h)	1.39 ± 0.19	1.27 ± 0.15

Table. Indinavir (Day 15) vs Indinavir (Day 1)

Parameter	**Ratio**	
	Estimate	**90% Confidence Interval**
AUC_{0-t}	78.73%	70.67 – 87.71
$AUC_{0-\infty}$	78.78%	70.74 – 87.73
Cmax	67.64%	59.22 – 77.25

Conclusions:

Megestrol acetate reduced Indinavir Cmax and AUC by 32% and 21%, respectively. Based on these in vivo drug interaction study results, we can conclude that megestrol acetate may have induced enzymes that metabolized Indinavir.

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Title: Randomized, 2-Way Crossover, Comparative Bioavailability Study of Megestrol Acetate 75 mg/mL Oral Suspension and Megace® 40 mg/mL Oral Suspension and Administered as 1 X 5 mL (375 mg) or 1 X 20 mL (800 mg) of Oral Suspension in Healthy Subjects Under Fasting Conditions

Objectives: The objective of this study was to compare the rate and extent of absorption of megestrol acetate 75 mg/mL oral suspension (test) versus Megace 40 mg/mL oral suspension (reference) administered as 1 x 5 mL (375 mg) or 1 x 20 mL (800 ng) of oral suspension under fasting conditions.

Methodology: This was a single center comparative bioavailability, open-label, randomized, two-way crossover study with a washout period of 14 days between doses.

Blood sampling points: at pre-dose and at 0.250, 0.500, 1.00, 1.50, 2.00, 2.50 300 3.50, 4.00, 4.50 5.00, 5.50 6.00, 7.00, 8.00, 12.0, 16.0, 20.0, 24.0, 36.0, 48.0, 72.0 and 96.0 hours postdose (n=24).

Statistical analysis:
ANOVA was performed on Ln-transformed AUC0-t, AUC0-inf, and Cmax and untransformed Tmax, Kel and T1/2. Ratios of least-squares means and 90% geometric confidence intervals were calculated for In-transformed AUC0-t, AUC0-inf, and Cmax.

Number of subjects: Enrolled and eligible Withdrawals Completed as per protocol Analyzed as per protocol	 44 1 43 40
Inclusion criteria:	Healthy (physical exam, laboratory tests, medical history and ECG), smoker and/or non-smoker adult males who were 18 years of age or older.
Test Treatment (A) Name Company responsible for placing product on the market Pharmaceutical formulation Strength Dose administered Lot No. Batch No. Control/Bulk/Lot. No. Expiry Date	 Megestrol Acetate Par Pharmaceutical Inc., USA Oral suspension 75 mg/mL 1 x 5 mL (375 mg) 036300 36879 036197 N/AV

Treatment duration	Single dose of the two treatments (A, B) on two different occasions, separated by a washout period of 14 days.
Evaluation criteria	**Pharmacokinetic parameters:** AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{1/2\ el}$.

Results:

Mean Plasma Concentrations (ng/mL)
MEGESTROL
N = 40

Sampling Time	Test (Megestrol Acetate (A))			Reference (Megace (B))		
(h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.26	0.95	359.62	0.00	0.00	-
0.250	59.66	62.62	104.95	6.71	9.01	134.26
0.500	446.31	256.34	57.44	60.33	36.48	60.47
1.00	721.51	300.75	41.68	132.75	58.82	44.31
1.50	659.89	264.31	40.05	149.81	69.91	46.67
2.00	608.76	238.95	39.25	157.11	67.79	43.15
2.50	605.03	291.15	48.12	157.55	71.79	45.57
3.00	526.52	215.74	40.97	154.70	69.02	44.61
3.50	473.49	169.82	35.86	152.46	75.46	49.50
4.00	435.20	172.74	39.69	150.86	84.80	56.21
4.50	398.45	188.59	47.33	154.84	80.20	51.80
5.00	351.68	211.51	60.14	145.05	80.56	55.54
5.50	291.49	169.26	58.07	130.33	72.91	55.94
6.00	255.95	147.78	57.74	124.40	74.03	59.51
7.00	196.23	111.46	56.80	121.48	70.85	58.32
8.00	166.74	81.34	48.78	125.46	75.65	60.30
12.0	109.53	48.03	43.85	115.99	45.95	39.62
16.0	80.38	35.51	44.18	98.36	35.47	36.06
20.0	63.15	26.24	41.56	95.89	27.61	28.79
24.0	65.89	30.79	46.73	124.08	41.30	33.28
36.0	42.33	18.80	44.42	98.84	39.94	40.41
48.0	27.67	13.18	47.62	81.63	33.32	40.82
72.0	16.99	10.01	58.95	45.45	28.59	62.89
96.0	11.06	7.37	66.63	25.97	20.98	80.80

Pharmacokinetic Parameters

Parameters		Test (Megestrol Acetate (A)) Mean	±	SD	CV (%)	Reference (Megace (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	6606.12	±	2451.03	37.10	7561.99	±	2520.69	33.33
AUC_{0-inf}**	(ng·h/mL)	7238.35	±	2873.57	39.70	8779.42	±	3904.29	44.47
C_{max}	(ng/mL)	810.16	±	313.72	38.72	193.01	±	86.60	44.87
T_{max}	(h)	1.56	±	0.91	58.71	6.91	±	9.13	132.21
T_{max}*	(h)	1.02	±	1.00	-	3.25	±	3.19	-
K_{el}**	(h^{-1})	0.0248	±	0.0096	38.76	0.0267	±	0.0092	34.25
$T_{½ el}$**	(h)	31.89	±	12.39	38.85	29.18	±	12.83	43.95

* Medians and interquartile ranges are presented

** For these parameters, N = 39.

Megestrol Acetate (A) vs Megace (B)

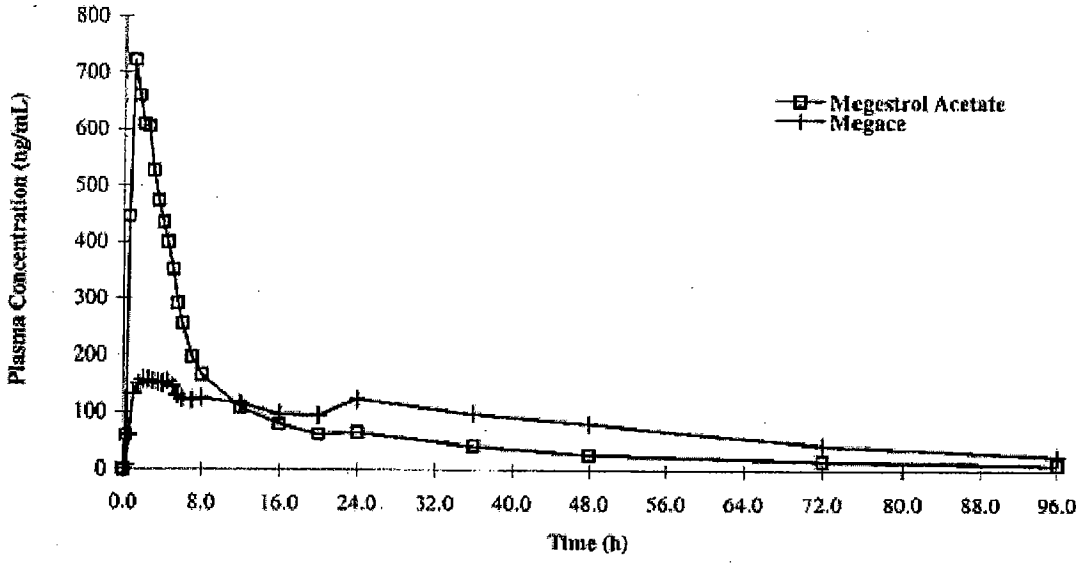
	AUC_{0-t}	AUC_{0-inf}**	C_{max}
Ratio[1]	86.94%	83.87%	426.11%
90 % Geometric C.I.[2]	80.40 % to 94.02 %	77.10 % to 91.24 %	391.60 % to 463.65 %
Intra-Subject CV	20.99 %	22.29 %	22.68 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Megestrol Acetate (A) - Megace (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

** For this parameter, N = 39.

Megestrol Mean Concentration - Time Profile
N = 40



Mean Plasma Concentrations (ng/mL)
METABOLITE B
N = 39

Sampling Time	Test (Megestrol Acetate (A))			Reference (Megace (B))		
(h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.45	1.68	370.03	0.19	0.59	312.89
0.250	48.32	41.88	86.67	7.51	8.62	114.82
0.500	176.52	90.45	51.24	33.16	20.82	62.78
1.00	268.24	179.73	67.00	56.57	25.45	45.00
1.50	220.08	79.20	35.99	58.92	23.70	40.22
2.00	206.85	76.92	37.18	60.50	26.04	43.05
2.50	196.38	74.22	37.79	62.44	29.99	48.03
3.00	181.08	72.86	40.23	61.99	28.54	46.04
3.50	168.31	57.17	33.97	59.93	26.16	43.65
4.00	154.91	51.85	33.47	62.13	32.85	52.88
4.50	145.76	48.28	33.12	71.90	35.52	49.40
5.00	152.55	63.18	41.41	73.43	38.27	52.12
5.50	144.40	70.17	48.59	71.28	38.36	53.83
6.00	129.58	64.92	50.10	65.42	34.08	52.10
7.00	104.95	47.62	45.38	60.54	30.00	49.56
8.00	97.41	42.85	43.99	59.48	27.57	46.34
12.0	76.38	34.07	44.61	56.04	29.48	52.60
16.0	68.54	37.66	54.95	59.06	32.64	55.27
20.0	55.61	34.12	61.35	52.09	22.00	42.24
24.0	57.39	31.74	55.31	57.80	20.32	35.16
36.0	48.22	49.58	102.82	59.03	33.86	57.36
48.0	34.87	29.64	85.03	51.95	31.51	60.66
72.0	23.90	24.65	103.11	36.01	25.25	70.13
96.0	16.67	19.00	113.95	22.60	19.04	84.27

METABOLITE B
N = 39

Pharmacokinetic Parameters

Parameters		Test (Megestrol Acetate (A)) Mean	±	SD	CV (%)	Reference (Megace (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	4684.51	±	2564.68	54.75	4475.50	±	2065.54	46.15
AUC_{0-inf}**	(ng·h/mL)	5521.24	±	4352.40	78.83	7250.07	±	9032.60	124.59
C_{max}	(ng/mL)	288.86	±	173.67	60.12	94.16	±	39.42	41.87
T_{max}	(h)	1.47	±	0.98	66.72	12.9	±	14.7	113.87
T_{max}*	(h)	1.00	±	1.00	-	5.00	±	21.53	-
K_{el}**	(h^{-1})	0.0245	±	0.0100	40.71	0.0223	±	0.0116	52.00
$T_{½ el}$**	(h)	35.93	±	21.55	59.98	53.87	±	80.28	149.03

* Medians and interquartile range are presented

** For these parameters, N = 32.

Megestrol Acetate (A) vs Megace (B)

	AUC_{0-t}	AUC_{0-Inf}**	C_{max}
Ratio[1]	102.17%	84.98%	299.34%
90 % Geometric C.I.[2]	94.83 % to 110.08 %	71.80 % to 100.59 %	275.84 % to 324.84 %
Intra-Subject CV	19.70 %	41.01 %	21.64 %

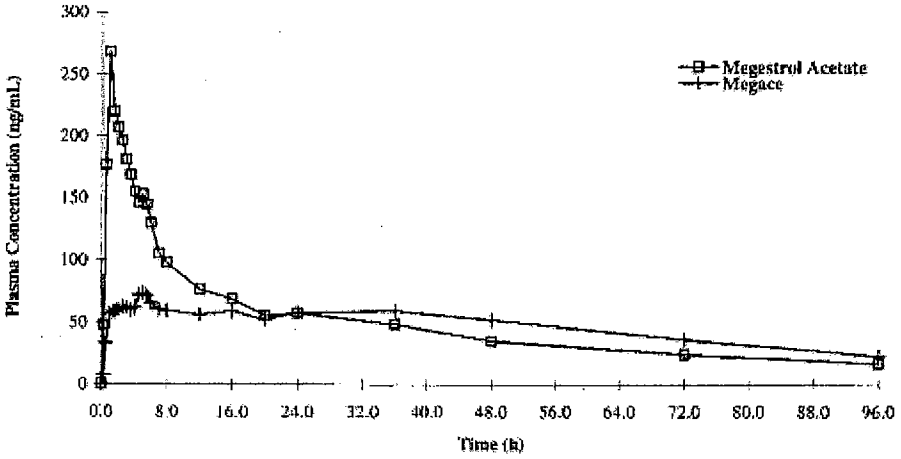
[1] Calculated using least-squares means according to the formula: $e^{(\text{Megestrol Acetate (A)} - \text{Megace (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

** For this parameter, N = 32.

Metabolite B Mean Concentration - Time Profile

N = 39



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Mean Plasma Concentrations (ng/mL)
METABOLITE C
N = 32

Sampling Time	Test (Megestrol Acetate (A))			Reference (Megace (B))		
(h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.00	23.32	37.52	160.89	20.38	36.54	179.30
0.25	42.44	45.24	106.59	20.02	34.66	173.12
0.50	175.17	81.90	46.75	43.02	38.09	88.54
1.00	485.72	186.90	38.48	104.27	54.35	52.12
1.50	675.07	276.00	40.89	150.96	69.37	45.95
2.00	795.15	319.65	40.20	196.67	86.90	44.18
2.50	962.36	406.97	42.29	243.06	111.13	45.72
3.00	1095.62	467.93	42.71	276.63	119.25	43.11
3.50	1216.72	534.65	43.94	310.02	140.62	45.36
4.00	1299.01	540.54	41.61	350.23	188.08	53.70
4.50	1299.84	515.46	39.66	385.61	180.59	46.83
5.00	1320.22	556.39	42.14	407.27	186.93	45.90
5.50	1614.84	944.89	58.51	430.83	202.87	47.09
6.00	1472.80	674.30	45.78	449.21	210.25	46.81
7.00	1554.37	708.95	45.61	497.16	229.46	46.15
8.00	1685.13	804.80	47.76	563.12	263.15	46.73
12.00	2005.59	1006.41	50.18	759.32	336.11	44.26
16.00	2061.48	906.72	43.98	888.58	411.70	46.33
20.00	2032.79	935.51	46.02	996.60	441.63	44.31
24.00	2096.47	1019.12	48.61	1156.91	478.75	41.38
36.00	2036.13	1042.37	51.19	1496.47	643.75	43.02
48.00	1808.76	913.03	50.48	1646.86	794.71	48.26
72.00	1408.09	801.71	56.94	1589.18	867.05	54.56
96.00	967.37	573.11	59.24	1247.24	779.32	62.48

METABOLITE C
N = 32

Pharmacokinetic Parameters

Parameters		Test (Megestrol Acetate (A))				Reference (Megace (B))			
		Mean	±	SD	CV (%)	Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	155937.06	±	74719.01	47.92	122983.93	±	58779.00	47.79
AUC_{0-inf}**	(ng·h/mL)	191782.00	±	133946.05	69.84	193471.95	±	140364.38	72.55
C_{max}	(ng/mL)	2494.89	±	1236.36	49.56	1764.93	±	839.75	47.58
T_{max}	(h)	20.3	±	10.7	52.61	56.6	±	18.6	32.78
T_{max}*	(h)	18.0	±	9.0	-	48.1	±	27.0	-
K_{el}**	(h^{-1})	0.0182	±	0.0073	40.05	0.0123	±	0.0057	46.65
$T_{\frac{1}{2}el}$**	(h)	47.43	±	30.96	65.26	67.55	±	28.11	41.61

* Medians and interquartile range are presented

** For these parameters, N = 17.

Megestrol Acetate (A) vs Megace (B)

	AUC_{0-t}	AUC_{0-inf}**	C_{max}
Ratio[1]	126.50%	96.52%	144.66%
90 % Geometric C.I.[2]	117.19 % to 136.56 %	84.82 % to 109.83 %	131.60 % to 159.01 %
Intra-Subject CV	18.03 %	21.39 %	22.40 %

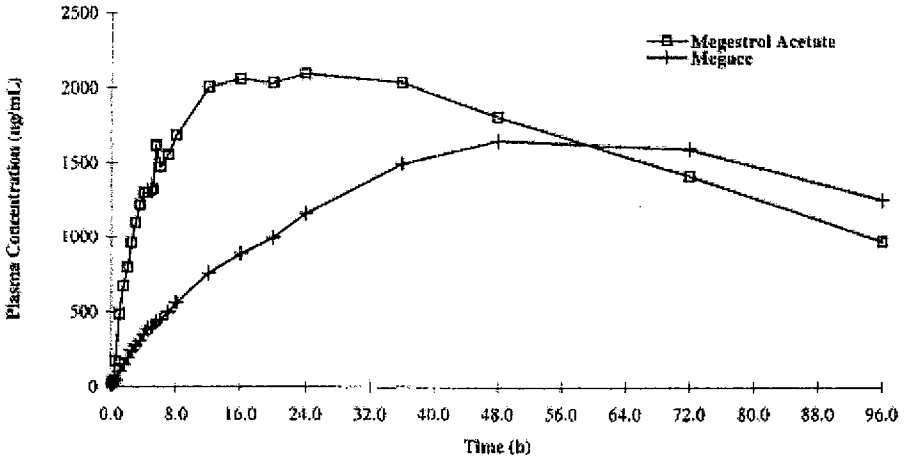
[1] Calculated using least-squares means according to the formula: $e^{[(\text{Megestrol Acetate (A)}) - (\text{Megace (B)})]} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

For this parameter, N = 17.

Metabolite C Mean Concentration - Time Profile

N = 32



METABOLITE D
N = 39

Sampling Time (h)	Test (Megestrol Acetate (A))			Reference (Megace (B))		
	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.22	0.58	270.21	0.28	1.37	484.19
0.250	2.56	2.57	100.44	0.45	1.39	308.82
0.500	35.34	22.63	64.04	5.15	3.50	67.97
1.00	92.22	54.41	59.00	17.63	10.33	58.58
1.50	116.47	67.64	58.07	26.97	16.73	62.02
2.00	137.50	84.38	61.36	35.21	23.03	65.41
2.50	157.57	90.25	57.28	43.49	32.28	74.21
3.00	170.05	102.43	60.24	48.74	34.67	71.12
3.50	185.65	113.40	61.08	52.87	37.28	70.52
4.00	190.69	114.62	60.11	59.88	44.52	74.35
4.50	199.43	130.81	65.59	66.99	48.60	72.56
5.00	198.65	130.67	65.78	66.88	47.19	70.56
5.50	196.18	128.27	65.38	69.31	46.22	66.68
6.00	205.59	131.70	64.06	72.61	49.54	68.23
7.00	199.60	129.61	64.93	76.48	52.06	68.07
8.00	204.57	134.68	65.83	80.29	49.41	61.55
12.0	199.70	118.01	59.10	93.48	60.76	65.00
16.0	183.15	93.08	50.82	100.04	60.00	59.97
20.0	167.02	86.30	51.67	110.36	65.98	59.79
24.0	166.86	78.00	46.75	121.05	68.62	56.69
36.0	129.58	50.78	39.19	139.99	72.02	51.44
48.0	106.87	47.55	44.49	138.08	71.65	51.89
72.0	59.67	35.03	58.70	104.16	62.65	60.15
96.0	31.15	21.04	67.54	58.46	47.23	80.79

METABOLITE D
N = 39

Pharmacokinetic Parameters

Parameters		Test (Megestrol Acetate (A))				Reference (Megace (B))			
		Mean	±	SD	CV (%)	Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	10525.44	±	4122.21	39.16	10067.05	±	5126.95	50.93
AUC_{0-inf}**	(ng·h/mL)	11956.02	±	4821.38	40.33	17358.59	±	16466.01	94.86
C_{max}	(ng/mL)	256.54	±	138.24	53.89	157.93	±	77.08	48.81
T_{max}	(h)	15.0	±	13.6	90.81	39.7	±	13.6	34.15
T_{max}*	(h)	12.0	±	10.8	-	36.1	±	12.0	-
K_{el}**	(h^{-1})	0.0291	±	0.0126	43.37	0.0220	±	0.0133	60.44
$T_{½ el}$**	(h)	28.61	±	12.56	43.90	52.61	±	51.56	98.01

* Medians and interquartile range are presented

* * For these parameters, N = 34.

Megestrol Acetate (A) vs Megace (B)

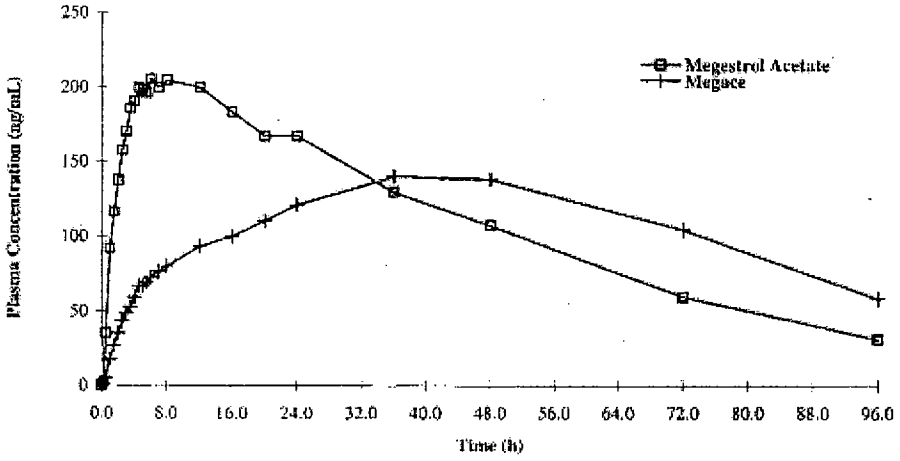
	AUC_{0-t}	AUC_{0-inf}**	C_{max}
Ratio[1]	110.09%	84.03%	157.73%
90 % Geometric C.I.[2]	101.25 % to 119.71 %	72.22 % to 97.78 %	143.90 % to 172.90 %
Intra-Subject CV	22.17 %	38.08 %	24.37 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Megestrol Acetate (A)} - \text{Megace (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

** For this parameter, N = 34.

Metabolite D Mean Concentration - Time Profile
N = 39



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CONCLUSION

The objective of this study was to compare the rate and extent of absorption of megestrol acetate 75 mg/mL oral suspension (test) versus Megace 40 mg/mL oral suspension (reference). The study products were administered as a single dose of 1 x 5 mL (375 mg) of oral suspension or as 1 x 20 mL (800 mg) oral suspension using a randomized, two-way crossover fasting study design. Each healthy smoker and/or non-smoker adult male was given either Treatment A or Treatment B after a supervised overnight fast of at least 10 hours, in accordance with the randomization schedule, with a washout period of 14 days between doses.

Of the 44 subjects who were enrolled in this study, 1 did not complete the crossover (subject no. 44). Thus, 43 subjects completed the study. In accordance with the study protocol, plasma samples from the first 40 subjects that completed the study were analyzed and used for pharmacokinetic and statistical analyses. There were pre-dose concentrations higher than 5% of their own C_{max} detected for metabolite B (subject No. 11), metabolite C (subjects No. 07, 09, 11, 14, 15, 22, 29 and 40) and metabolite D (subject No. 11), for these subjects, they were removed from the pharmacokinetic and statistical analysis. The elimination rate constant could not be estimated properly for some subjects due to low correlation values for megestrol, metabolite B, metabolite C and metabolite D (refer to section 3.2.4 for details). These subjects were excluded from all analyses involving $AUC_{0\text{-}inf}$, $T_{1/2\,el}$ and K_{el}.

During each study period, blood samples (1 X 7 mL) were taken from each subject at pre-dose and at 0.250, 0.500, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 12.0, 16.0, 20.0, 24.0, 36.0, 48.0, 72.0 and 96.0 hours post-dose (n = 24). Two aliquots of at least 1.2 mL of plasma (see Section 1.1.13, Protocol Deviations) were dispensed into labelled [redacted] tubes, as soon as possible, before being transferred to a -20°C±5°C freezer, pending megestrol, metabolite B, metabolite C and metabolite D analysis. Upon completion of the study, the plasma aliquots were transferred on dry ice to [redacted] for analysis.

During the study, most adverse events were mild or moderate in severity. No serious, severe or significant adverse events were reported. Thus, the products were well tolerated overall.

Megestrol, metabolite B, metabolite C and metabolite D were measured in plasma using a validated LC/MS/MS method. Methods were specific and sensitive. The standard curve ranges used for the analysis of plasma samples were from [redacted] ng/mL for megestrol, from [redacted] ng/mL for metabolite B, from [redacted] ng/mL for metabolite C and from [redacted] ng/mL for metabolite D.

ANOVA detected statistically significant differences between treatments for ln-transformed $AUC_{0\text{-}t}$, for megestrol and metabolite C, ln-transformed $AUC_{0\text{-}inf}$, for megestrol only and for ln-transformed C_{max} for all 4 analytes. Additionally, ANOVA detected statistically significant differences between treatments for untransformed T_{max} for all analytes, also ANOVA detected statistically significant differences between treatments for untransformed $T_{½\,el}$ for metabolite C and metabolite D, for K_{el} for megestrol, metabolite C and metabolite D.

First, for megestrol, the ratios of least-squares means and 90% confidence intervals were 86.94% (80.40% to 94.02%), 83.87% (77.10% to 91.24%) and 426.11% (391.60% to 463.65%) for AUC_{0-t}, AUC_{0-inf} and for C_{max}, respectively.

Secondly, for metabolite B, the ratios of least-squares means and 90% confidence intervals were 102.17% (94.83% to 110.08%), 84.98% (71.80% to 100.59%) and 299.34% (275.84% to 324.84%) for AUC_{0-t}, AUC_{0-inf} and for C_{max}, respectively.

For metabolite C, the ratios of least-squares means and 90% confidence intervals were 126.50% (117.19% to 136.56%), 96.52% (84.82% to 109.83%) and 144.66% (131.60% to 159.01%) for AUC_{0-t}, AUC_{0-inf} and for C_{max}, respectively.

Lastly, for metabolite D, the ratios of least-squares means and 90% confidence intervals were 110.09% (101.25% to 119.71%), 84.03% (72.22% to 97.78%) and 157.73% (143.90% to 172.90%) for AUC_{0-t}, AUC_{0-inf} and for C_{max}, respectively.

30147

STUDY SYNOPSIS

Company name:	Par Pharmaceutical
Drug name:	Megestrol Acetate
Study Title:	Randomized, 2-Way Crossover, Comparative Bioavailability Study of Megestrol Acetate 75 mg/mL Oral Suspension and Megace 40 mg/mL Oral Suspension Administered as 1 x 5 mL (375 mg) or 1 x 20 mL (800 mg) of Oral Suspension in Healthy Subjects Under Fed Conditions
Study performed by:	[redacted]
Objective:	The objective of this study was to compare the rate and extent of absorption of megestrol acetate 75 mg/mL oral suspension (test) versus Megace 40 mg/mL oral suspension (reference) administered as 1 x 5 mL (375 mg) or 1 x 20 mL of oral suspension under fed conditions.
Methodology: 1) Clinical [redacted]	This was a single center, randomized, single dose, fed, two-way crossover study with a washout period of 14 days between doses. Dosing dates - Period 1: 2003-06-22 Period 2: 2003-07-06 Blood sampling points: at pre-dose and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 12.0, 16.0, 20.0, 24.0, 36.0, 48.0, 72.0 and 96.0 hours post-dose (n = 24).
2) Analytical [redacted]	Plasma concentrations of megestrol acetate were measured by LC/MS/MS. Lower limit of quantitation: 2.02 ng/mL Standard curve range: [redacted] ng/mL Analyses - Start date: 2003-10-02 End date: 2003-12-01 The following metabolites were also analysed (data not shown): - 17a-acetoxy-2a-hydroxy-6-methylpregna-4,6-diene-3,20-dione - megestrol-6-hydroxymethyl - 17a-acetoxy-2a-hydroxy-6-hydroxymethylpregna-4,6-diene-3,20-dione
3) Statistical [redacted]	ANOVA was performed on ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, K_{el} and $T_{1/2\ el}$. Ratios of least-squares means (ln-transformed data) and 90% geometric confidence intervals were calculated for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. All analyses were performed according to FDA's guidelines.

STUDY SYNOPSIS (Continued)

Number of subjects: Enrolled and eligible Withdrawal Completed as per protocol Analyzed as per protocol Used in statistical analyses	 44 0 44 40 39
Inclusion criteria:	Healthy (physical exam, laboratory tests, medical history and ECG), smoker and/or non-smoker males who were at least 18 years old.
Test Treatment (A) Name Company responsible for placing product on the market Pharmaceutical formulation Strength Dose administered Batch No. Expiry Date	 Megestrol Acetate [redacted] Par Pharmaceutical, USA Oral Suspension 75 mg/mL 1 x 5 mL (375 mg) 36879 N/AV
Reference Treatment (B) Name Company responsible for placing product on the market Pharmaceutical formulation Strength Dose administered Lot No. Expiry Date	 Megestrol Acetate (Megace®) Bristol-Myers Squibb, USA Oral Suspension 40 mg/mL 1 x 20 mL (800 mg) 1K52545 Nov 2003
Treatment duration	Single dose of the two treatments (A, B) on two different occasions, separated by a washout period of 14 days.
Evaluation criteria	**Pharmacokinetic parameters:** AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{1/2\ el}$.

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SUMMARY OF RESULTS
MEGESTROL ACETATE
N = 39

Pharmacokinetic Parameters

Parameters		Test (Megestrol acetate (75 mg/mL) (A)) Mean	±	SD	CV (%)	Reference (Megace (40 mg/mL) (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng-h/mL)	10463.26	±	4855.15	46.40	22169.36	±	10222.65	46.11
AUC_{0-inf}	(ng-h/mL)	12192.87	±	7408.23	60.76	25488.71	±	14772.38	57.96
C_{max}	(ng/mL)	958.12	±	321.89	33.60	1711.09	±	456.59	26.68
T_{max}	(h)	3.42	±	1.86	54.22	3.94	±	0.95	24.23
T_{max}*	(h)	4.02	±	2.00	-	4.50	±	1.50	-
K_{el}	(h^{-1})	0.0220	±	0.0104	47.39	0.0218	±	0.0075	34.34
$T_{½ el}$	(h)	38.00	±	16.64	43.78	35.85	±	15.23	42.49

* Medians and interquartile ranges are presented

Megestrol acetate (75 mg/mL) (A) vs Megace (40 mg/mL) (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	47.14%	47.47%	55.19%
90 % Geometric C.I.[2]	45.39 % to 48.95 %	45.43 % to 49.62 %	51.36 % to 59.31 %
Intra-Subject CV	9.90 %	11.58 %	19.00 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Megestrol acetate (75 mg/mL) (A)} - \text{Megace (40 mg/mL) (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

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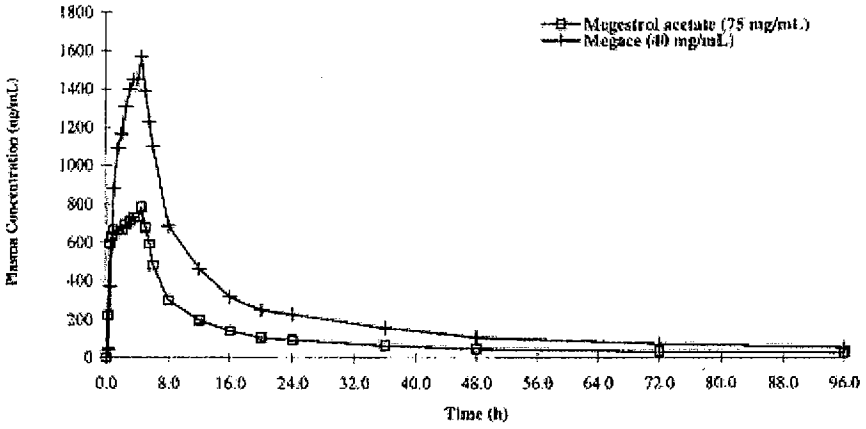
Megestrol Acetate Mean Concentration - Time Profile
N = 39



Megestrol Acetate Ln (Mean Concentration) - Time Profile
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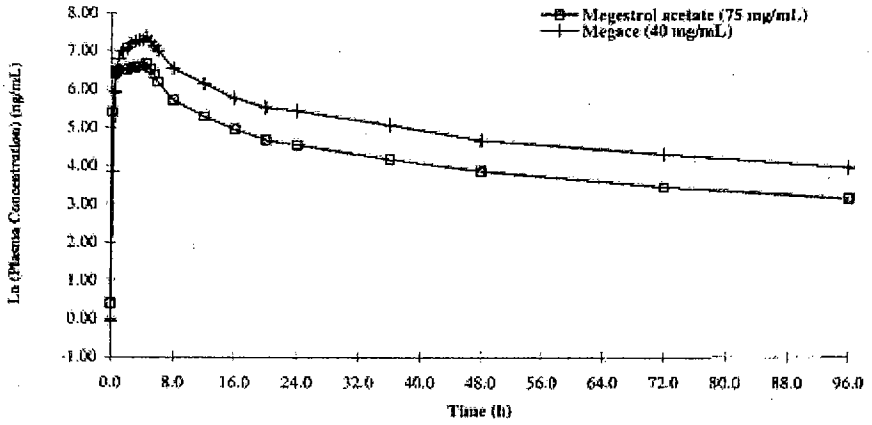

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Mean Plasma Concentrations (ng/mL)
MEGESTROL ACETATE
N = 39

Sampling Time	Test (Megestrol acetate (75 mg/mL) (A))			Reference (Megace (40 mg/mL) (B))		
(h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	1.48	3.03	204.79	0.94	4.24	450.24
0.250	224.58	198.02	88.17	46.83	53.11	113.41
0.500	594.98	394.10	66.24	371.13	211.50	56.99
0.750	632.12	341.29	53.99	619.81	284.00	45.82
1.00	667.41	314.62	47.14	884.00	296.31	33.52
1.50	665.97	245.05	36.80	1088.54	320.00	29.40
2.00	668.86	238.11	35.60	1168.11	333.17	28.52
2.50	697.00	226.71	32.53	1310.12	369.06	28.17
3.00	713.15	237.73	33.34	1398.55	380.11	27.18
3.50	733.23	249.15	33.98	1449.34	368.59	25.43
4.00	731.91	247.78	33.85	1453.24	401.45	27.62
4.50	785.63	270.49	34.43	1571.88	484.58	30.83
5.00	680.46	225.85	33.19	1391.99	461.62	33.16
5.50	591.98	264.00	44.60	1230.11	436.21	35.46
6.00	482.01	204.40	42.40	1100.68	399.77	36.32
8.00	302.72	123.75	40.88	687.81	263.33	38.29
12.0	198.47	90.06	45.37	462.68	197.92	42.78
16.0	141.80	69.74	49.18	318.66	155.24	48.72
20.0	107.28	58.10	54.16	250.80	135.99	54.22
24.0	93.33	57.43	61.53	227.61	132.50	58.22
36.0	64.25	43.55	67.78	157.66	115.44	73.22
48.0	47.41	39.41	83.12	106.44	83.45	78.41
72.0	31.10	30.04	96.59	72.65	75.90	104.47
96.0	23.19	26.39	113.79	51.76	54.69	105.66

CONCLUSION

This study compared the rate and extent of absorption of megestrol acetate 75 mg/mL oral suspension (test) (Treatment A) versus megestrol acetate 40 mg/mL oral suspension (Megace) (reference) (Treatment B). The study products were administered as a single oral dose of 1 x 5 mL (375 mg) or 1 x 20 mL (800 mg) of oral suspension using a randomized, two-way crossover fed study design. Each healthy smoker and/or non-smoker adult male was given either Treatment A or Treatment B after completion of a standard high-fat, high-caloric breakfast, in accordance with the randomization schedule, with a washout period of 14 days between doses.

All 44 subjects who were enrolled in this study completed the crossover. In accordance with the study protocol, plasma samples from the first 40 subjects completing the study were to be analyzed. However, subject No. 25 was excluded from analysis because of use of concomitant medication in Period 2. This subject was replaced by subject No. 42 (same randomization sequence) in order to maintain a balanced group. Plasma samples from subjects No. 01 to 24, 26 to 32, 34 to 40 and 42 were used for pharmacokinetic and statistical analyses; subject No. 33 was excluded from all analyses due to a pre-dose concentration value that was higher than 5% of the C_{max} value.

During each study period, blood samples (1 x 7 mL each) were taken from each subject at pre-dose and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 12.0, 16.0, 20.0, 24.0, 36.0, 48.0, 72.0 and 96.0 hours post-dose (n = 24). Plasma was harvested from each blood sample and placed in suitably labeled [redacted] tubes, as soon as possible, before being transferred to a $-20\pm5^{\circ}C$ freezer, pending analysis of megestrol acetate. Upon completion of the study, the plasma aliquots were transferred on [redacted] for analysis.

During the study, adverse events were mild or moderate in severity and no serious, severe or significant adverse events were reported. Thus, the products were well tolerated overall.

Megestrol acetate was measured in plasma using a validated LC/MS/MS method. The standard curve range used for the analysis of plasma samples was [redacted] ng/mL.

ANOVA detected a statistically significant difference between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, but not for untransformed T_{max}, $T_{1/2\,el}$ and K_{el}.

The ratios of least-squares means (and 90% geometric confidence intervals) were respectively 47.14% (45.39% to 48.95%) for AUC_{0-t}, 47.47% (45.43% to 49.62%) for AUC_{0-inf} and 55.19% (51.36% to 59.31%) for C_{max}.

272-1052-01
Title: Determination of the Inhibitory Potential of Megestrol on the Activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in Human Liver Microsomes

Objective: To determine the potential of Megestrol to inhibit the activities of CYP Isoforms CYP1A2, CYP2A6, CYP2C9, CYP2CI9, CYP2Do, CYP2EI, and CYP3A4 in human liver microsomes.

Experimental Methods:

Incubation Conditions and Sample Size

All incubations were conducted at 37 ± 1 °C in a shaking water bath. The sample size was N = 3 replicates for experimental groups, and N = 6 replicates for control groups.

Test Article Information and Preparation

The test article was identified in this study as follows:

- Megestrol (Megestrol Acetate USP Micronized; molecular weight = 384.52)

Megestrol was prepared in methanol at 1,000 times (1,000X) the final concentration. The 1,000X stock solution was mixed with 0.1 M Tris buffer, NADPH regenerating system (NRS), a CYP substrate, and liver microsomes. The final test article concentrations were 0.385 µg/mL (1 µM), 1.27 µg/mL (3.3 µM), 3.85 µg/mL (10 µM), 12.8 µg/mL (33.3 µM), and 19.2 µg/mL (50 µM), each containing 0.1% methanol. The highest tested concentration was 50 µM instead of 100 µM, as stated in the protocol, because the 1,000X Megestrol (100 mM) was not soluble in methanol.

12 Page(s) Withheld

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Withheld Track Number: Clin Pharm/Bio- 1

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/s/

Xiao-xiong Wei
4/7/05 10:09:36 AM
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individual study review for Megestrol Acetate NCD

Hae-Young Ahn
4/12/05 10:27:43 AM
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