CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-781

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

AUG 7 [illegible]

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA: 19-781

Compound: Prometrium® (100 mg micronized progesterone soft gelatin capsule)

Submission Dates: 2/8/96 (Amendment Serial No. AZ)
6/14/96 (Amendment Serial No. BB)

Sponsor: Schering Corporation

Type of Submission: NDA Amendment (response to non-approval letter)

Code: 3S

Reviewer: K. Gary Barnette, Ph.D.

Synopsis:
NDA 19-781 was submitted to the FDA on September 30, 1987 by Besins Pharmaceuticals and resubmitted by LaSalle Laboratories, the US affiliate of Besins-Iscovesco Pharmaceuticals, Inc. The indication for micronized progesterone under NDA 19-781 is the treatment of secondary amenorrhea (cessation of menses in a woman who has previously menstruated). A non-approval letter was issued by the Agency on August 17, 1990. A copy of this letter is included in Attachment 1. On July 23, 1991 a meeting addressing the non-approval letter was held. The sponsor agreed at that time to conduct two pharmacokinetic studies to evaluate the dose proportionality and the effect of food on Prometrium® kinetics. The current submission contains the response to each of the biopharmaceutic comments in the deficiency letter of August 17, 1990 as well as the results of the dose proportionality study and food effect study (previously reviewed by DPE II, March 26, 1993) that were agreed upon by the Agency on July 23, 1991.

Teleconferences between Dr. Lechner of Schering Corporation and this reviewer and Dr. Banfield, Dr. Lechner, Ms. Matlosz and Ms. Salfi of Schering Corporation and this reviewer were held on March 15 and 21, 1996, respectively. The sponsor submitted additional information in response to these teleconferences in the form of an amendment (Serial No.BB) to NDA 19-781 on June 14, 1996. The review of this submission is also included in this document. Also included herein is the proposed package insert (Attachment 2).

It should be noted that the name Prometrium® (the latest proposed name) is synonymous with Utrogestan as this NDA has changed hands during the course of development as has the name.

Background:
The oral administration of micronized progesterone for ten days to premenopausal women with secondary amenorrhea is intended to induce withdrawal bleeding. The cause of the bleeding is progestational activity in endometrial secretory phase transformation. This was reportedly confirmed in a study in which Prometrium® significantly induced secretory changes in women compared to placebo (study not submitted at this time, therefore not reviewed herein).

A summary of the pharmacokinetic studies previously submitted to NDA 19-781 is presented in Table 1 and a summary of the pharmacokinetic studies submitted on February 8, 1996 is included in Table 2.

Table 1: Summary of PK Studies Previously Submitted to NDA 19-781

Study #	Study Design	n	Sex (m/f)	Race (w/b)	Mean Age (range)	Treatment Dose, Dosing Frequency
Study 1 T91-005	Randomized, Open-label, Crossover	15	0/15	14/1	51	Placebo Fast: 2 x 100 mg, QD x 5d Fed: 2 x 100 mg, QD x 5d
Study 2 T91-004	Randomized, Open-label, Crossover	15	0/15	14/1	52	1 x 100 mg, QD x 5d 2 x 100 mg, QD x 5d 3 x 100 mg, QD x 5d
Study 3 T91-003	Randomized, Open-label, Crossover	15	0/15	14/1	53	Utrogestan: 2 x 100 mg, QD x 2d Progesterone: 50 mg IM, QD x 2d

► These studies were not submitted to the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II at this time. Thus, reviews of these studies are NOT contained herein.

Table 2: Summary of PK Studies Submitted to NDA 19-781 on 2/8/96

Study #	Study Type	Study Design	n	Sex (m/f)	Race (w/b)	Mean Age (range)	Dose, Dosing Frequency
C91-259	Dose Escalation	Randomized Open-Label Crossover	25	25/0	18/7	32	• 1x100mg, QDx7d • 2x100mg, QDx7d • 3x100mg, QDx7d • 4x100mg, QDx7d
C91-255	Food Effect	Randomized Open-Label Crossover	24	24/0	17/4 1 Asian 2 others	23	• Fasted 3x100mg • w/Food 3x100mg • 2h p/Food 3x100mg • 4h p/Food 3x100mg

The results and conclusions from Study 1 (T91-005) and Study 2 (T91-004) conducted by the previous sponsor of this NDA, Besins Pharmaceuticals, were dismissed due to inadequate sampling times. Food effect and dose proportionality studies have been "re"-run and are or have been submitted for review. Study 3 (T91-003), a

relative bioavailability study has been previously reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and is further commented upon herein.

Sponsor's Response to Deficiencies in Letter of August 17, 1990: Complete documentation of the sponsor's response to deficiencies outlined in the non-approval letter issued by the Agency on August 17, 1990 is included in Attachment 3.

Reviewer's Comments on Sponsor's Response to Deficiencies (non-approval letter dated August 17, 1990):

Bioavailability and Bioequivalence:

2a. The response is adequate.

2b. The sponsor has conducted Study C91-255 (food effect study) and C91-259 (multiple dose, dose proportionality study) to address the insufficiencies outlined in comment 2b. The review of these studies is contained herein (Attachment 4).

2c. I have not reviewed nor reanalyzed the raw data from Study 3. This should be unnecessary due to previous review. However, from the sponsor's analysis, since the elimination phase of the IM dose was missed and the portion of the curve being used to extrapolate to AUC_∞ may include the distribution phase of progesterone, the calculation of AUC_∞ is inaccurate. Therefore, a bioavailability analysis between the IM and oral doses of micronized progesterone is not appropriate with available data.

2d. Once again in Study 3, the calculated AUC_∞ after IM dosing is probably inaccurate (see Comment 2c, above). Therefore only the Cmax value is evaluable and no sequence, subject or phase effect was observed on this parameter. ANOVA was used in Studies C91-255 and C91-259 to determine the effect of phase, subject and treatment on the pharmacokinetic parameters. Only the treatment showed a consistent statistically significant effect. However, probably due to high interindividual variability in progesterone kinetics, a subject effect was seen in some parameters.

2e. The response is adequate.

2f. The response is adequate.

2g. The response is adequate.

2h. An appropriate study has been completed and reviewed to assess the effect of a high fat meal on the pharmacokinetics of a 300 mg dose. Study C91-255 utilized a 3x100mg dose of Prometrium® and a food effect was observed and is included in the labeling under the section entitled, *"Food-Drug Interaction"*.

Labeling:

3a. The response is adequate.

3b. The response is adequate. However, according to current regulations, a request was made in a teleconference between this reviewer and Dr. Lechner, Schering Laboratories, on March 14, 1996 the Clinical Pharmacology section under the major heading Pharmacokinetics be reformatted into the subheadings; Absorption, Distribution, Metabolism and Excretion with a Special Population section detailing the PK in renally impaired, hepatically impaired and obese populations. The reformatted labeling was promptly submitted and is included in Attachment 2.

3c. The response is adequate.

3d. The response is adequate.

3e. The response is adequate.

3f. The response is adequate.

Biopharmaceutic Comments:

1. The response is adequate.

2. The response is adequate.

3. The response is adequate.

4. The response is adequate.

5. Study C91-255, a food effect study was conducted and submitted to the FDA on February 8, 1996. The review of this study is included in Attachment 4.

Teleconferences:

- A teleconference was held with Dr. Banfield, Dr. Lechner, Ms. Matlosz and Ms. Salfi of Schering Corporation on March 21, 1996. The following comments and question were made by this reviewer.

1) In Study C91-259, Subject had AUC and Cmax values >10 fold higher than the mean values of the other subjects studied. The quality control samples, blood sample collection, analysis and handling as well as the demographics and adverse events from this study should be evaluated for possible explanations for the unusual parameters observed in Subject

2) Analysis for a body weight effect on the pharmacokinetics of Prometrium® should be submitted.

3) Do women experiencing secondary amenorrhea have lower progesterone levels than normal women?

Sponsor's Response to Comments and Questions of March 21, 1996:
Complete responses are included in Attachment 5.

Reviewer's Comments:

1) With the exception that Subject was the youngest of all subjects studied, none of the suggested analyses or reevaluations (quality control, blood sampling and handling, demographics and adverse events) yielded a valid explanation for the high systemic exposure (AUC and Cmax) observed in this subject.

2) There does not appear to be a correlation between body weight and AUC or Cmax. However, it should be noted that the range of weights included in the reported studies was lbs and no obese subjects were enrolled.

3) The sponsor states that, "progesterone levels are NOT routinely drawn in this setting". Therefore, I would conclude that it is not known if insufficient progesterone levels or a receptor binding phenomenon is the probable causative event leading to secondary amenorrhea.

- A teleconference between this reviewer and Dr. Lechner of Schering Corporation was held on March 15, 1996. It was requested that the Pharmacokinetic portion of the Clinical Pharmacology section of the proposed labeling be reformatted to include subsections of Absorption, Distribution, Metabolism, Excretion, and Special Populations. The revised labeling is included in Attachment 2.

Summary of Pharmacokinetic Studies Submitted 2/8/96 (Attachment 4)
A significant and comparable food effect was seen when Prometrium® was administered at the time of a meal and 2 hr after a meal (see Table 3). However, a further increase in bioavailability was

observed when dosing 4 hr after meal compared to all other treatments tested (fasting, with meal and 2 hr after meal).

Table 3: Mean (N=24) Pharmacokinetic Parameters of Progesterone

Parameter	Mean (%CV)			
	Treatment A (Fasted)	Treatment B (w/breakfast)	Treatment C (2 hr after meal)	Treatment D (4 hr after meal)
Cmax (ng/ml)	58 (125)	64 (122)	61 (93)	133 (86)
Tmax (hr)	2.0 (63)	3.3 (87)	3.5 (71)	2.0 (46)
AUC_∞ (ng*hr/ml)†	135 (90)	184 (69)	183 (60)	243 (58)
$t_{1/2}$ (hr)	13.0 (41)	13.6 (49)	13.6 (34)	16.9 (35)

† N=19, "due to high variability in progesterone concentrations in the terminal phase, $t_{1/2}$ and AUC_∞ could not be accurately determined in subjects 11, 13, 15, 16 and 24."

In Study C91-259 it was determined that dose proportionality could not be established in normal male volunteers between doses of 300 and 400 mg QD (see Table 4).

Table 4: Mean (N=24) Steady-State Pharmacokinetic Parameters of Progesterone

Parameter	Mean (%CV)			
	Treatment A (1x100 mg QD)	Treatment B (2x100 mg QD)	Treatment C (3x100 mg QD)	Treatment D (4x100 mg QD)
Cmax (ng/ml)	9.85 (137)	22.8 (179)	40.7 (178)	47.0 (132)
Tmax (hr)	2.94 (70)	2.85 (63)	3.00 (61)	2.42 (78)
AUC0-24 (ng*hr/ml)†	38.5 (109)	87.0 (163)	157 (165)	180 (112)
$t_{1/2}$ (hr)‡	17.2 (23)	17.0 (33)	16.8 (35)	16.0 (32)

† AUC_{0-24} at steady-state is also AUC(τ) where τ represent the dosing interval.

‡ N=22, due to variability in progesterone concentrations in the terminal phase, $t_{1/2}$ could not be calculated for subjects

However, Subject in Study C91-259 had AUC_∞ and Cmax values almost 10 times higher than the mean of all subjects (n=24, see Table 5, below). There is no explanation for this observation. It should be noted that these subjects were male and fasting (the recommended target population is pre-menopausal women with secondary amenorrhea and recommended dosing is with food). According to study C91-255, a statistically significant increased bioavailability is seen with food. Therefore, in a female patient (lower body weight) with this type of absorption profile and dosing with food, the amount of systemic exposure of progesterone may be much higher.

Table 5

	AUC ng*h/ml				Cmax ng/ml			
	1x100mg	2x100mg	3x100mg	4x100mg	1x100mg	2x100mg	3x100mg	4x100mg
Sub	227.27	738.29	1340.13	1948.99	70.84	205.96	372.45	287.13
Mean (%CV)	38.53 (108.55)	36.99 (162.77)	156.68 (165.31)	180.27 (112.28)	9.85 (136.62)	22.81 (179.20)	10.65 (178.36)	47.02 (131.56)

Reviewer Comments:

1. The high systemic exposure to progesterone (AUC∞ ≈10 fold higher than the average of the other subjects included in Study C91-259) observed after all four doses (100, 200, 300 and 400 mg) in Subject has been evaluated. However, no explanation for this phenomenon is readily available and Subject can be considered an outlier.

- It should be noted that the ~~t½~~ of this subject is comparable to that seen in other subjects (see Table 6). Therefore, the clearance of progesterone does not appear to be altered in this subject and is not the cause of the high systemic exposure seen in Subject

Table 6. T½ (hr)

Dose	Subject	Mean ± SD (n=23)
1 × 100 mg	22.52	16.89 ± 3.76
2 × 100 mg	14.66	16.77 ± 5.62
3 × 100 mg	11.18	17.50 ± 6.66
4 × 100 mg	14.39	15.85 ± 5.05

- Although the serum progesterone levels at time = zero (pre-dose) are higher than the average of the other 23 subjects this relatively small difference does not account for the high systemic levels observed in subject (see Table 7).

Table 7. Cp (ng/ml) at Time = 0 (pre-dose)

Dose	Subject	Mean ± SD (n=23)
1 × 100 mg	0.39	0.23 ± 0.10
2 × 100 mg	0.51	0.23 ± 0.12
3 × 100 mg	0.51	0.22 ± 0.11
4 × 100 mg	0.37	0.23 ± 0.10

- The blood and urine chemistries and demographics of Subject

were generally within normal limits and the high systemic exposure seen in this subject could not be attributed to these data.

- The standard curve and quality control samples assayed with serum samples from Subject were within the acceptable limits and re-analysis of various samples from this subject confirmed the comparatively high serum concentrations of progesterone.

- Although the absolute and relative bioavailability of Prometrium® is not known, it is apparent that it is low, probably less than 10%. Therefore, an alteration in absorption could result in serum levels 10 fold higher, but there is no obvious explanation for or proof of this phenomenon.

2. Linear pharmacokinetics do not appear to exist between the proposed doses of 300 mg QD and 400 mg QD (see Table 5, above), but the high inter-subject variability is acknowledged. It should be noted that the AUC and Cmax values of the 300 mg dose are markedly higher in subject 24 than those of the 400 mg dose. Since these numbers are so high compared to those seen in the other subjects, this alone may account for the appearance of non-linear kinetics over this portion of the dose range. An analysis of these data excluding subject 24 is included in Table 8 and indicates dose proportionality. Therefore, it is concluded that the lack of dose proportionality of Prometrium® in these 24 subjects is not due to the formulation and dose proportionality exists between doses of 100 and 400 mg.

Table 8

	Mean AUC (CV) ng*h/ml				Mean Cmax (CV) ng/ml			
	1x100mg	2x100mg	3x100mg	4x100mg	1x100mg	2x100mg	3x100mg	4x100mg
Includ. Sub	38.53 (108.55)	86.98 (162.77)	156.68 (165.31)	180.27 (112.28)	9.85 (136.62)	22.81 (179.20)	40.65 (178.36)	47.02 (131.56)
Exclud. Sub	30.3 (38.07)	58.7 (48.20)	105 (56.55)	142 (57.25)	7.20 (48.57)	14.8 (82.45)	26.2 (61.69)	36.6 (95.09)

3. Due to a food effect that exists at least up to 4 hours post prandial, the proposed dosing regimen is single daily doses of 300 mg or 400 mg WITH the evening meal for 10 days.

4. It is stated in the proposed labeling (page 3,

Pharmacokinetics, *Absorption*) that the relative bioavailability to IM injection is approximately 6%. However, as stated above the sampling times used to assess the plasma concentration versus time profile of progesterone after IM injection did NOT adequately assess the elimination portion of the curve. Therefore, AUC_∞ can not be accurately estimated and the aforementioned statement should be removed from the labeling.

5. It should be included in the labeling for this product that the pharmacokinetics of this formulation has NOT been assessed in subjects with weights outside the range of lbs and this testing was in males only. Therefore, neither obese nor individuals with low body weight have been assessed pharmacokinetically.

6. Since the pharmacokinetics of the 400 mg dose in the target population has not been assessed, the labeling should be amended to include data from the dose proportionality study in healthy male volunteers pending study of this dose in the target population.

Recommendation:
The amendment to the NDA 19-781 submitted to the Agency on February 8, 1996 and the supplement submitted June 14, 1996 have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II. Based on the clinical pharmacology and biopharmaceutics information from Studies C91-255 and C91-259 and the responses to the deficiency letter of August 17, 1990 it is recommended that approval of Prometrium® for the indication of 10 day treatment of secondary amenorrhea and the dosing regimen of 300 or 400 mg/day with the evening meal be granted. However the following additional recommendations are made, although not conditions for approval;

- If a labeling claim of the relative bioavailability of Prometrium® to an IM injection is desired, an appropriate study should be conducted, including proper sampling times.

- The sponsor should assess the pharmacokinetics of the 400 mg dose of Prometrium® in the target population and amend labeling to include these data.

- Pending approval of this application by the Division of Urologic and Reproductive Drug Products (HFD-580), The Office of Clinical Pharmacology and Biopharmaceutics requests the opportunity to review the product's final labeling prior to marketing.

The Recommendation and Comments 4, 5 and 6 should be communicated to the sponsor as appropriate.

1st

K. Gary Barnette, Ph.D.
Division Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 8/5/96
FT signed by Angelica Dorantes, Ph.D., Team Leader Dorantes 8/6/96

cc: **NDA 19-781, HFD-580, HFD-580 (Cropp, Kish), HFD-870 (M.Chen, Hunt, Dorantes, Barnette), HFD-340 (Viswanathan), HFD-850 (Lesko), Drug File, Chron file, Reviewer (Clarence Bott, HFD-870), HFD-205 (FOI).**

MAY 7 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA: 19-781

Compound: Prometrium™ (100 mg progesterone capsules)
Sponsor: Schering Corporation
Type of Submission: Revised Draft Labeling
Date of Submission: May 1, 1998
May 6, 1998

Reviewer: Sam H. Haidar, R.Ph., Ph.D.

Background:
NDA 19-781 (Prometrium® Capsules for the treatment of Secondary Amenorrhea) was originally submitted on September 30, 1987, and amended on February 8, 1996. An approvable letter was sent to the sponsor (Schering) on March 28, 1997. The sponsor submitted a revised draft labeling on May 1, 1998, then again on May 6, 1998, following a phone conversation with the project manager, Mrs. Diane Moore.

Comments:

1. The Pharmacokinetics section under Clinical Pharmacology in the revised draft labeling is acceptable and no changes are recommended.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the draft labeling submitted on May 6, 1998. OCPB/DPEII finds this submission acceptable.

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 5/07/98
FT signed by Angelica Dorantes, Ph.D., Team Leader 5/7/98

cc:
NDA 19-781
HFD-870 (M. Chen, A. Dorantes, S. Haidar)
HFD-580 (D. Moore, T. van der Vlugt)
CDR (Barbara Murphy For Drug)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-781

BIOEQUIVALENCE REVIEW(S)

Progesterone
Utrogestan (100mg Capsules)
NDA 19-781
Reviewer: Pradeep M.Sathe, Ph.D.
PC
1-D, 1-O, 3-S

La Salle Laboratories, Inc.
331 Madison Avenue,
New York, New York 10017
Submission Date: 03/17/1989

APR 30 1990

REVIEW OF THE PHARMACOKINETIC DATA

I. BACKGROUND

Progesterone is a steroid hormone which plays an important role in the preparation and maintenance of pregnancy. Under its influence the numerous minute glands which line the uterine cavity are transformed into secreting glands. This alteration is a part of the change which is essential to provide for the implantation of a fertilized ovum and for the continuing development of the placenta. Progesterone is synthesized from cholesterol via pregnenalone, then rapidly metabolized to pregnanediol, for the most part in the liver. The ovary and placenta are major production sites, but a small amount is also synthesized by the adrenal cortex in both men and women.

Circulating progesterone levels, which are characteristically low during the folicular phase (<1.5ng/ml), increase sharply during the luteal phase of the menstrual cycle, reaching a maximum (≥20ng/ml) some 5 to 10 days after the midcycle LH peak. Unless pregnancy occurs, a steep decline to folicular level sets in about 4 days prior to the next menstrual period. During pregnancy, the levels may range from ng/ml during the first trimester and may increase to a range of ng/ml in the third trimester.

Following are some physical parameters of the drug

Molecular wt : 314.47

M.P. : 126-131 degrees celsius.

Solubility : Progesterone is practically insoluble in water. It is soluble in alcohol, acetone, dioxane and sparingly soluble in vegetable oils.

Following is the list of the approved Progesterone products.

Formulation	Strength	NDA Number
Progesterone:		
Injectable,Injection	50mg/ml	09-238
Lilly	25mg/ml	09-238

Injectable,Injection Steris Labs	50mg/ml	17-362
Insert, Extended release Intrauterine Alza	38mg	17-553

The firm wants to market the formulation as a 100mg capsule. The recommended dosage for various disease states is however 200 to 300mg for 5 to 10 days. On page 384 of (volume 3 of 5) the submission the firm mentions that "the Utrogestan product tested in the pharmacokinetic studies submitted in this application has a formulation identical to the product proposed for marketing in the U.S.".

II. STUDY RESULTS

In addition to the labelling, NDA 19-781 consists of three drug studies and one modified disintegration test (Capsule rupture test). Study 1 is to evaluate the "food effect", Study 2 is to get an idea of the "dose proportionality" while Study 3 is to demonstrate the "bioequivalence" of the drug product.

A. STUDY 1

1. Objectives : The objectives of this study are 1) to demonstrate what effect on blood levels, if any, is produced by administering Utrogestan with food and alternatively without food. 2) to evaluate baseline serum progesterone levels in postmenopausal women following the administration of placebo.

2. a. Clinical Investigator :

b. Clinical Site :

c. Study Dates : 1986/87

3. a) Test Formulation (Treatment C): Utrogestan, 200 mg (2*100mg capsules) once daily, for a period of five (5) days. The study medication was administered in the early morning, immediately subsequent to a standardized breakfast containing 505-739 calories with 13-26 gm of protein.

b) Reference Formulations (Treatment B): Utrogestan, 200 mg (2*100mg capsules) once daily, for a period of five (5) days. The study medication was administered in the early morning on a fasting

stomach. A standardized breakfast containing 505-739 calories with 13-26 gm of protein was given two (2) hours later. Attachment 1.1 lists the food content of the breakfast.

c) Baseline (Treatment A): Placebo for a period of five (5) days.

4. Subject Selection : The study involved fifteen (15) postmenopausal women. The subject selection is in accordance with the exclusion criterion. The subjects are in the age group of 27 to 60 years and weight group 49 to 104 kgs.

(Note : For Study numbers 1, 2 and 3 many of the same subjects were enrolled in some or all three studies).

5. Study Design : The study is a three treatment, randomized, balanced and crossover design. There is a seven day washout period between the two phases.

6. Specimens Collected : On day 1 and 5, the blood samples are collected at 0 hr and at 1.0, 2.0, 3.0, 4.0, 6.0, and 10.0hrs following the drug administration. On days 2, 3 and 4 the samples are drawn at 0, 1, 2 and 3hrs post administration.

7. Analytical Methodology :

STUDY 3

DAY 1 0-24 hours

PATIENT ID NO.	UTROGESTAN 200 mg CMAX	UTROGESTAN 200 mg TMAX	UTROGESTAN 200 mg AUC	IM 50 mg CMAX	IM 50 mg TMAX	IM 50 mg AUC
	61.3	1	122.127	17.0	10	273.954
	32.0	2	86.160	10.0	10	186.566
	156.0	1	269.281	14.0	10	247.520
	12.4	2	71.641	19.3	10	332.517
	17.0	2	93.157	18.4	10	308.560
	8.0	2	43.797	34.4	6	365.798
	2.7	6	32.203	18.0	6	224.523
	6.2	4	44.027	10.5	10	196.456
	4.6	6	50.702	15.0	6	218.441
	7.5	2	58.936	11.3	10	180.569
	24.4	2	95.457	14.0	10	226.583
	40.5	2	103.110	15.0	10	217.783
	6.0	1	51.332	8.0	6	111.628
	13.0	2	57.208	23.4	6	310.749
	22.3	2	89.203	21.0	10	304.902

DAY 2-5 0-72 hour

PATIENT ID NO.	UTROGESTAN 200 mg CMAX	UTROGESTAN 200 mg TMAX	UTROGESTAN 200 mg AUC	IM 50 mg CMAX	IM 50 mg TMAX	IM 50 mg AUC
	23.4	2	146.636	19.0	4	773.018
	1.0	0	36.475	19.4	10	574.535
	32.3	3	197.515	23.0	6	630.377
	10.5	2	128.858	31.0	10	659.696
	13.0	4	152.685	23.2	10	630.090
	17.1	1	122.882	29.0	6	546.328
	13.0	1	109.497	20.0	4	507.399
	14.0	1	103.657	18.5	4	544.275
	8.0	1	128.305	19.2	6	573.754
	13.0	2	155.309	16.1	6	425.380
	12.0	2	152.907	39.4	10	1111.647
	11.0	2	129.362	29.4	10	619.079
	11.3	1	98.213	18.0	2	548.708
	11.0	1	97.789	31.2	6	675.591
	39.0	3	132.835	23.4	10	507.123

ATTACHMENT 3

Sensitivity : The sensitivity of the assay is 0.1 ng/ml.

Precision Control : The intraassay coefficient of variation is less than %, the interassay coefficient of variation is less than %.

Accuracy : The assay appears to be fairly accurate. For control standards whose low, medium and high concentrations were 1.2, 3.6 and 17.3ng/ml, for n=10 per control sample concentration, the assayed potency was within 10.5% of the expected potency. Similarly for n=45 per control sample concentration, the assayed potency was within 5.8% of the expected potency for the control standards whose low, medium and high concentrations were ng/ml.

Linearity : The assay method appears to be linear over the range ng/ml.

Based upon the provided assay validation data, the appears to be acceptable.

8. Adverse Experiences : The firm's summary of adverse experiences for what appears to be for all three studies, is attached in Appendix II.

9. In-Vivo Results:

a. Pharmacokinetic Results : 1) The baseline could not be studied properly, the concentrations being below the limit of quantitation. The comparison with a baseline is therefore not possible.

2) Attachment 1.2 lists the individual plasma concentration time data for study 1. The pharmacokinetic parameters such as Cmax, Tmax and AUC are given in Attachment 1.3. The mean parameters of the "food" study are as follows.

PARAMETER	WITHOUT FOOD (mean +/- s.d)	WITH FOOD (mean +/- s.d.)	P VALUE
	DAY 1		
AUC 0-24hr	91.5 +/- 45.8	182.5 +/- 150.6	0.0197
AUC 0-24hr*	82.7	143.0	0.003
CMAX	19.4 +/- 17.9	81.6 +/- 113.4	0.0458
CMAX*	13.8	37.1	0.009
TMAX	2.7 +/- 2.2	3.1 +/- 2.7	0.1350

AUC 0-24(FOOD)/AUC 0-24(WITHOUT FOOD) = 2.0 +/- 1.4

* = LOG TRANSFORMED

Units : AUC = ng/ml*hr
Cmax = ng/ml
Tmax = hr.

DAY 5

	(mean +/- s.d.)	(mean +/- s.d.)	
AUC 0-10	81.1 +/- 38.6	186.9 +/- 294	0.192
AUC 0-10*	73.4	116.2	0.033
CMAX	19.6 +/- 15.5	91.0 +/- 204.4	0.219
CMAX*	15.8	34.8	0.026
TMAX	3.1 +/- 2.1	3.3 +/- 2.7	0.445

AUC 0-10(FOOD)/AUC 0-10(WITHOUT FOOD) = 2.2 +/- 2.6

* = LOG TRANSFORMED as per method of Chiou W.L., J.Pharmac.Biopharm., 6, 1978, pp 539-546.

b. Statistical Analysis : The above parameter means are compared by a paired t-test. From the p-values and calculated parameter means, it appears that the CMAX (reflecting partly the rate of absorption) and AUC (extent of absorption) have increased significantly when Utrogestan is given with meals.

10. Deficiencies : See the Overall Deficiencies section of this review.

11. FDA Comments:

A. 1) Food appears to increase the oral availability of the drug. Using less than accurate mean AUC values and mean Cmax values there is approximately two fold increase in the AUC and a four fold increase in Cmax when Utrogestan was given with food using a 200 mg Q.D. dosing regimen.

Note : The standardized breakfast utilized in pharmacokinetic study 1, had a mean calorie content of 646 calories and mean protein content of 18 grams. It is to be noted however that the mean caloric content of the standardized breakfast was lower than the FDA recommended breakfast with a mean caloric content of 870-1020 calories.

2) From the drug concentration versus time plots it appears that the time of the maximal concentration is different in different subjects indicating a possible influence of gastric emptying within subjects.

3) The possibilities for the increased oral availability due to food are a) facilitated dissolution due to food. In this case, the drug being given as a micronized drug suspension in peanut oil that is filled in a soft gelatin capsule, food may influence the rupture and release of the drug, b) a decrease in the first pass metabolism due to competition for the same enzyme substrate, c) increase in the splachnic blood flow rate leading to a decrease in the first pass metabolism or d) biliary secretion where bile salts may help drug solubility or e) a combination of one or more of the above factors.

4) Large coefficients of variation (?) of the pharmacokinetic bio-parameters indicate large inter-subject variability for this drug product.

5) The baseline could not be studied, most of the drug concentrations were below the limit of quantitation.

12. Conclusion :

Standardized proteinaceous, fatty food appears to increase the extent of oral availability of Utrogestan approximately two fold based upon mean AUC values with the mean peak progesterone concentration increasing approximately four fold when compared to Utrogestan given under fasting conditions. There is a lot of intersubject variability associated with the bio-parameters under both the fasting and nonfasting conditions.

ATTACHMENT 1.1

MENU PLAN NUTRITION ASSESSMENT

Menu Plan No.1	Kcal	Approximate Values in Grams Fat	Carb	Protein
1/2 cup juice	56	.3	13.0	-
Fresh fruit[1]	81	.5	21.1	-
Breakfast Bread[2]	122	2.2	22.8	4.8
Cereal (Hot or Cold)	115	.7	27.9	4.0
1 egg	95	7.1	1.4	6.0
2 pats margarine[3]	68	3.8	-	-
1 pk. sugar	15	-	4.0	-
1 pk. jelly	49	-	12.7	-
1 carton milk	121	11.7	4.9	8.1
Coffee or tea if desired	-	-	-	-
	722	26.3	107.8	22.9

Menu Plan No.2	Kcal	Fat	Carb	Protein
1/2 cup juice	56	.3	13.0	-
1 egg	95	7.1	1.4	6.0
2 sausage links	80	5.0	2.0	8.0
Breakfast Bread	122	2.2	22.8	4.8
2 pats margarine	68	3.8	-	-
1 hashbrown	170	9.0	21.9	2.5
Coffee or tea if desired	-	-	-	-
	591	27.4	61.1	21.3

Menu Plan No.3	Kcal	Fat	Carb	Protein
1/2 cup juice	56	.3	13.0	-
Fresh Fruit	81	.5	21.1	-
Breakfast Bread	122	2.2	22.8	4.8
Cereal (Hot or Cold)	115	.7	27.9	4.0
Milk	121	11.7	4.9	8.1
2 pats margarine	68	3.8	-	-
Coffee or tea if desired	-	-	-	-
	563	19.2	89.7	16.9

Menu Plan No.4	Kcal	Fat	Carb	Protein
1/2 cup juice	56	.3	13.0	-
Fresh Fruit	81	.5	21.1	-
2 pancakes	212	1.5	42.6	7.1
2 sausage links	80	5.0	2.0	8.0
2 pats margarine	68	3.8	-	-
Syrup	200	-	51.2	-
Coffee or tea if desired	-	-	-	-
	697	11.1	129.9	15.1

Menu Plan No.5	Kcal	Fat	Carb	Protein
1/2 cup juice	56	.3	13.0	-
Fresh Fruit	81	.5	21.1	-
2 slices french toast	306	13.4	34.4	11.0
2 sausage patties	396	34.4	3.8	16.8
1 pat margarine	34	1.9	-	-
Syrup	200	-	51.2	-
Coffee or tea if desired	-	-	-	-
	1,073	50.5	123.5	27.8

Menu Plan No.6	Kcal	Fat	Carb	Protein
1/2 cup juice	56	.3	13.0	-
Fresh Fruit	81	.5	21.1	-
Cheese Omelet				
(2 eggs, 1/2 oz. cheese)	313	27.1	1.3	15.9
Breakfast Bread	122	2.2	22.8	4.8
1 pat margarine	34	1.9	-	-
2 strips bacon	109	9.4	0.1	5.8
Coffee or tea if desired	-	-	-	-
	715	41.4	58.3	26.5

Menu Plan No.7	Kcal	Fat	Carb	Protein
1/2 cup juice	56	.3	13.0	-
Fresh Fruit	81	.5	21.1	-
6 oz. yogurt (fruited)	190	4.0	32.0	7.0
Cereal (cold or hot)	115	.7	27.9	4.0
1/2 cup milk	61	5.9	2.5	4.0
1 pk. sugar	15	-	4.0	-
Coffee or tea if desired	-	-	-	-
	518	11.4	100.5	15.0

Menu Plan No.8	Kcal	Fat	Carb	Protein
Fruit and cheese plate with:				
2 servings fresh fruit and	162	1.0	42.4	-
2 oz cheese	210	16.8	1.6	13.2
Breakfast Bread	122	2.2	22.8	4.8
2 pats margarine	68	3.8	-	-
Coffee or tea if desired	-	-	-	-
	562	23.8	66.8	18.0

1 Canned fruit or extra juice (1/2 cup) may be substituted for fresh fruit.

2 Breakfast Bread = 1 biscuit, bagel, muffin, donut, pastry or 2 slices ww toast.

3 1 tablespoon cream cheese may be substituted for 1 pat margarine.

Source: A. de Planter Bowes: Bowes and Church's Food Values of Portions Commonly Used, 15th Ed. Revised by J.A.J. Pennington. NY: Harper & Row, 1989.

PERCENT FAT, CARBOHYDRATE AND PROTEIN
IN INDIVIDUAL MENU PLANS

Menu	Total Grams	% Fat	% Carb	% Protein
Plan No. 1	157.0	16.75	68.66	14.59
Plan No. 2	109.8	24.95	55.65	19.40
Plan No. 3	125.8	15.26	71.30	13.44
Plan No. 4	156.1	7.11	83.22	9.67
Plan No. 5	201.8	25.02	61.20	13.78
Plan No. 6	126.2	32.80	46.20	21.00
Plan No. 7	126.9	8.98	79.20	11.82
Plan No. 8	108.6	21.92	61.51	16.57

STUDY 1 - EFFECT OF FOOD ON UTROGESTAN

DAY 1 0-24 hours

PATIENT ID NO.	PLACEBO CMAX	PLACEBO TMAX	PLACEBO AUC	200 MG WITH FOOD CMAX	200 MG WITH FOOD TMAX	200 MG WITH FOOD AUC	200 MG FASTING CMAX	200 MG FASTING TMAX	200 MG FASTING AUC	NF/F
	0.0	0	0.000	339.0	1	404.107	29.1	4	158.477	2.6
	0.2	0	3.914	36.5	1	115.995	8.0	1	71.296	1.6
	0.0	0	0.000	8.0+	4	71.318-	60.0	3	163.440	0.44
	0.1	0	0.150	30.0	6	156.894	17.0	3	91.869	1.7
	0.3	0	4.362	29.0	3	105.521	17.4	1	83.441	1.3
	0.0	0	0.000	31.5	1	113.103	6.0	2	46.681	2.4
	0.0	0	0.000	32.0	6	112.517	11.0	2	73.095	1.5
	0.2	0	2.889	282.0	1	454.598	12.5	3	71.372	6.4
	0.2	4	2.539	19.0	1	106.557	4.0	10	58.482	1.8
	0.2	1	2.000	61.3	1	113.014	50.0	2	102.050	1.11
	0.4	0	6.699	3.5-	10	53.725-	9.0	3	59.665	0.90
	0.2	0	3.300	11.0	4	75.743	6.1	3	40.556	1.9
	0.3	2	4.471	271.0	1	399.884	44.2	1	170.766	2.3
	0.4	0	6.577	40.0	4	136.550	9.2	2	67.346	2.0
	0.2	4	3.139	30.0	2	78.376	8.0	1	59.417	1.3

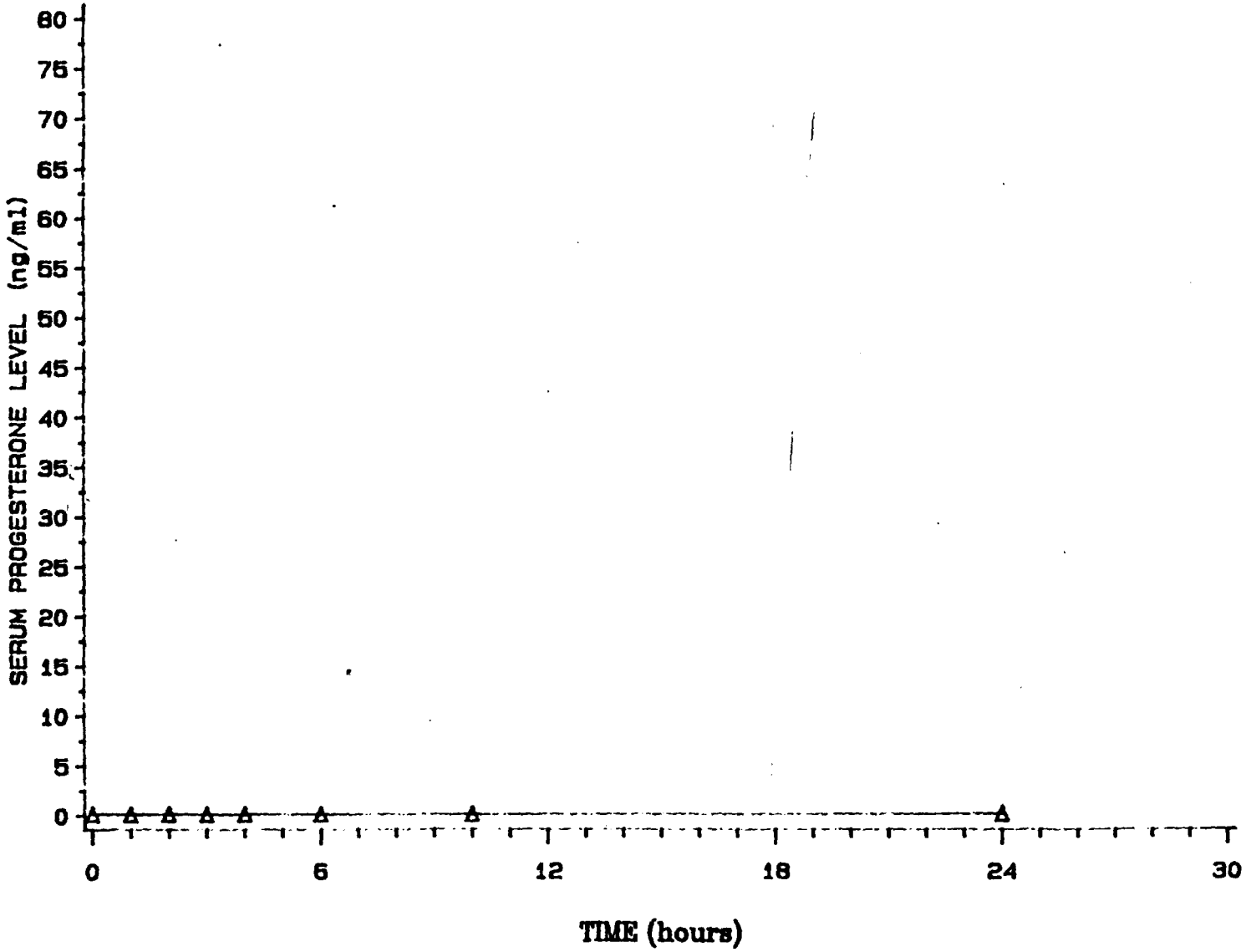
DAY 5 0-10 hours

PATIENT ID NO.	PLACEBO CMAX	PLACEBO TMAX	PLACEBO AUC	200 MG WITH FOOD CMAX	200 MG WITH FOOD TMAX	200 MG WITH FOOD AUC	200 MG FASTING CMAX	200 MG FASTING TMAX	200 MG FASTING AUC	NF/F
	0.0	0	0.000	28.5	1	83.236	51.0	4	162.164	0.51
	0.1	0	0.450	28.0	1	97.404	12.4	1	70.578	1.4
	0.2	4	1.600	184.0	1	332.934	19.0	4	75.945	4.4
	0.0	0	0.000	31.0	3	100.849	16.4	3	95.541	1.1
	0.2	0	0.894	37.1	4	102.616	22.3	3	77.219	1.3
	0.0	0	0.000	22.0	1	75.275	12.4	2	46.631	1.6
	0.2	1	1.689	29.0	1	110.769	59.0	1	122.892	0.90
	0.3	6	1.200	34.0	3	129.086	26.5	3	115.203	0.1
	0.2	10	0.700	13.2	6	73.359	9.4	3	44.325	1.7
	0.2	6	0.600	12.0	4	46.552	11.0	2	45.373	1.0
	0.4	3	3.437	9.4	6	57.940	6.0	3	38.386	1.5
	0.6	0	4.933	24.0	4	70.537	8.0	4	42.790	1.6
	0.1	0	0.250	785.0	1	1070.532-	19.2	3	107.570	9.9
	0.3	0	2.147	37.0	10	103.330	12.0	1	59.516	1.7
	0.2	1	0.944	11.2	3	47.713	10.0	10	76.998	0.62

ATTACHMENT 1.3

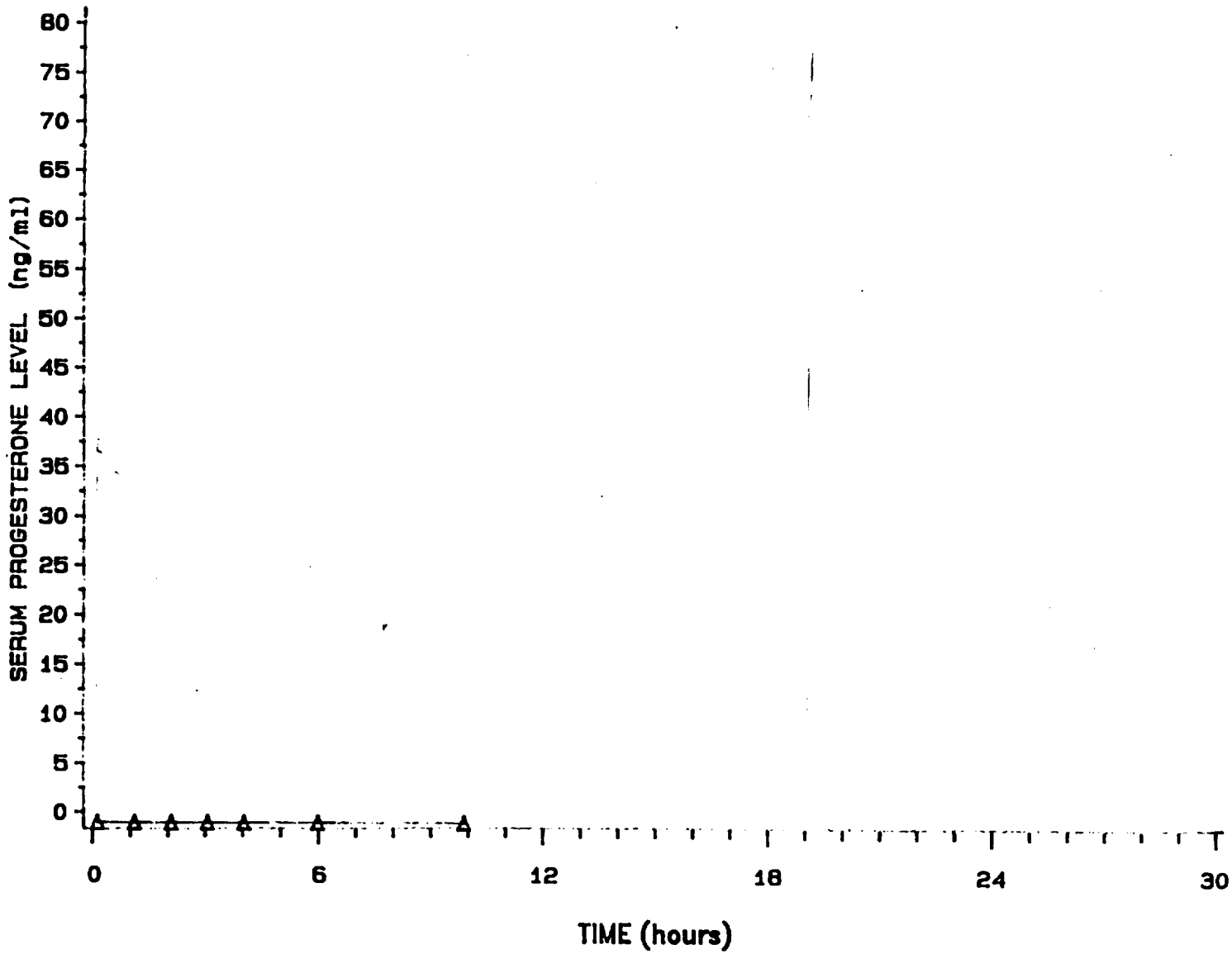
MEAN SERUM PROGESTERONE LEVELS

STUDY I: PLACEBO DAY 1



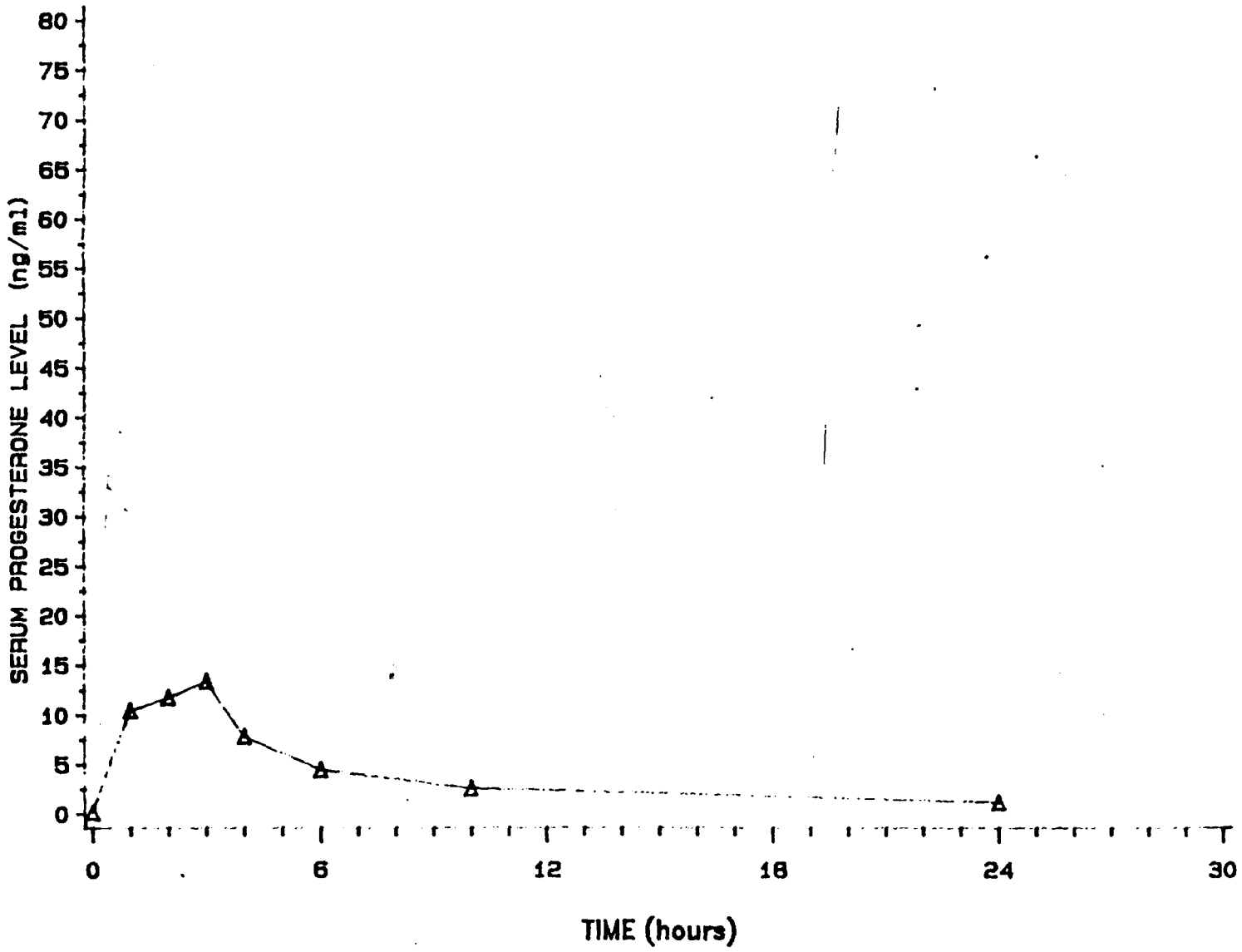
MEAN SERUM PROGESTERONE LEVELS

STUDY I: PLACEBO DAY 5



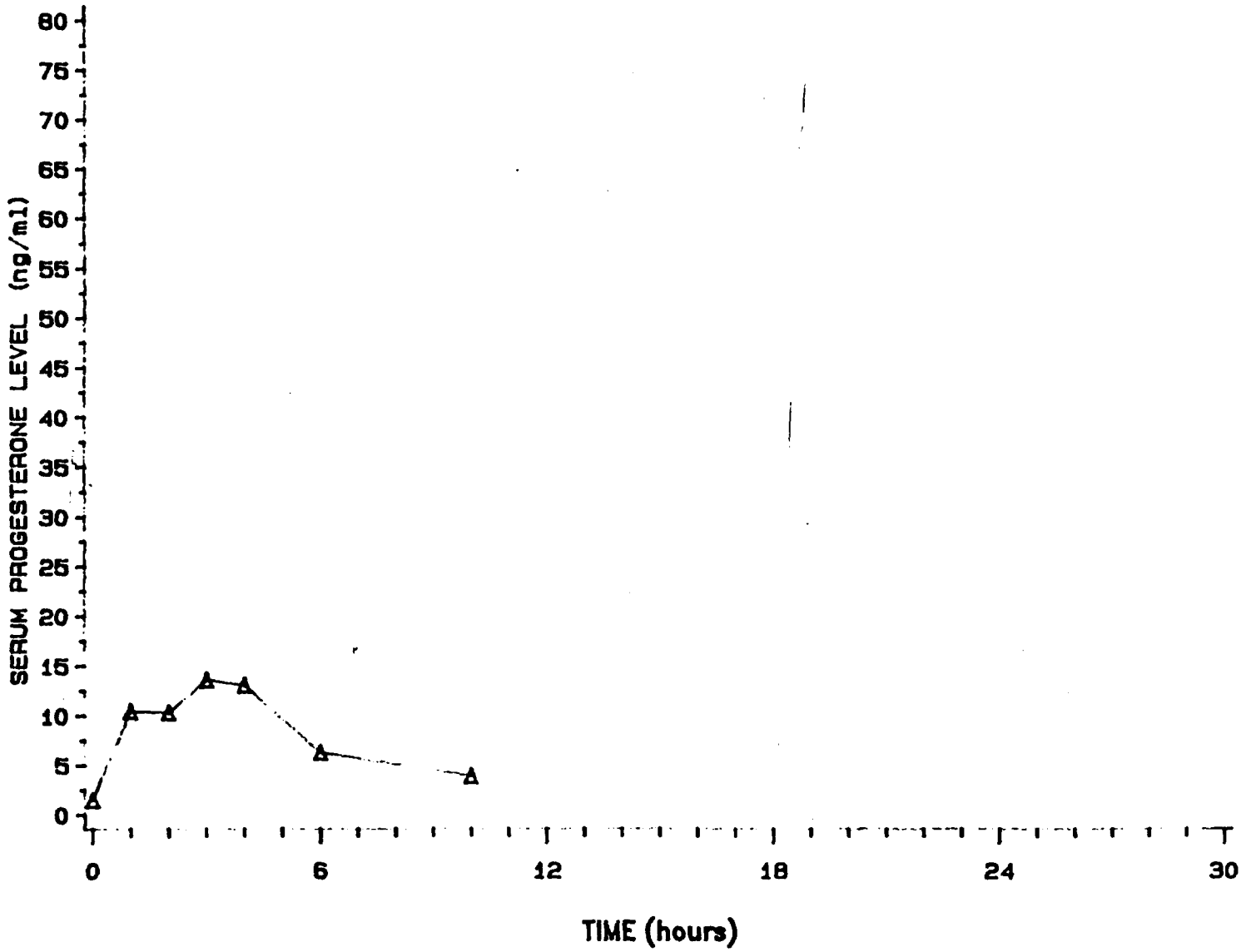
MEAN SERUM PROGESTERONE LEVELS

STUDY I: UTROGESTAN 200 mg WITHOUT FOOD DAY 1



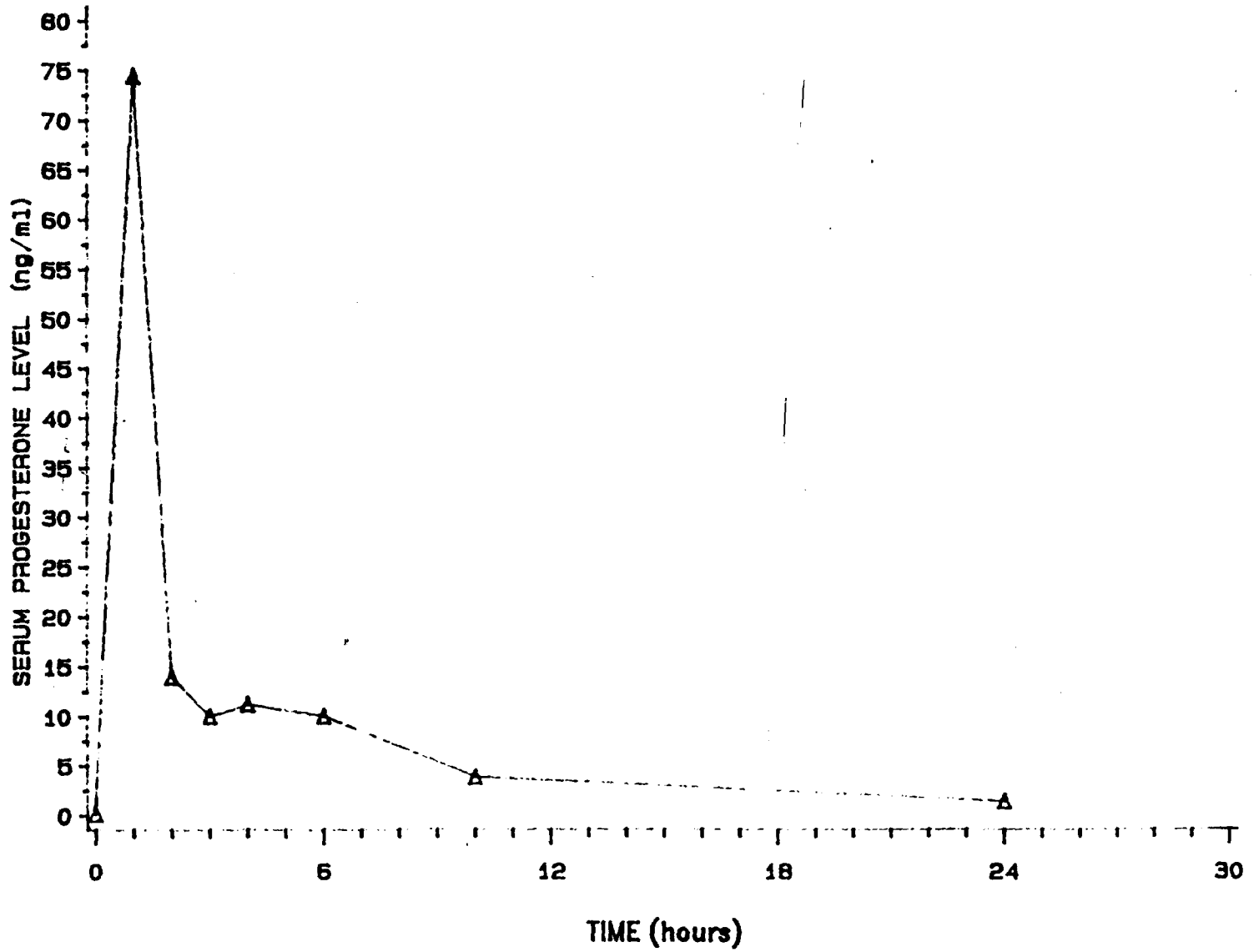
MEAN SERUM PROGESTERONE LEVELS

STUDY I: UTROGESTAN 200 mg WITHOUT FOOD DAY 5



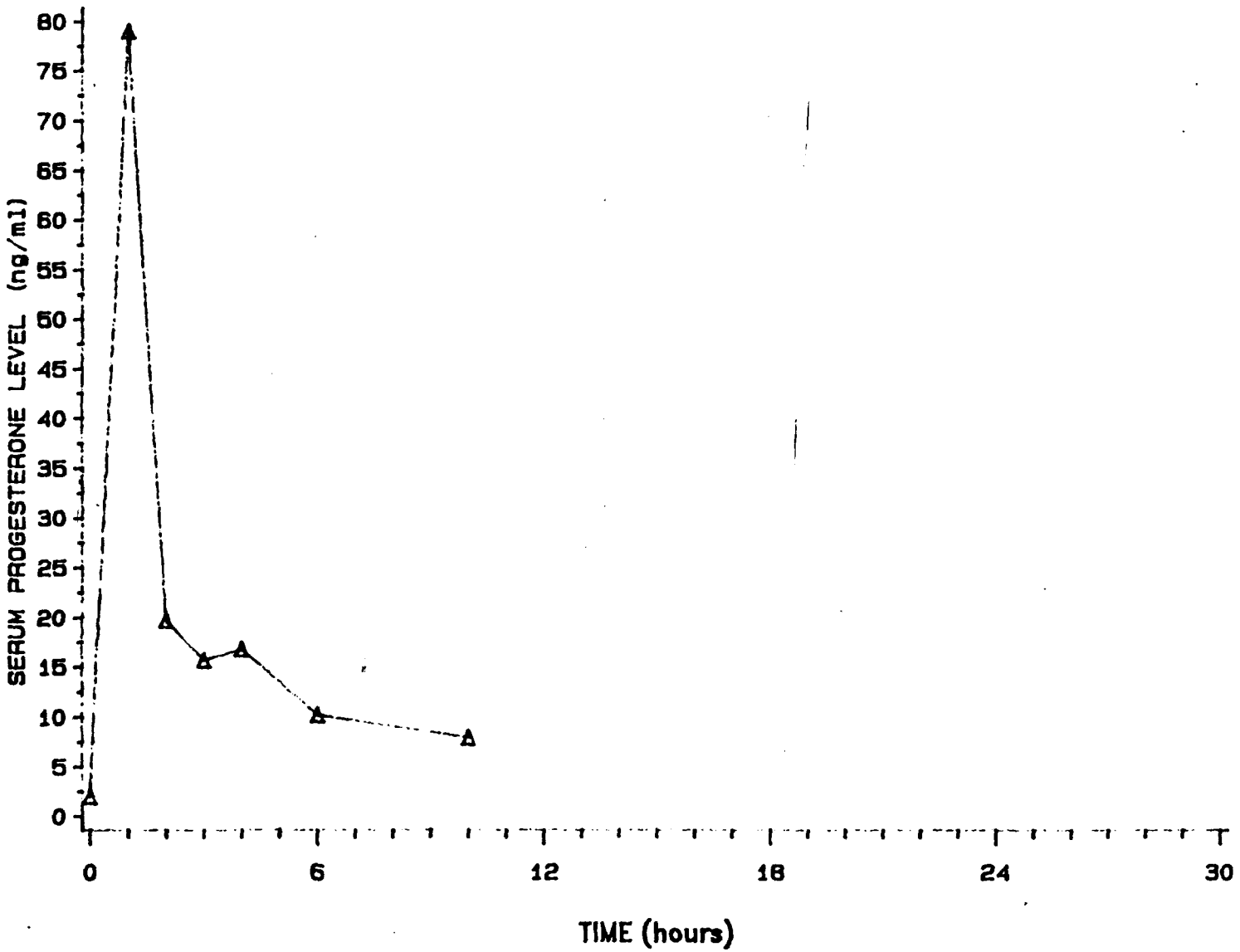
MEAN SERUM PROGESTERONE LEVELS

STUDY I: UTROGESTAN 200 mg WITH FOOD DAY 1



MEAN SERUM PROGESTERONE LEVELS

STUDY I: UTROGESTAN 200 mg WITH FOOD DAY 5



B. STUDY 2

1. Objective : The objective of this study is to evaluate the dose-proportionality of Utrogestan following oral administration of 100, 200, and 300mg dose once daily for 5 days.

2. a. Clinical Investigator :

b. Clinical Site :

c. Study Dates : 1986/87

3. Study Dosage : Utrogestan, 100 (1*100mg capsule), 200 (2*100mg capsule) and 300mg (3*100mg capsule) was administered to patients in a fasting state once daily (in the early morning), for a period of five (5) days for each dose level.

4. Subject Selection : The study involved fifteen postmenopausal women. The subject selection is in accordance with the exclusion criterion. The subjects are in the age group of 27 to 60 years and weight group 49 to 106 kgs. The subjects were randomly assigned into three subgroups consisting of 5 subjects each.

5. Study Design : The study is an open three treatment, randomized, balanced and crossover design. There is a seven day washout period between the two phases.

6. Specimens Collected : On day 1 and 5, the blood samples are collected at 0 hr and at 1.0, 2.0, 3.0, 4.0, 6.0, and 10.0hrs following the drug administration. On days 2, 3 and 4 the samples are drawn at 0, 1, 2 and 3hrs post dose. For each sample enough blood is collected to yield 3-5 ml of serum.

7. Analytical Methodology :

8. Adverse Experiences : See Appendix II.

9. In-Vivo Results:

a. Pharmacokinetic Results : Attachment 2.1 gives the plasma concentration time data for the three treatments. The individual Cmax, Tmax and AUC's are given in Attachment 2.2. The reported mean ($\pm$s.d) pharmacokinetic parameters of the "Dose Proportionality" study are as follows.

DAY 1

PARAMETER	100mg	200mg	300mg	P VALE
AUC 0-24hr (ng/ml*hr)	46.9(14.7)	86.9(44.7)	148.4(56.2)	0.01
AUC(normlzed.)	0.47(0.15)	0.43(0.22)	0.49(0.19)	0.417
CMAX (ng/ml)	10.2(8.4)	19.9(20.8)	49.8(31.9)	0.01
CMAX(normlzed)	0.10(0.08)	0.10(0.10)	0.17(0.11)	0.026
TMAX (hr)	2.7(1.0)	2.2(1.4)	2.0(1.36)	0.282

DAY 5

PARAMETER	100mg	200mg	300mg	P VALE
AUC 0-10hr	43.3(30.8)	101.2(66.0)	175.7(170.3)	0.001
AUC(normlzed)	0.43(0.30)	0.51(0.33)	0.59(0.57)	0.321
CMAX	17.3(21.8)	38.1(37.8)	60.6(72.5)	0.008
CMAX(normlzed)	0.17(0.22)	0.19(0.19)	0.20(0.24)	0.837
TMAX	1.5(0.8)	2.3(1.4)	1.7(0.6)	0.102

Values in brackets indicate +/- standard deviation.
(normlzed) = Normalized.

b. Statistical Analysis : The sponsors have compared the parameter means by repeated measures analysis of variance. A repeated measures analysis of variance is also performed on dose normalized AUC and Cmax values.

10. Deficiencies : See Overall Deficiencies.

11. FDA Comments:

1. From the results of Day 1, it appears that the normalized AUC values are not significantly different. The AUC(0-24) ratios using mean AUC values for 100mg:200mg:300mg doses are 1:1.853:3.164. The Cmax ratios for the same dosage levels are 1:1.95:4.9. The Tmax's appear to be equivalent (p = 0.282). The normalized Cmax for 300mg dose is significantly different than the normalized Cmax's for 100mg and 200mg doses. For Day 5, the less than accurate normalized AUC(0-10) values appear to be equivalent (p=0.321); the AUC ratios for 100mg:200mg:300mg, however are 1:2.3:4.0. The Cmax ratios for the same dosage level are 1:2.202:3.503. The Tmax's appear to be equivalent (p = 0.102).

2. Large standard deviations or co-efficients of variation(?), are noted for different pharmacokinetic bio-parameters.

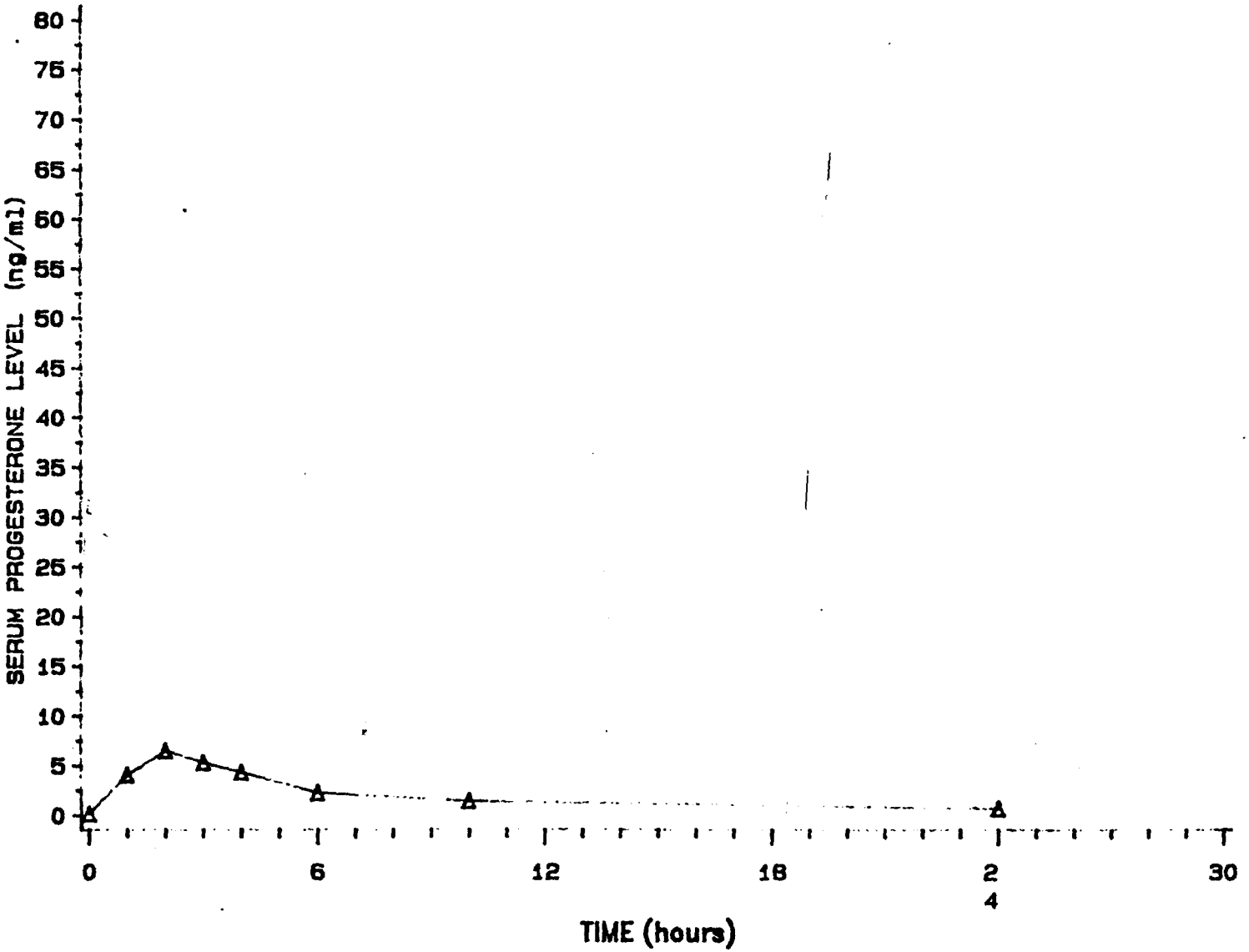
3. It appears that the sponsor has used a power approach for the comparisons, the necessary power analysis is however not reported.

12. Conclusions :

The AUC(0-24) values for Day 1, for doses 100mg, 200mg and 300mg suggest linear dose proportionality. For Day 5 where the less than accurate AUC values are calculated only up to 10hrs, there is a slight apparent deviation with respect to dose proportionality. The normalized Cmax values for Day 5 are comparable, however for Day 1 the normalized Cmax for the 300mg dose is significantly greater than either 100mg or 200mg. The reason for this is not clear.

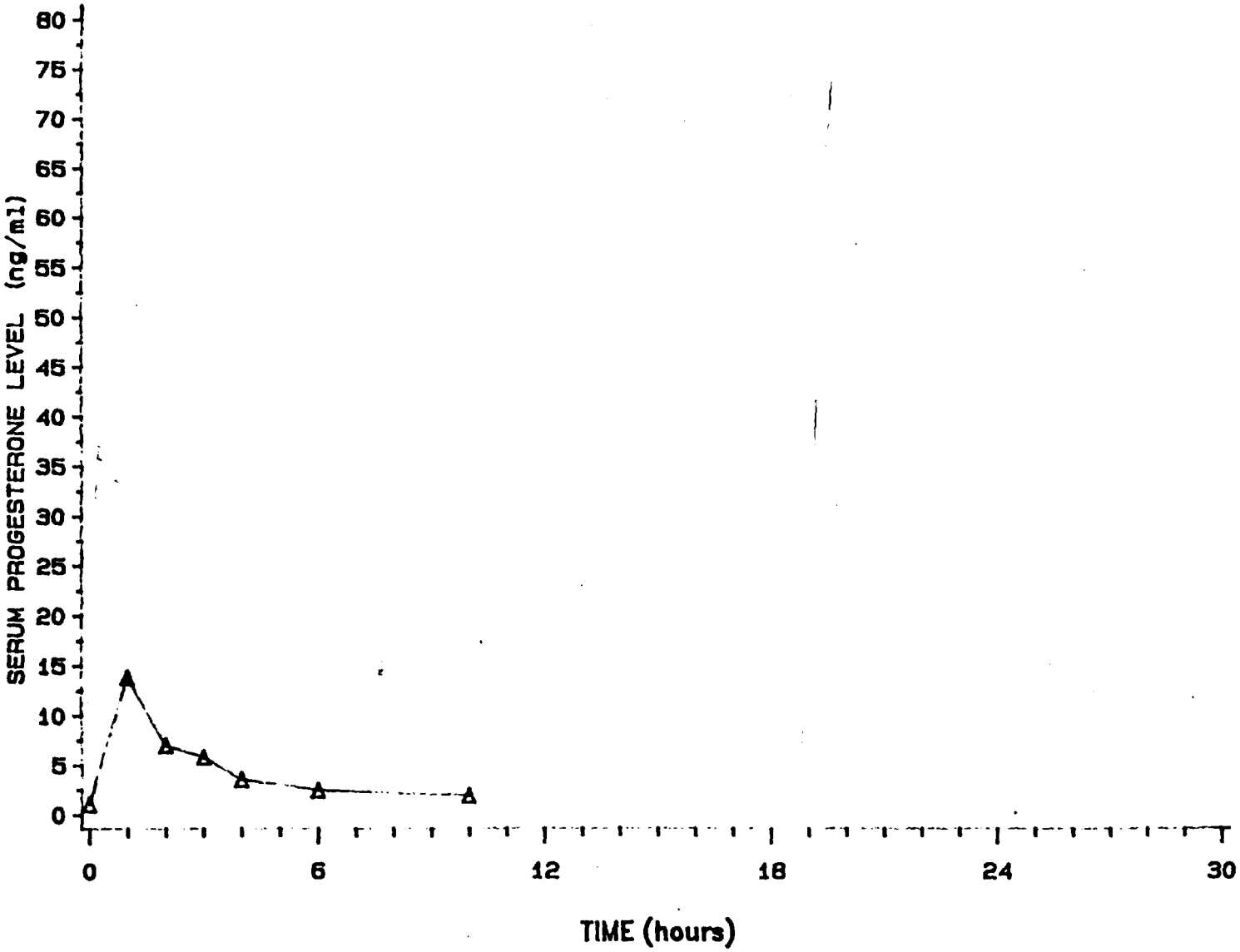
MEAN SERUM PP ESTERONE LEVELS

STUDY II: UTH STAN 100 mg DAY 1



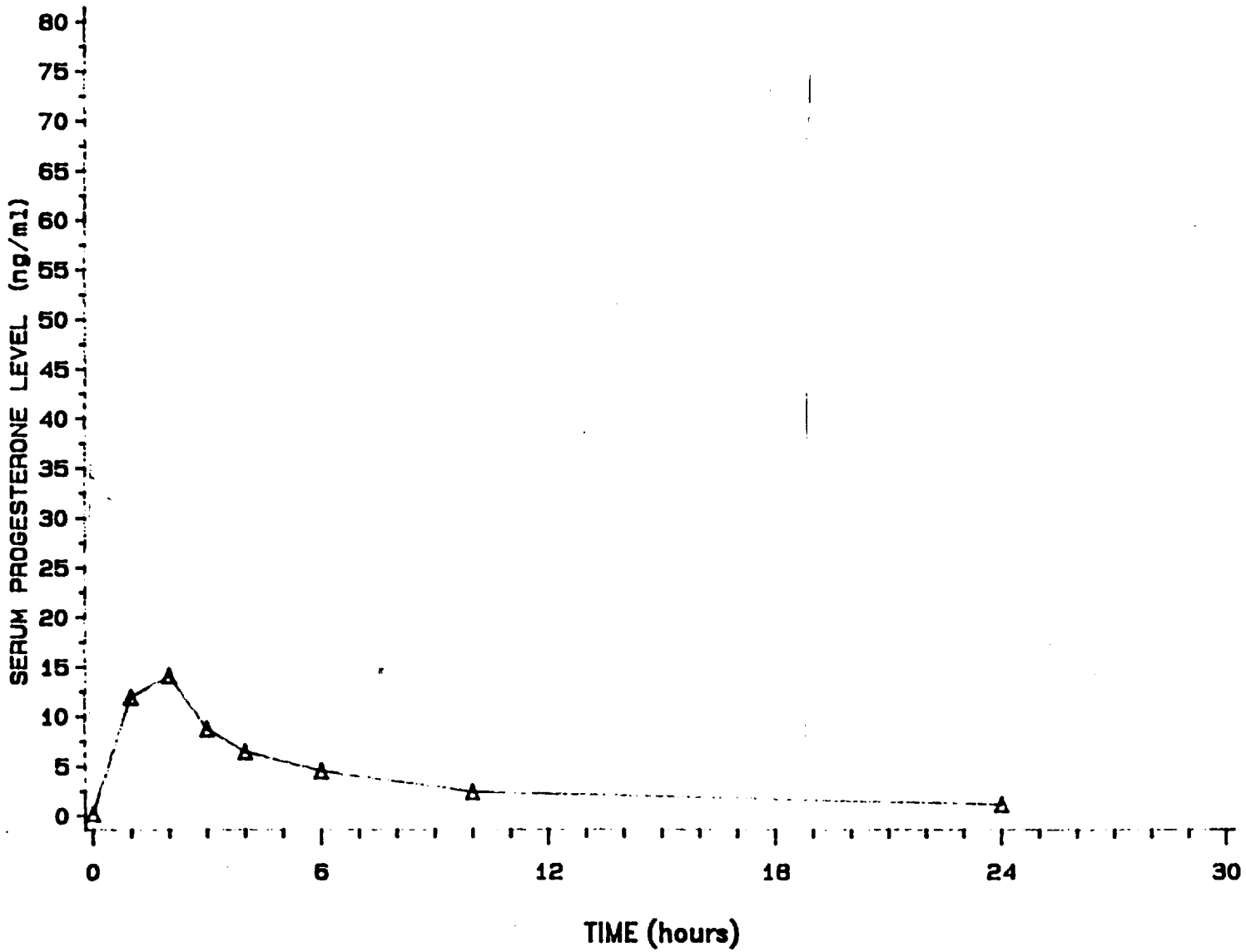
MEAN SERUM PROGESTERONE LEVELS

STUDY II: UTROGESTAN 100 mg DAY 5



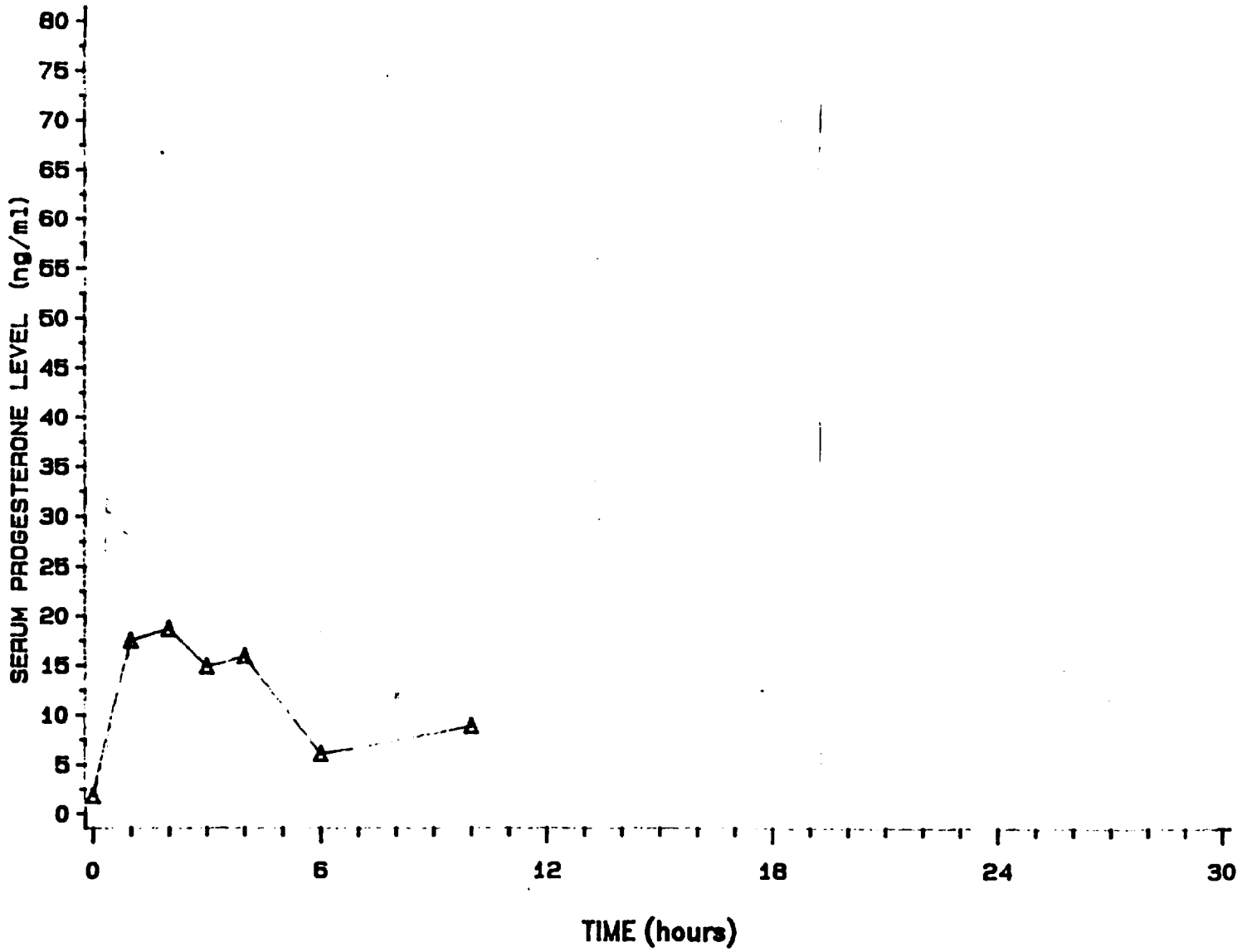
MEAN SERUM PROGESTERONE LEVELS

STUDY II: UTROGESTAN 200 mg DAY 1



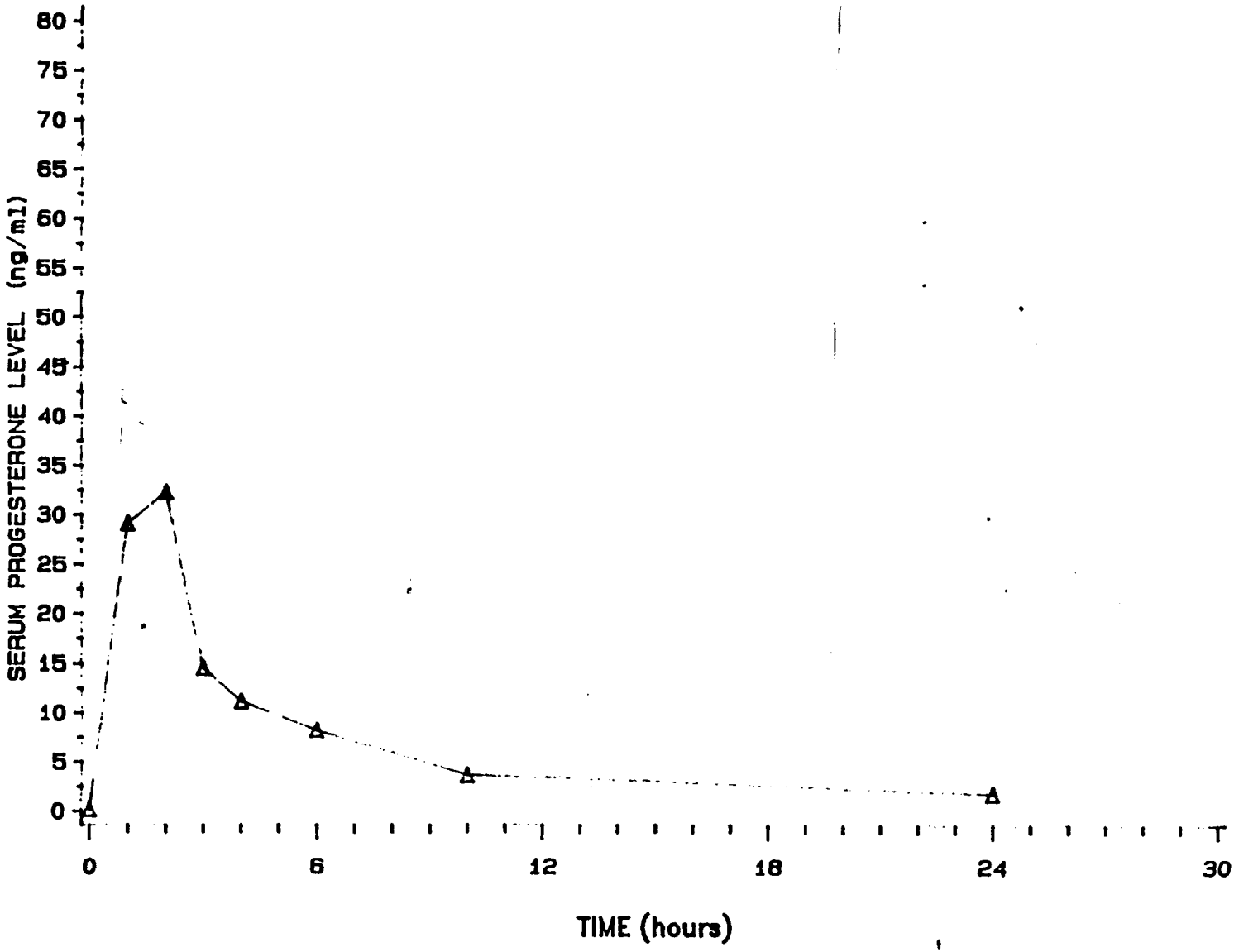
MEAN SERUM PROGESTERONE LEVELS

STUDY II: UTROGESTAN 200 mg DAY 5



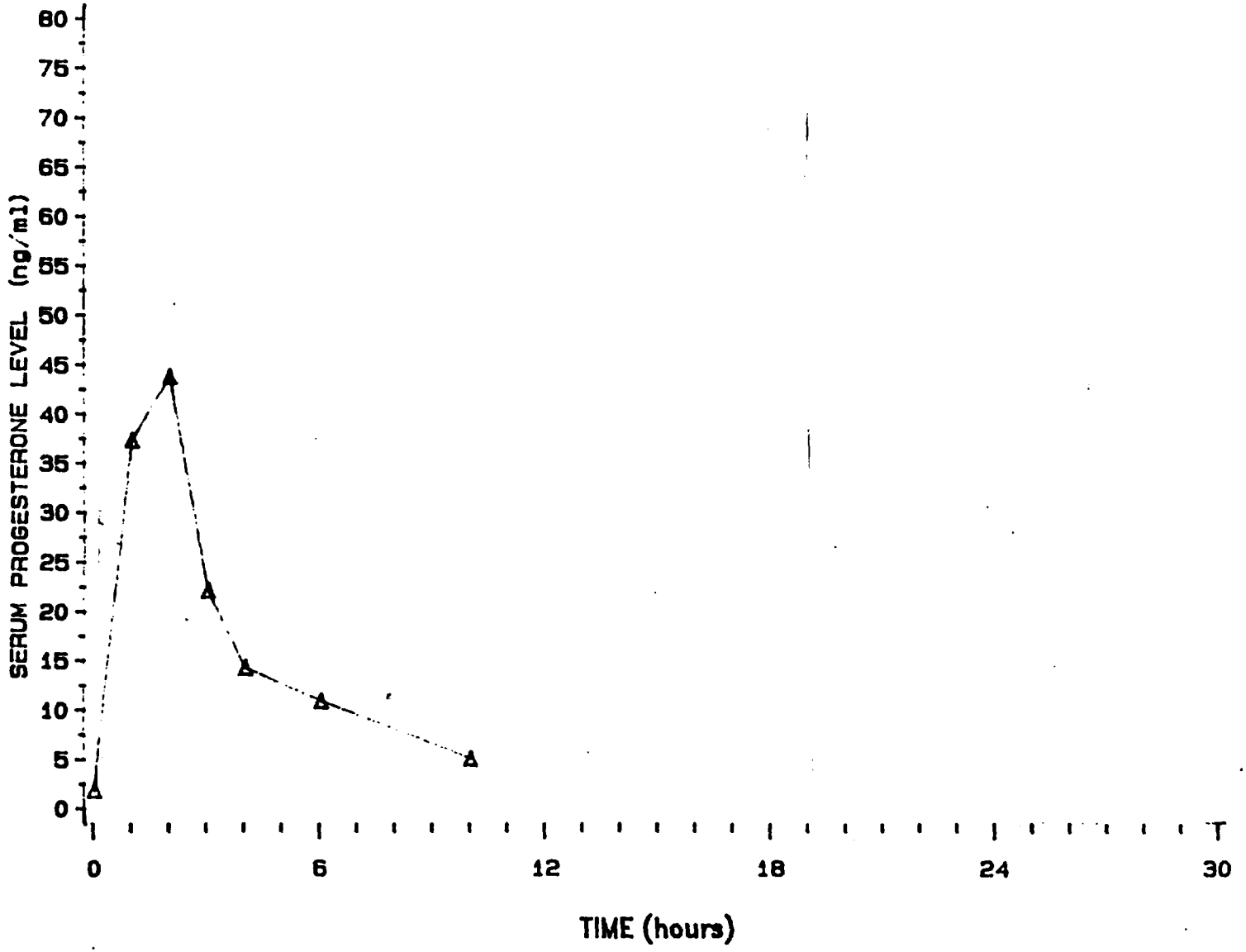
MEAN SERUM PROGESTERONE LEVELS

STUDY II: UTROGESTAN 300 mg DAY 1



MEAN SERUM PROGESTERONE LEVELS

STUDY II: UTROGESTAN 300 mg DAY 5



C. STUDY 3

1. Objective : The objective of this study is to compare the serum concentration time profile of oral Utrogestan administered in a regimen of 200mg once daily for two days to that of intramuscular progesterone in oil, administered in a regimen of 50mg daily for two days.

2. a. Clinical Investigator :

b. Clinical Site :

c. Study Dates : 1986/87

3. a. Test Formulation : Utrogestan, 200mg (2*100mg capsule) administered orally to patients in a fasting state once daily, for a period of two (2) days.

b. Reference Formulation : Progesterone in oil, 50mg administered by intramuscular injection once daily for a period of two (2) days.

4. Subject Selection : The study involves fifteen postmenopausal women. The subject selection is in accordance with the exclusion criterion. The subjects are in the age group of 27 to 67 years and weight group 49 to 106 kgs. The subjects are randomly assigned into two subgroups and are given either of the two treatments.

5. Study Design : The study is an open two treatment, randomized, balanced and crossover design. There is a seven day washout period between the two phases.

6. Specimens Collected : On day 1 and 2, the blood samples are collected at 0 hr and at 1.0, 2.0, 3.0, 4.0, 6.0, and 10.0hrs following the drug administration. On the days 3-5 the samples are drawn at 24, 48, and 72hrs following dose on day 2. For each sample enough blood is collected to yield 3-5 ml of serum.

7. Analytical Methodology :

8. Adverse Experiences : See Appendix II.

9. In-Vivo Results:

a. Pharmacokinetic Results : Attachment 3.1 gives the individual plasma concentration time points. The individual Cmax, Tmax, AUC

values are listed in Attachment 3.2. Following are the reported study results. The relative bioavailability (F) is calculated by dividing the AUC values following oral administration by AUC values obtained following IM administration and correcting for the dose.

DAY 1

PARAMETER	ORAL 200mg	INTRAMUSCULAR 50mg	P VALUE
AUC 0-24hr (ng/ml*hr)	88.5(62.3)	254.6(70.4)	0.0001
AUC(normlzed.)	22.1(15.6)	254.6(70.4)	0.0001
AUC oral(normlzed)/AUC IM(normlzed) = 0.09(0.06)			
CMAX (ng/ml)	27.6(39.0)	16.6(6.5)	0.309
CMAX(normlzed)	6.9(9.7)	16.6(6.5)	0.009
TMAX (hr)	2.5(1.6)	8.7(2.0)	0.0001

DAY 5

PARAMETER	ORAL 200mg	INTRAMUSCULAR 50mg	P VALUE
AUC 0-72hr	103.4(29.9)	452.9(147.6)	0.001
AUC(normlzed)	25.9(7.5)	452.9(147.6)	0.001
AUC oral(normlzed)/AUC IM(normlzed) = 0.06(0.02)			
CMAX	15.3(9.6)	23.9(6.6)	0.013
CMAX(normlzed)	3.8(2.4)	23.9(6.6)	0.001
TMAX	1.8(0.9)	6.9(2.8)	0.001

Values in brackets indicate +/- standard deviation.
(normlzed) = Normalized.

b. Statistical Analysis : The sponsor has compared the parameter means for day 1 and day 5, by a paired t-test. The null hypothesis of equality of the treatment means is considered rejected if the p-value is equal to or less than 0.05. AUC and Cmax values are normalized to a dose of 50mg.

10. Deficiencies : See Overall Deficiencies.

11. FDA Comments:

1. The sponsor has attempted to assess the relative bioavailability of oral Utrogestan (200mg) versus Intramuscular progesterone (50mg) using truncated AUC values (i.e.AUC(0-24) for Day 1 and AUC (0-72) for Days 2-5). Based upon the study design, AUC (0-infinity) should be estimated using both days blood levels to get a more accurate assessment.

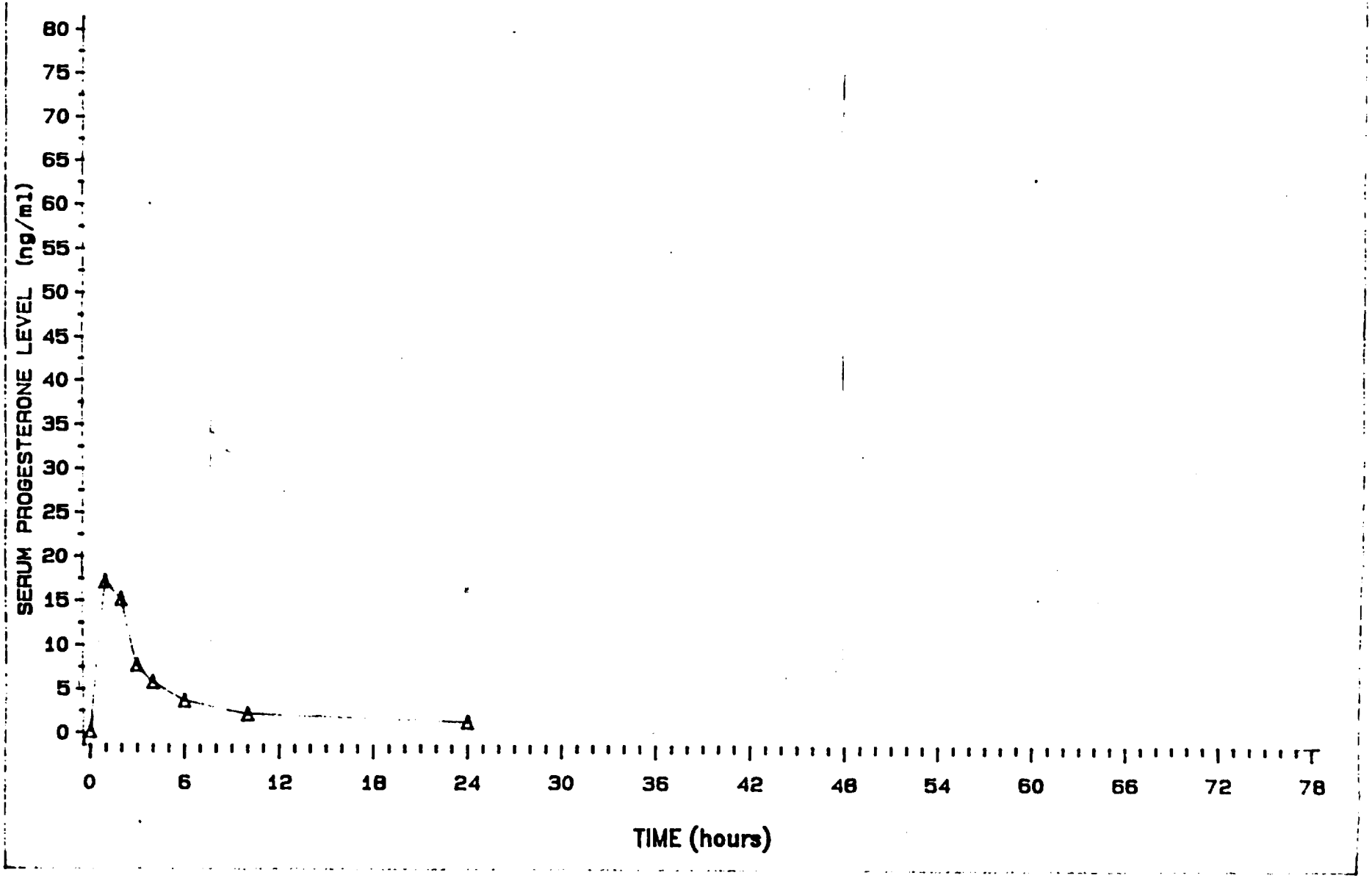
2. Using the firm's analysis, the mean AUC(normalized) values indicate that the relative bioavailability of oral Utrogestan is about 9% compared to intramuscular progesterone for Day 1 and 6% compared to intramuscular progesterone for Days 2-5. The normalized Cmax of Oral Utrogestan appears to be 42% compared to intramuscular progesterone for Day 1 and 15.9% compared to intramuscular progesterone for Days 2-5. A significant difference in the Tmax for intramuscular progesterone (8.7hr compared to oral 2.5hr on Day 1 and 6.9hr intramuscular compared to 1.8hr oral Utrogestan on Days 2-5) is also noteworthy.

12. Conclusion :

Based upon the less than accurate firm's AUC analysis, the extent of availability of intramuscular progesterone is significantly greater than oral Utrogestan. The absorption rate of oral Utrogestan is faster than intramuscular progesterone.

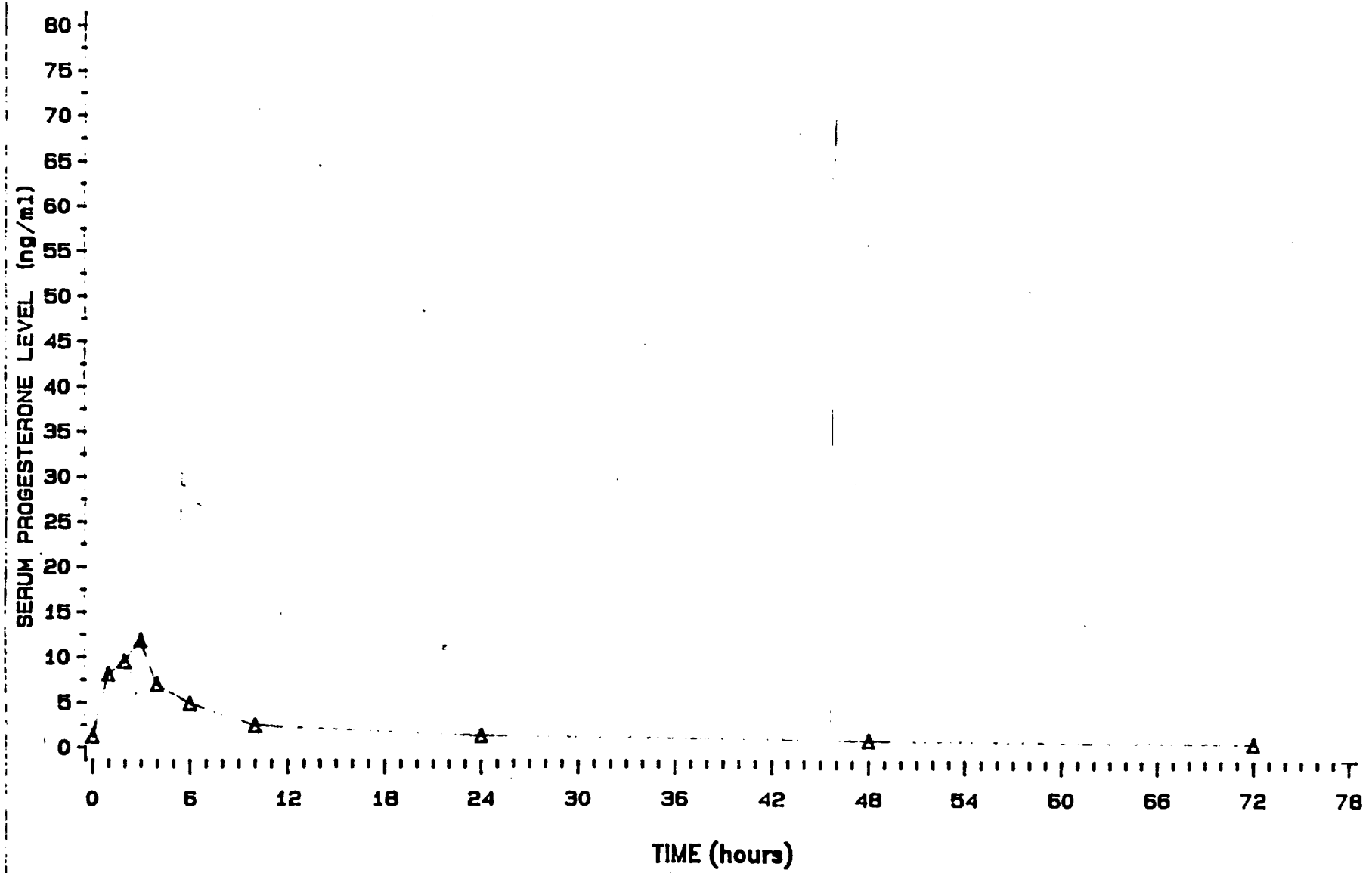
MEAN SERUM PROGESTERONE LEVELS

STUDY III: UTROGESTAN 200 mg DAY 1



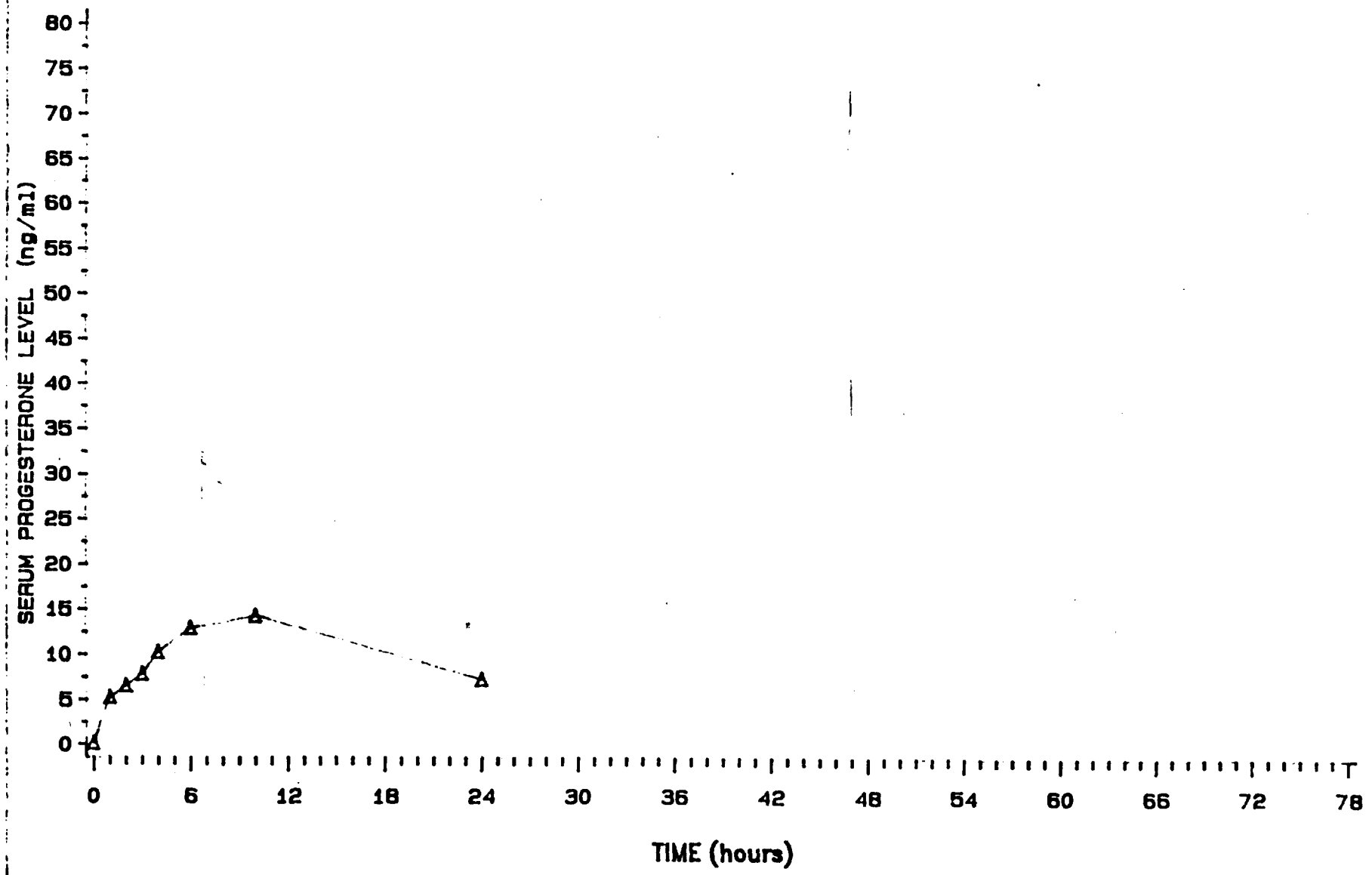
MEAN SERUM PROGESTERONE LEVELS

STUDY III: UTROGESTAN 200 mg DAYS 2-5



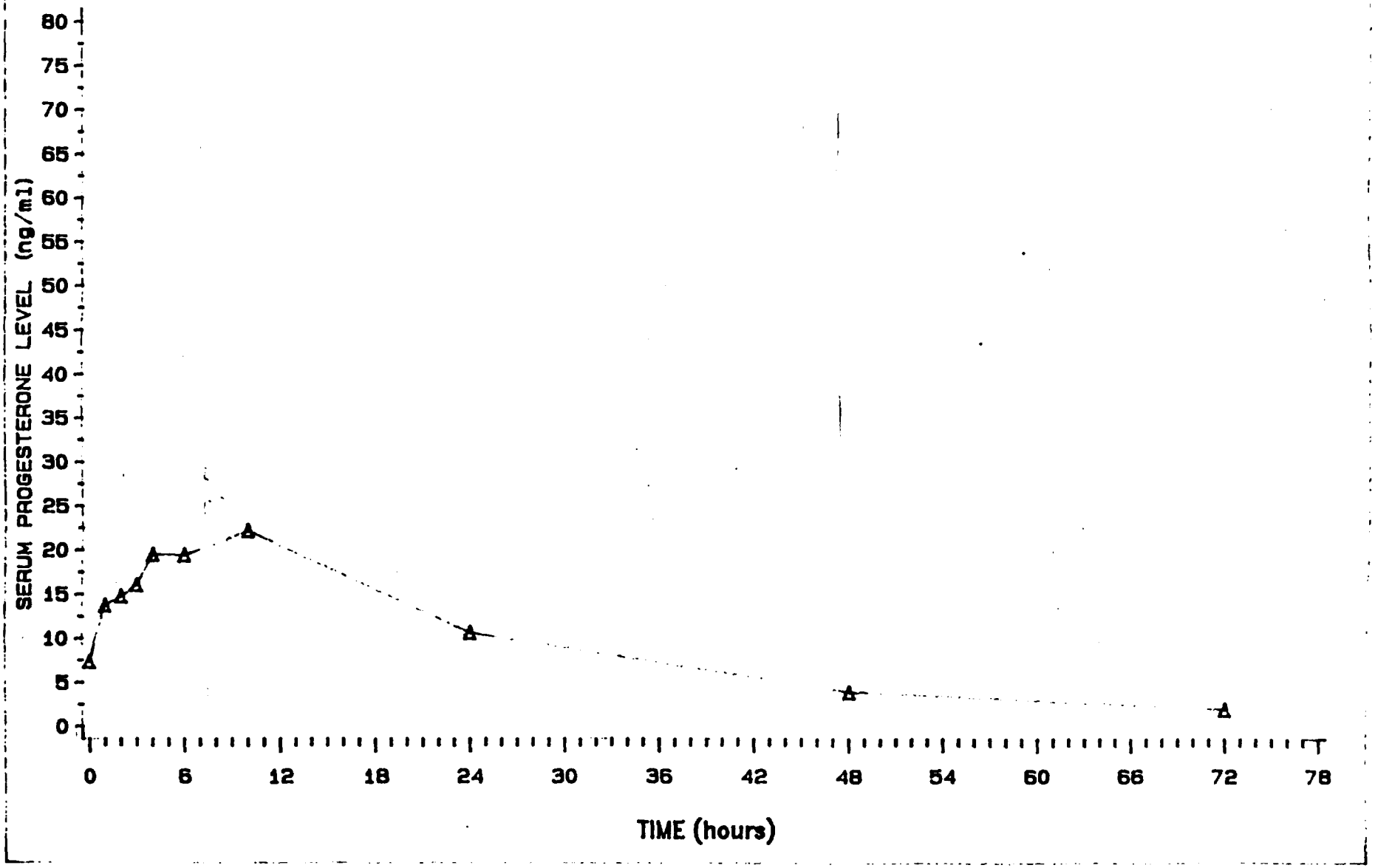
MEAN SERUM PROGESTERONE LEVELS

STUDY III: PROGESTERONE IN OIL 50 mg DAY 1



MEAN SERUM P..OGESTERONE LEVELS

STUDY III: PROGESTERONE IN OIL 50 mg DAYS 2–5



D. DISSOLUTION STUDY:

Capsule Rupture Test :

1. Background : In a letter dated April 18, 1988, HFD-510 indicated to the sponsor that comparative dissolution data would not be necessary for this application since USP states that liquid filled soft gelatin capsules are exempt from any dissolution and disintegration requirements. The sponsor however was asked to consult with the Division of Biopharmaceutics to discuss the need for an in-vitro quality control test. In a conference call dated September 22, 1988, between The Guidelines Inc. and HFD-426, representatives of the Guidelines Inc. indicated that an in-vitro dissolution test was not feasible for this product. In response, because the product contained a micronized drug suspension, the agency suggested that in lieu of this, a "burst" test should be adequate in addition to in-process controls which evaluate the particle size of the raw material. The sponsor developed a Capsule Rupture Test to address this request.

2. Tests : a. The following in-process controls have been implemented for the micronized progesterone raw material to control particle size variation. Incoming active ingredient is microscopically analyzed and must meet the following particle size distribution criteria:

Less than	microns	% minimum
Less than	microns	% minimum
Less than	microns	% minimum

b. The capsule rupture test records the splitting of the capsule and emergence of the white progesterone/peanut oil suspension as the endpoint. The immersion test fluid is water. A disc is added to each tube for the splitting time test. The sponsors have used as the maximal time limit for the rupture test.

3. Deficiency :

The sponsor has not provided the individual capsule rupture times. The data should be provided with the mean and the coefficient of variation.

4. Conclusion :

No conclusion about the rupture test could be drawn in the absence of the capsule rupture time data.

III. OVERALL DEFICIENCIES :

1. Cursory review of the calculated AUC values for the different pharmacokinetic studies indicates that different values were submitted in the original NDA filing dated Sept 30, 1987 as

compared to the values filed in the 03/17/89 submission. Example, for Study 1 for patient an AUC(0-24) value of 471.55 was given in volume 3 of 5 (submission date Sept. 30, 1987) on page 713 as compared to a value of 404.307 in the resubmission filed 3/17/89, page 143. Please explain the discrepencies in the calculated AUC values for the different studies and indicate which values are correct. If the different studies' conclusions are based upon incorrectly calculated AUC values then new data analyses on the currect values will be required.

2. In Study Nos. 1 and 2, the sponsor employed study designs that were less than ideal from a bioavailability/pharmacokinetic perspective. That is, on Day 5 (assuming steady state) a complete blood level profile was not characterized over the entire 24hr dosing interval (i.e. samples were only collected up to 10hr post dose). This approach limits the utility of the obtained results for accurately assessing drug accumulation (i.e. using AUC), the overall effect of food on progesterone oral availability under chronic administration and steady state dose proportionality analysis for the package insert's proposed dosing regimen. The sponsor should address these concerns and provide justification and analyse additional data as appropriate (e.g., the degree of error that is imposed as a result of using truncated AUC values on Day 5, etc.) to help support the accuracy of the conclusions for these studies.

3. For Study No. 3, two consecutive doses each of oral Utrogestan (200mg Q.D.) and a marketed intramuscular (IM) product (50mg Q.D.) were given where blood samples were collected from Day 1 to 72hr post dose on Day 2. From this study the sponsor has attempted to assess the relative bioavailability of the proposed market capsule to a marketed intramuscular reference product using AUC(0-72) following the Day 2 dose (i.e., actually AUC24-96 following the dose at time zero on Day 1). Based upon this approach, the determined results are probably less than accurate.

Example, inspection of the observed blood level results indicates i) for neither of the two study treatments are progesterone levels back to baseline before the Day 2 dose and ii) steady state is not achieved by Day 2 (especially for the intramuscular dose) for which Day 2, AUC(0-24) values could have been used if steady state was achieved. Due to progesterone levels being carried over from the first dose on Day 1 and the continuing accumulation of progesterone on Day 2 (especially for the IM route), the net result is that the relative bioavailability calculations using only Day 2 AUC(0-72) values will be biased. Therefore for a more accurate assessment of relative bioavailability based upon the study design employed, it would be better to use AUC calculated from Day 1 plus Day 2 to infinity. The sponsor should determine the elimination rate constants/half lives for progesterone for each product and then carry out the relative bioavailability data analysis accordingly.

4. The sponsor has only used t-tests for statistical comparisons and should have used analysis of variance (ANOVA) in order to analyse different sources of variation. The use of only a t-test does not allow one to ascertain effects other than the treatment comparison. The ANOVAs should use the following statistical model : Response = Sequence, Subject(Sequence), Period, and Treatment. This should be provided for all studies where ever applicable and then the Two One Sided Test Procedure should be employed for the treatment comparisons (see Journal of Pharmacokinetics and Biopharmaceutics, vol 15, no.6, 1987, pp 657-680) like for the dose normalized values (e.g. AUC and Cmax) for study 2.

5. For Study numbers 1 and 2, the sponsor should establish when steady state was acheived in these studies (e.g. statistical analysis using Cmin values using the ANOVA and the Two One Sided t-test Procedure).

6. In the sponsor's submission (volume 3 of 5, page 384), it has been indicated that, "The Utrogestan product tested in the pharmacokinetic studies submitted in the application has a formulation identical to the product proposed for marketing in the U.S.". It is further indicated that, "The formulation submitted to the IND with the study protocol was not used. Prior to initiation of the pharmacokinetic studies, the formulation of the capsule shell was changed to remove the parabens". The sponsor should address the following :

a) Was the capsule formulation used in each of the pivotal clinical safety and efficacy studies the exact same formulation used in the pharmacokinetic studies which is to be marketed?

b) Provided should be a table that gives each pivotal clinical and pharmacokinetic study number, the formulation of the capsule tested in each study, the batch number, the size of the batch, information whether it was a pilot or production size batch and whether it was made on production size equipment plus information about the mean size and range of the drug particles per study batch.

7. The firm should clearly indicate how it has gotten the drug concentrations that are higher than that of the highest concentration of the linear dynamic range of the assay's standard curve for the collected blood samples. (The procedure involved such as dilution or linear interpolation should be clarified and documented).

8. The firm should state clearly what they really mean when they write s.d. or cv, (Example..on page 382 of vol.1.3, the summary table lists the parameters as mean ± cv (coefficient of variation). The tables IV to VIII on pages 459 through 464 list the same parameters as mean ± s.d.(standard deviation).

9. Metabolism as well as protein binding data needs to be

submitted. This data could be submitted from the literature.

10. Ideally it would be helpful if the sponsor provided for each study, the plasma concentration vs time plots for each study subject (preferably comparative treatment plots on the same scale). The data points should be joined in the plots in order to get a better idea of the fluctuations or patterns in drug blood levels. Attachment 5 lists a plot as supplied by the firm.

11. For appropriate evaluation of the rupture test the sponsor should provide the individual capsule rupture times. The data should be provided with the mean and coefficient of variation.

12. The proposed package insert provides no pharmacokinetic information regarding this product's performance as has been obtained or could be calculated from the sponsor's conducted pharmacokinetic/bioavailability studies (e.g. Tmax, Cmax, $t_{1/2}$, effect of food, accumulation, dose proportionality, clearance etc.). Therefore, such information should be included in the proposed package insert, taking into consideration the other deficiencies that have been cited.

13. In Study No.1 that evaluated the effect of food on Utrogestan absorption, it was shown that food increased the extent of progesterone oral availability about two fold based upon mean AUC values and increased peak drug concentrations about four fold based upon mean peak concentrations. The sponsor should indicate if in the pivotal clinical safety and efficacy studies patients were instructed to take Utrogestan with or without meals or whether they were uncontrolled as to when Utrogestan was given in relation to meals. Additionally, it should be indicated what the dosing regimens were in all of the pivotal clinical studies, knowing that food appears to significantly effect the oral availability of progesterone. A package insert labelling statement should be included to address the food effect plus information related to the way the pivotal clinical studies were conducted if appropriate.

14. In Study No.2, the dose proportionality of progesterone was studied at 100, 200 (2*100mg capsule) and 300mg (3*100mg capsule) under fasting conditions. (Note: 200 and 300mg daily are recommended in the package insert). Knowing the significant effect of enhanced oral availability of progesterone when given with food at the 200mg dose, the consequences of food on the dose proportionality of the 300mg dose is unknown. The sponsor should address this concern as related to how the clinical safety and efficacy studies were conducted.

15. The currently proposed package insert indicates that Utrogestan is to be administered, "in doses of 200 to 300mg daily for from 5 to 10 days". Since Utrogestan is only available as a 100mg capsule and based upon the recommended "daily" dosage, could a physician feel at liberty to give dosage regimens of 100mg b.i.d. or 100mg

t.i.d.? If the clinical safety and efficacy studies were conducted only using a once a day dosing regimen as the pharmacokinetic studies were, it seems that a better proposed dosing recommendation in the package insert would be to state that a 200mg or 300mg dose is to be given once a day. This would more likely limit any possible interpretations of allowing Utrogestan's "daily" dose to be given in different regimens that have not been clinically tested.

IV. OVERALL COMMENT :

Reviewed have been the sponsor's bio-studies that were filed under NDA 19-781. As pointed out in the Overall Deficiencies section of this review, there are some study design flaws (Study Nos. 1 and 2) which are not correctable. Assuming that the capsule formulation used in the pivotal clinical safety and efficacy studies is not different from the capsule formulation used in the bio-studies and assuming that the sponsor's responses to the deficiencies don't reveal or result in additional complications and problems, the results obtained from these studies, although less than ideal, could be used on a semi-quantitative basis if that is acceptable. Knowing this, if it is decided that additional clinical studies are required prior to NDA approval then it would seem to be appropriate/reasonable to obtain additional bio-data from either these new clinical studies or a seperate bio-study(ies). On the other hand, if this NDA is approvable, based on the clinical data, then obtaining the requested information (assuming the sponsor's responses to the deficiencies are not problematic) post NDA approval may be an option.

V. OVERALL RECOMMENDATION :

The Division of Biopharmaceutics has reviewed the bio-studies and labelling information that has been resubmitted under NDA 19-781 on 03/17/89. Based upon that review, it is felt that a number of deficiencies need to be addressed by the sponsor. Please forward this recommendation and deficiencies nos. 1-15 to the sponsor. The medical officer should also be made aware of the firm's reported adverse experiences for the filed bio-studies (see Appendix II). Also, the medical officer should be made aware of the Overall Comment No.IV.

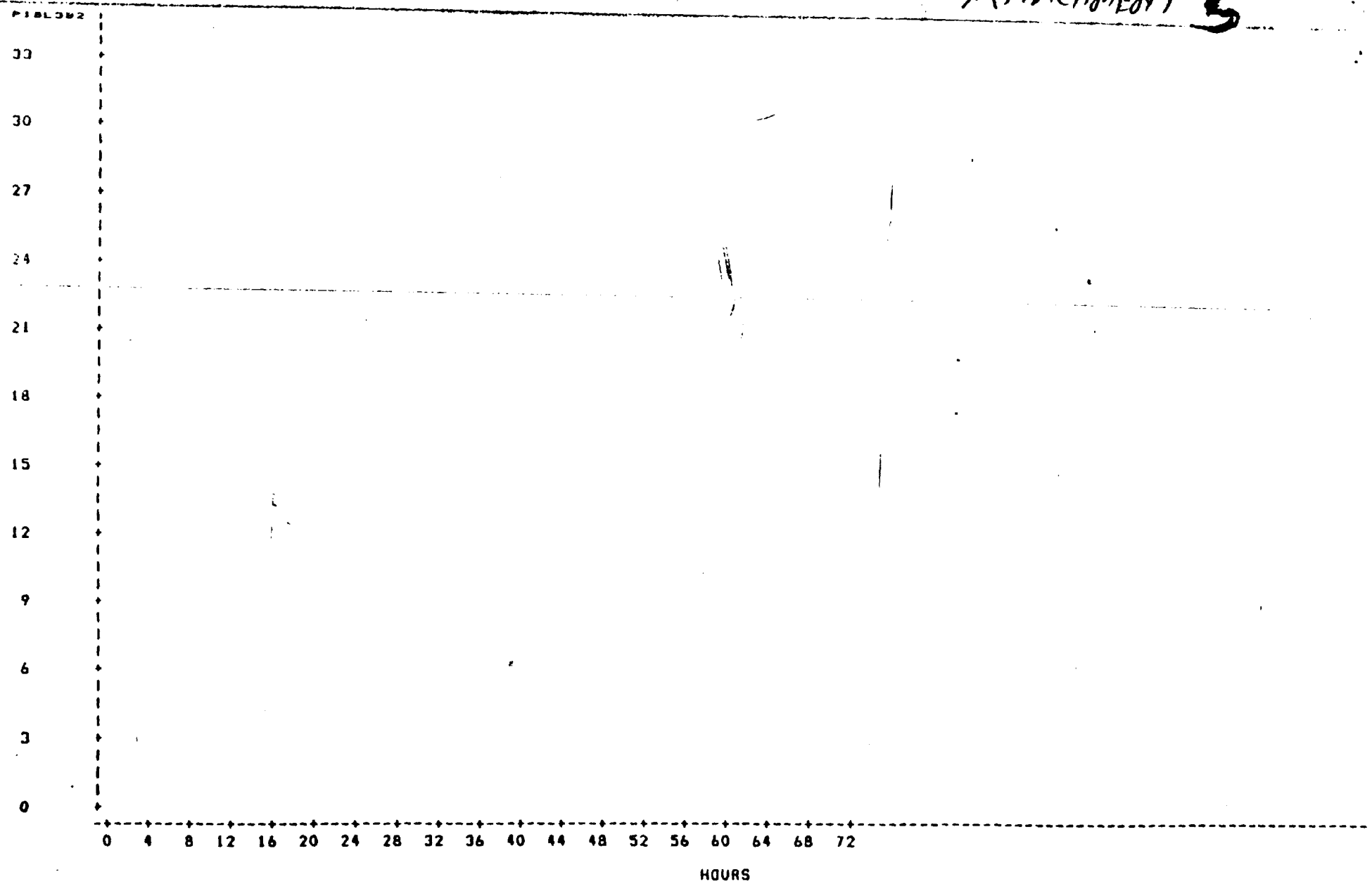
/S/

Pradeep Sathe, Ph.D.
Pharmacokinetics Evaluation Branch.

RD Initialed by Randy Dockens, Ph.D. 02/28/90
FT Initialed by John P.Hunt 4/24/90

cc: NDA 19-781 (Orig.), HFD-510, HFD-426 (Sathe, Dockens, Hunt), HFD-19 (FOI), HFD-344 (Turner), Chron, Reviewer and Drug Files.

ATTACHMENT 5



Appendix I

Specificity

The Coat-A-Count Progesterone antiserum is highly specific for progesterone, with a particularly low crossreactivity to other steroids which might be present in patient samples. Compounds flagged as "ND" were not detectable by the assay.

Compound	Approximate Percent Crossreactivity
Progesterone	100%
Androstenediol	ND
Corticosterone	0.4%
Cortisol	ND
Danazol	ND
11-Deoxycorticosterone	1.7%
11-Deoxycortisol	2.4%
20α-Dihydroprogesterone	2.0%
Estradiol	ND
17α-Hydroxyprogesterone	0.3%
Medroxyprogesterone	ND
Pregnane	ND
5β-Pregnan-3α-ol-20-one	0.2%
5α-Pregnan-3,20-dione	0.8%
5β-Pregnan-3,20-dione	1.3%
Pregnenolone	ND
Testosterone	ND

qualified for the study. The menopausal status of these two individuals, despite their histories, was not confirmed by their laboratory assessment. Demographic information on the patients actually studied is attached (Attachment 2). All remaining individuals completed at least one limb of the study. Eleven individuals (Attachment 3) finished all three studies (I, feeding effect; II, dose-proportionality; and III, concentration/time comparison with IM progesterone). No individuals left the study because of complications or side effects. Several individuals felt the time commitment was too great and others objected to the multiple blood samples.

Adverse Experiences

No serious complications were noted by any of the study participants. However, many of the participants (10/21, 47.6%) did experience some degree of lightheadedness, weakness, fatigue, drowsiness, and/or dizziness transiently after taking the medication (Attachment 3). While the number of patients reporting these phenomena is high, it is probably an underestimate. Several patients, for example, were found sleeping and snoring in a busy waiting room approximately one hour after the drug was administered. However, these patients did not report any adverse reaction. There were no apparent differences in the severity of the symptoms whether or not the drug was administered before or after food ingestion. There was a subjective increase in the severity of the symptoms reported by those patients receiving 300 mg compared with either the 200 mg or 100 mg doses. All symptoms were reported to be transient. They occurred approximately one hour after drug administration and lasted for about one hour. In general, patients demonstrated some tachyphylaxis with regard to these symptoms during the daily dosing interval. By the last doses of a treatment (i.e. 5 days), few or no adverse reactions were appreciated. There appeared to be no permanent residual effects noted during the drug-free interval, but symptoms recurred with the same initial intensity when Utrogestan was re-instituted in another treatment arm or phase of the study.

It should be noted that the observed transient findings of lightheadedness, weakness, fatigue, drowsiness, and/or dizziness with Utrogestan are consistent in onset, degree and duration with the dose-dependent, hypnotic effect previously described for progesterone and other natural and synthetic steroids (1-3).

One patient experienced severe palpitations and chest pain during initiation of Utrogestan treatment. As this symptom had not been reported previously, and was suggestive of cardiac disease, a cardiologist was asked to consult. Cardiac enzymes, an electrocardiogram and complete cardiologic clinical evaluation was performed with no unusual or suspicious findings. On further discussion with

previous episodes in the past after consuming large amounts of coffee and other biologic stimulants. She recovered uneventfully from this initial episode in several hours. When the results of her cardiac evaluation were known, she was maintained on the study. A second episode of lesser duration and intensity occurred the following day. The patient desired to continue in the study, and no further episodes of chest pain or palpitations were reported. The etiology of this reaction remains unclear. It may have been unrelated to the Utrogestan.

References

1. Gyermek L, Iriarte J, Crabbe P. (1968)
Steroids. CCCX. Structure-activity relationship of some steroidal hypnotic agents.
J. Med. Chem. 11:117-125

2. Holzbauer M. (1976)
Physiological aspects of steroids with anesthetic properties (Review)
Medical Biology 54:227-242

3. Merryman W, Boiman R, Barnes L, Rothchild I. (1954)
Progesterone "anesthesia" in human subjects (Letter)
J. Clin. Endocrinol. 14:1567-1569

appeared to be a positive correlation between dose and adverse experiences reported.

TABLE X

Adverse Experience Summary by Body System for All Studies

Body System	No. of Complaints	No. of Patients Reporting
Central Nervous System		
Dizzy	15	6
Tired	14	8
Sleepy	14	6
Lightheaded	7	5
Out of Contact/Spaced	7	4
Drowsy	3	2
Weak	3	1
Faint feeling	2	2
Vertigo	1	1
Cardiovascular		
Chest pains	2	1
Gastrointestinal		
Nausea	1	1
Dry mouth	1	1
Constipation	1	1
Genitourinary		
Urinary frequency	1	1
Musculoskeletal		
Low back pain	1	1
	73	11

(4)

TABLE XI

...of Adverse Experiences Reported by Dose Administered

	Utrogrestan 200mg/Fasting (n=30)	Utrogestan 200mg/Food (n=15)	Utrogestan 100mg (n=15)	Utrogestan 300mg (n=15)	Progesterone in Oil 50 mg (n=15)
No. of adverse experiences reported	19	14	1	36	3

APPEARS THIS WAY
ON ORIGINAL

466

HFN-810

Progesterone
(Micronized)
(100 mg Capsules)
NDA 19-781
Reviewer: Anita Shah
Wang #3143X
1-N

Besins Pharmaceuticals, Inc.
c/o Akin, Gump, Strauss, Hauer
Washington, D.C. 20036
Submission Date:
September 30, 1987

AP 2

DRV
filed

Review of an NDA

Utrogestan soft gelatin capsules contain 100 mg of micronized progesterone. Progesterone is indicated in the treatment of secondary amenorrhea; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

This NDA contains three studies as described in attachment 1. However these studies will not be reviewed at this time because HFN-810 has refused to file this NDA. In a cursory review of this submission the following deficiencies were noted:

1) The firm should tabulate the various pharmacokinetic parameters for each subject in each study. The firm has only provided the mean values for the AUC, Tmax and Cmax for all three studies.

2) The firm has submitted the assay procedure used to quantitate the plasma samples. They have not provided proper assay validation data. They should provide the various standard curve values for all the different runs. They should also calculate the accuracy and precision of the assay and should indicate the sensitivity of the assay as validated in their laboratory.

3) The firm has indicated that comparative dissolution data is not necessary for this application since USP states that liquid filled soft gelatin capsules are exempt from any dissolution and disintegration requirements. However the firm should consult with the Division of Biopharmaceutics to discuss the need for a in vitro quality control test.

In case the firm resubmits this NDA. The above mentioned data should be included for review.

/S/ 4/11/88

Anita Shah, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed by John P. Hunt 4/11/88
FT Initialed by C.T. Viswanathan, Ph.D CTV 4/11/88

cc: NDA 19-781 Orig., HFN-810, HFN-226(A. Shah), HFN-344(Turner), Drug, Chron and FOI files

AS:1/4:3143X:1_14_88

Attachment 1

UTROGESTAN

Besins Pharmaceuticals, Inc.

A. Pharmacokinetic Study Summary

Study	Treatment	Route	Dosage Form(s)	Study Design	Dose	Batch No.	Plant	No. of Subjects
I	1	oral	capsule	Food effect	placebo	E-13412	Scherer-Clearwater	15
	2			3-way	200mg/Fast	E-13401		
	3			cross-over	200mg/Food	E-13401		
				open-label				
II	1	oral	capsule	Dose-Ranging	100 mg	E-13401	Scherer-Clearwater	15
	2			3-way	200 mg	E-13401		
	3			cross-over	300 mg	E-13401		
				open-label				
III	1	oral	capsule	Bioavail.	200 mg	E-13041	Scherer-Clearwater	15
	2	vs	vs	comparison	vs			
		IM	injection	2-way	50 mg	300-7400	Rugby Corp.	
				cross-over				
				open-label				