CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-756

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ORIGINAL

MAY 13 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA: 20-756

Compound: Crinone™ (progesterone gel)

Submission Dates: 11/13/96
4/14/97 (Supplement BL)

Sponsor: Columbia Research Laboratories, Inc.

Type of Submission: Original NDA

Code: 3P

Reviewer: K. Gary Barnette, Ph.D.

I. SYNOPSIS

NDA 20-756 for Crinone™ (8% progesterone gel for vaginal administration), was submitted by Columbia Research Laboratories, Inc. on November 13, 1996. The progesterone in Crinone™ is identical to endogenous progesterone and the proposed indication is progesterone supplementation or replacement as part of assisted reproductive technologies (ART) treatment for infertile women with documented progesterone deficiency. The proposed dose of Crinone™ for the indication sought herein is 90 mg (8% vaginal gel) once (QD) or twice daily (BID).

The submission to NDA 20-756 crossreferences the pharmacokinetic and pharmacodynamic studies that were submitted to NDA 20-701 on July 31, 1996, Crinone™ (4% and 8% progesterone gels for vaginal administration) for the indication of treatment of secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, currently under review by the Division of Reproductive and Urologic Drug Products (HFD-580).

Seven pharmacokinetic (PK) studies were submitted to NDA 20-701 for review, five of these studies are considered pivotal for the approval of Crinone™ for use in ART. The single dose relative bioavailability (BA) of Crinone™ vaginal administration compared to IM administration of progesterone was assessed in Study 006112. A comparative BA study (Study 005323) assessing single dose and multiple daily dosing of Crinone™ administered vaginally versus micronized progesterone capsules administered vaginally and orally was conducted. Two additional multiple dose studies were conducted to assess the PK of Crinone™ 90 mg (8% gel) after daily and twice daily administration (Studies COL1620-001US and COL1620-002US, respectively). The effect of sexual intercourse on the pharmacokinetics of Crinone™ (4% and 8%) was assessed in Study COL1620-003US.

One study (QCL/101) is a multiple dose PK study with dosing every other day. Since every other day dosing is not sought in NDA 20-756, Study QCL/101 is not pivotal to the approval of Crinone™ for the indication sought in NDA 20-756. An additional comparative bioavailability study (Study COL1620-F03) was conducted. However, in a telecon on May 2, 1997 it was stated by Dr. Howard Levine, Columbia Research, that the analysis of progesterone concentrations in Study F03 was suspect and limited confidence exists in these data and this study was repeated and submitted as Study Inveresk 005323. Therefore, the results of Study COL1620-F03 are included as supportive.

Three additional studies were submitted as supportive information to NDA 20-756. Study .010129 was conducted to assess the absorption of Crinone™ in the penis. Therefore, assessing the safety issues surrounding absorption of progesterone through the penis during intercourse. Study COL1620-F04 was conducted in estrogenised women suffering from premature ovarian failure to evaluate the effects on the

endometrium and serum hormone levels and Study COL1620-B01 was conducted in postmenopausal women and is used only as supportive safety information.

Additional *In vitro* dissolution data was submitted to NDA 20-701 on February 17, 1997 and to NDA 20-756 on April 14, 1997 for review and validation information of two different progesterone assays were also included.

A submission to NDA 20-756 by facsimile from the sponsor, dated May 8, 1997 provided pivotal *in vitro* release rate equivalence data to support a manufacturing site change and is included herein.

II. RECOMMENDATION

NDA 20-756 submitted on November 13, 1996 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the sponsor has provided appropriate information to satisfy the clinical pharmacology and biopharmaceutic regulations outlined in 21 CFR 320.

The Recommendation should be communicated to the sponsor as appropriate.

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

RD initialed by John Hunt, Deputy Division Director
FT signed by John Hunt, Deputy Division Director 5/13/97

cc: **NDA 20-756, HFD-580 (Bennett, Moore), HFD-870 (M.Chen 13B-17, Dorantes, Barnette), Drug file (CDR, Barbara Murphy)**

TABLE OF CONTENTS:

III. Background

Progesterone is a naturally occurring steroid that is the precursor in the biosynthesis of other steroids. Endogenous progesterone is synthesized in the ovary and adrenals and normal serum concentrations are in the range of ng/ml during the luteal phase of the menstrual cycle and <1 ng/ml during the follicular phase. The role that progesterone plays in pregnancy is in the development of decidual tissue, increasing endometrial receptivity for implantation of an embryo and maintenance of pregnancy. The progesterone included in Crinone™ is identical to endogenous progesterone. The chemical structure of progesterone is included below.

The primary role of exogenous progesterone in assisted reproduction is to increase the receptivity of the endometrium for implantation, thereby optimizing the opportunity for implantation and successful pregnancy.

Crinone™ is not marketed in any country. However, it has been approved for the indication sought herein (ART) in United Kingdom (6/95), France (7/95), Finland (11/95) and Ireland (9/96) and has been submitted for approval in Italy, Portugal, Greece, the Nordic Countries, Germany, Belgium and Switzerland.

IV. Formulation

The proposed to-be-marketed formulation of Crinone™ are included in Table 1.

Table 1. Proposed to-be-marketed Formulation of Crinone™

	Crinone™ 8%	
Active Ingredients	mg/1.125g dose	%w/w
Progesterone		
Glycerin		
Hydrogenated Palm Oil Glyceride		
Carbomer-934P		
Polycarbophil		
Sorbic Acid		
NaOH		
Purified Water		

Reviewer Comment:

1. *It should be noted that the to-be-marketed formulation of Crinone™ was used in studies [redacted] 010129, [redacted] 006112, [redacted] 005323, 001US, 002US, and 003US. However, the formulation used in Studies QCL/101, F03, F04, and B01 were not the to-be-marketed formulation, since [redacted] mg was added to the formulation (batches 20B, 20F and 20F2) used in these studies.*

2. *The formulation used in the pivotal clinical trials was the to-be-marketed formulation of Crinone™. However, the manufacturer of the formulations used in the pivotal clinical trial was 3M. The proposed commercial manufacturer of Crinone™ is Fleet.*

V. Analytical Methodology

Serum progesterone levels after administration of Crinone™ were determined with commercially available kits. The validation of the used in each of the pivotal pharmacokinetic studies is included in Table 2. The specificity (cross reactivity) of the kits used herein is presented in Table 3.

Table 2.

Study(ies)	Biological Fluid	Kit Name	Manufacturer	LLQ (ng/ml)	Inter assay Precision (%)	Accuracy (%)
005323	serum					
006112	serum					
001US, 002US, 003US	serum					

Table 3.

Metabolite	Coat-a-Count	DSL-3400
Progesterone	100	100
Androstenediol	ND	ND
Corticosterone	0.4	0.35
Cortisol	ND	ND
Danzol	ND	ND
11-Deoxycorticosterone	1.7	0.88
11-Deoxycorticol	2.4	0.27
20α-Dyhydroprogesterone	2.0	0.35
Estradiol	ND	ND
17α-Hydroxyprogesterone	0.3	0.88
Medroxyprogesterone	ND	0.88
Pregnane	ND	NM
5β-Pregnan-3α-ol-20-one	0.2	ND
5α-Pregnan-3,20-dione	0.8	5.0
5β-Pregnan-3,20-dione	1.3	0.88
Pregnenolone	ND	ND
Testosterone	ND	ND
6β-Dihydroprogesterone	NM	NM
16α-Hydroxyprogesterone	NM	NM
5β-Dihydroprogesterone	NM	NM
17β-Hydroxyprogesterone	NM	NM

ND = not detected; NM = not measured

In Study 005323, where the relative bioavailability of Crinone™ with orally administered micronized progesterone was assessed, the serum samples were analyzed by the as described above and by a method. The use of the critical due to differences in the serum progesterone concentration versus time profiles after oral administration between methods.

The validation of the assay used in Study 005323 is included in Table 4.

Table 4. Assay Validation

LLQ	0.25 ng/ml		
Target Concentration	[redacted] ng/ml	[redacted] ng/ml	[redacted] ng/ml
Intra-assay Accuracy (%)			
Intra-assay Precision (% CV)			
Inter-assay Accuracy (%)			
Inter-assay Precision (%CV)			

Reviewer Comment:

1. *The assay methodology used appears acceptable.*

2. *For further comment and review of Study 005323, see the* ***Pharmacokinetic*** *section,* ***Bioavailability*** *subsection page XX or the specific review of Study 005323,* ***Attachment 2****, page XX.*

VI. *In Vitro* Dissolution/Drug Release Testing

The dissolution method proposed by the sponsor for the quality control and release of drug product is as follows;

Apparatus:	USP Apparatus 1
Medium:	methanol/distilled water: 20/80
Volume:	1000 ml
Rotation Speed:	100 rpm
Temperature:	37°C ± 0.5°C

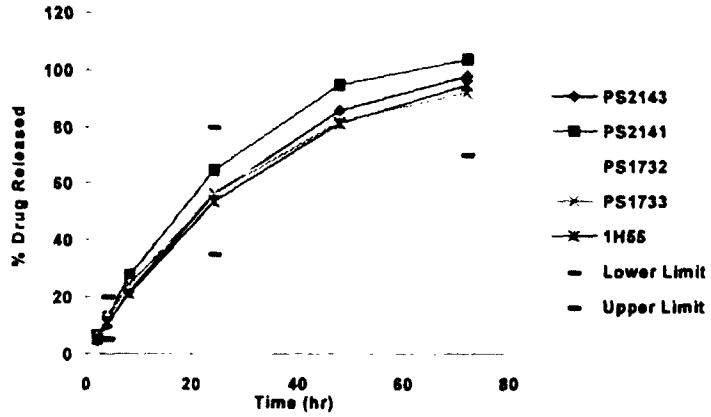
Proposed Specifications:

Time (hours)	% Label Claim
	5-20
	35-80
	>70

It should be noted that the proposed specifications are derived from the range of drug release observations at 4, 24 and 72 hours from the batches used in the pivotal clinical and pharmacokinetic trials after various shelf-lives (0, 6, 9, 12, 18, 24, 30 and 36 months).

The mean *in vitro* drug release profiles of the biobatches are included in Figure 1.

Figure 1.



It should be noted that the data represented in Figure 1 is from samples at various times after production (shelf-life), from 0 to 36 months.

The membrane (disk) is placed on a scale and weighed. "One drop" of the gel is then placed in the center of the membrane with a syringe and the weight of gel must be 100 mg ± 2%. The membrane is then affixed to the basket and placed in the dissolution medium.

Reviewer Comments:
The proposed in vitro drug release specifications were established by taking the range of drug release (% label claim) from the proposed to-be-marketed formulation of Crinone™ used in the pivotal clinical trials. Due to high variability in drug release profiles, the proposed release specifications are very wide (see below). However, in a telecon with Dr. Howard Levine, Columbia Labs on May 13, 1997 it was stated that the variability in in vitro drug release is inherent in the gel and not due to variability in surface area of the 100 mg sample of Crinone™.

VII. Pharmacokinetics

A summary of the pharmacokinetic and pharmacodynamic/safety studies submitted to support the approval of Crinone™ is included in Table 5 and a detailed description of these studies is included in Attachment XX.

Table 5. Study Summary

Study #	Study Design	Dosing	Subjects	Pg#
PIVOTAL PHARMACOKINETIC STUDIES				
Inveresk 006112	RELATIVE BIOAVAILABILITY: Single-dose, crossover, open-label randomized, parallel	COL1620 45 mg (4%), Progesterone in Oil 45 mg COL1620 90 mg (8%), Progesterone in Oil 90 mg	10 ♀ 10 ♀	22
Inveresk 005323	RELATIVE BIOAVAILABILITY: Single dose, open-label, parallel, randomized	COL1620 90 mg (8%) Utrogestan® (vaginal) 100 mg Utrogestan® (oral) 100 mg	6 ♀ 6 ♀ 6 ♀	25
COL1620-001US	DOSE PROPORTIONALITY: Multiple dose, single dose, partially randomized, parallel, open-label	COL1620 45 mg (4%) QD, QOD, 45 mg COL1620 90 mg (8%) QD, QOD, 90 mg COL1620 180 mg QD, QOD, 180 mg	21 ♀ 21 ♀ 21 ♀	28
COL1620-002US	MULTIPLE DOSE PK: Multiple dose, open-label	COL1620 90 mg BID	10 ♀	31
COL1620-003US	EFFECT OF INTERCOURSE: Multiple dose, open-label, randomized.	COL1620 45 mg (4%) QOD x 6 doses COL1620 90 mg (%8) QOD x 6 doses	10 ♂ 10 ♂	33
SUPPORTIVE STUDIES (Pharmacokinetic and Pharmacodynamic/Safety)				
COL1620-F03	RELATIVE BIOAVAILABILITY: Single and multiple dose, open-label, randomized crossover	COL1620 90 mg (8%), 90 mg QD Utrogestan® (vaginal) 100 mg, 300 mg QD Utrogestan® (oral) 100 mg, 300 mg QD	7 ♀ 7 ♀ 7 ♀	36
QCL/101	DOSE PROPORTIONALITY: Multiple Dose, open-label, randomized, parallel	COL1620 45 mg (4%) QOD x 6 doses COL1620 90 mg (8%) QOD x 6 doses COL1620 180 mg QOD x 6 doses	15 ♀ 15 ♀ 15 ♀	39
Inveresk 010129	BIOAVAILABILITY IN PENIS: Single Dose	COL1620 90 mg (8%)	10 ♀	42
COL1620-F04	DOSE RANGING PD/SAFETY: Multiple dose, double blind, randomized, parallel	COL1620 45 mg (4%) QOD x 7 doses COL1620 90 mg (%8) QOD x 7 doses COL1620 180 mg QOD x 7 doses	7 ♀ 8 ♀ 7 ♀	44
COL1620-B01	DOSE RANGING PD/SAFETY: Multiple dose, randomized, double blind, parallel	COL1620 45 mg (4%) QOD x 6 doses COL1620 90 mg (%8) QOD x 6 doses COL1620 180 mg QOD x 6 doses	6 ♀ 6 ♀ 6 ♀	47

A. Single Dose

The pharmacokinetic parameters from each pivotal study where single dose pharmacokinetics was assessed are included in Table 6.

Table 6.

Study	Dose (mg)	n	AUC(0-t) (ng*h/ml)	AUC/dose (ng*h/ml/mg)	Cmax (ng/ml)	Cmax/dose (ng/ml/mg)	Tmax (h)	t½ (h)
005323	90	6	208.1±55.3	-----	10 3±1 4	-----	8.3±2.9	17.2±6.3
006112	45	10	303.9±291.4	-----	13.2±6.5	-----	5.6±1.8	na
	90	10	296.8±129.9	-----	14 9±6.3	-----	6.8±3 3	na
001US	45	10	162.1±70.9	3.60±1.58	8.6±3.3	0.19±0.07	6 (4 - 8 1)	30.7±10.0
	90	10	287 4±115.4	3.19±1.28	11.2±4.1	0 12±0.05	6 (1 5 - 12)	41.1±9.8
	180	10	316 4±171.5	1 76±0.95	13.4±6.1	0.07±0.03	7 (4 1 - 12)	33.5±26 5

AUC(0-t) = 0-96 hrs for studies 005323, 006112 and 001US.

Reviewer Comment:

1. *The proposed dose of Crinone™ for the indication of assisted reproductive technologies treatment is daily or twice daily administration of 90 mg (8% vaginal gel).*

2. *Since approval of only the 90 mg dose of Crinone™ is being sought for the indication of use in assisted reproductive technologies, the dose proportionality information gained from Study COL1620-001US provides no significant information to support approval of NDA 20-756.*

3. *A between study comparison indicates that the AUC and Cmax values after 90 mg doses in Studies 006112 and 001US are very similar (no statistical methods were applied).*

B. Multiple Dose

The multiple dose pharmacokinetic parameters from Studies 001US and 002US are included in Table 7.

Table 7.

Study	Dose (mg)	n	AUC (ng*h/ml)	Cmax (ng/ml)	Tmax (h)	t½ (h)
DAILY DOSING (QD)						
001US	90	10	212 ± 83	16.0 ± 5.05	6 (4 - 6)	45.0 ± 34.7
TWICE A DAY DOSING (BID)						
002US	90	10	139 ± 41	14.6 ± 4.49	3.55 ± 2.48	25.9 ± 6 15

The AUC reported here is 0-τ , 24 hours for Study 001US and 12 hours in Study 002US.

Reviewer Comments:

1. *The recommended initial dose of Crinone™ is 90 mg (8% gel formulation) daily. If the patient does not respond to the daily dose, twice a day dosing is recommended.*

2. *Since in both studies reported in Table 7, steady state PK was assessed, it is unclear why a between study comparison of the AUC0-τ , Tmax and t½ indicate a great difference.*

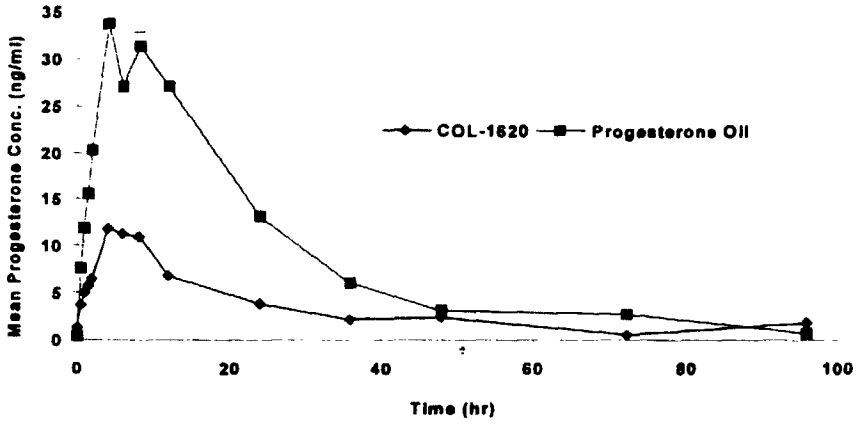
C. Bioavailability

The relative bioavailability of a single 90 mg dose of Crinone™ (8% vaginal gel) and a single 90 mg intramuscular (IM) administration of progesterone was assessed in Study 006112. The pharmacokinetic parameters from this study are included in Table 8. The serum progesterone concentration versus time profiles of these routes of administration are included in Figure 2.

Table 8.

	Crinone™ (8%)	Progesterone (IM)
AUC0-96 (ng*h/ml)	296.78 ± 129.90	1378.91 ± 176.39
f (%)	20	
Cmax (ng/ml)	14.87 ± 6.32	53.76 ± 14.88
Tmax (h)	6 8 ± 3.3	9.2 ± 2 7

Figure 2



An additional pivotal study (Studies 005323) was conducted to assess the single dose bioavailability of 90 mg Crinone™ (8%) and orally administered 100 mg micronized progesterone tablet and vaginally administered 100 mg micronized progesterone tablet. The pharmacokinetic parameters from this study are included in Table 9.

Table 9. Mean (± SD) Progesterone Pharmacokinetic Parameters (samples analyzed at Cephac)

	COL-1620 (vaginal)	Utrogestan® (oral)	Utrogestan® (vaginal)
Cmax (nmol/ml)	32.0±4.2	61.7±44.0	21.6±5.3
Tmax (h)	8.3±2.9	9.0±7.1	1.8±1.2
AUC0-t (nmol*h/ml)	584.1±106.8	309.6±132.6	666.7±361.5
ke (1/h)	0.045±0.019	0.027±0.006	0.050±0.014
t½ (h)	17.2±6.3	26.5±5.7	14.6±3.9
ka (1/h)	4.73±0.77	0.65±0.35	3.60±0.75

* normalized to 100 mg dose

The progesterone concentrations used to generate the pharmacokinetic parameters in Table 9 are from It should be noted that the samples from Study 005323 (single dose) were also estimated by The mean ± standard deviation AUC0-t from each assay are included in Table 10. The serum progesterone concentration versus time profiles of the 90 mg vaginal dose of Crinone™ (8%) and the 100 mg oral dose of micronized progesterone as estimated by are included in Figures 3 and 4, respectively.

Table 10.

COL-1620 Vaginal (90 mg)	584.1 ± 106.8	480.4 ± 86.4
Utrogestan Oral (100 mg)	309.6 ± 132.6	20.3 ± 33.4
Utrogestan Vaginal (100 mg)	666.7 ± 361.5	765.7 ± 418.2

Figure 3 Analytical Method

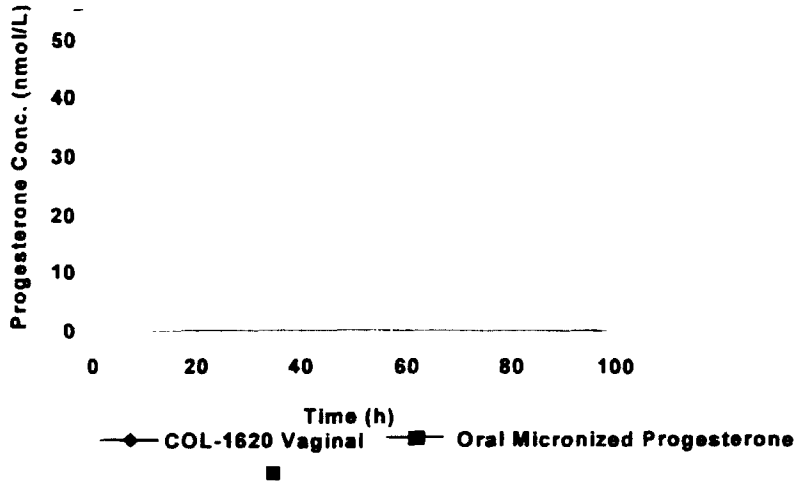
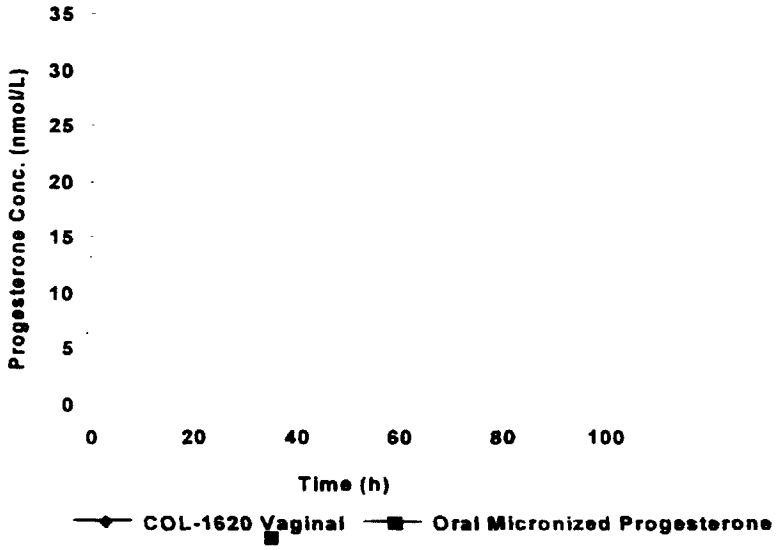


Figure 4. Analytical Method



Reviewer Comments:

1. *The relative bioavailability of Crinone™ compared to intramuscular progesterone is approximately 20%.*

2. *The data from Study 005323 indicate that the mean (±SD) relative bioavailability of oral progesterone as measured by is % of that estimated by It is likely that there is a metabolite(s) of progesterone that is formed during first pass metabolism that cross-reacts with the method.*

3. *These data also indicate that the dose normalized mean (± SD) relative bioavailability of orally administered progesterone is % compared to progesterone from Crinone™ as measured by*

D. Bioequivalence

The to-be-marketed formulation of Crinone™ (8%) was used in the pivotal clinical trials (studies not submitted to OCPB/DPE II for review). However, the manufacturer of the clinically tested formulation (was not the

proposed commercial manufacturer For a manufacturing site change of a semi-solid dosage form without changes in the manufacturing process and equipment, *in vitro* release equivalence data are required. Therefore, it was recommended that the sponsor conduct appropriate *in vitro* testing to compare the proposed to-be-marketed formulation of Crinone™ manufactured at (proposed commercial manufacturer) to the proposed to-be-marketed formulation of Crinone™ manufactured at manufacturer of the clinically tested batches). For equivalence assessment, the median *in vitro* release rate of the product manufactured by (average of estimated slope from each cell) should be within the limits defined by the 90% confidence interval that is obtained from *in vitro* release data for the product made at This recommendation was communicated to the sponsor in a telecon on May 2, 1997 between this reviewer and Dr. Howard Levine, Columbia Research.

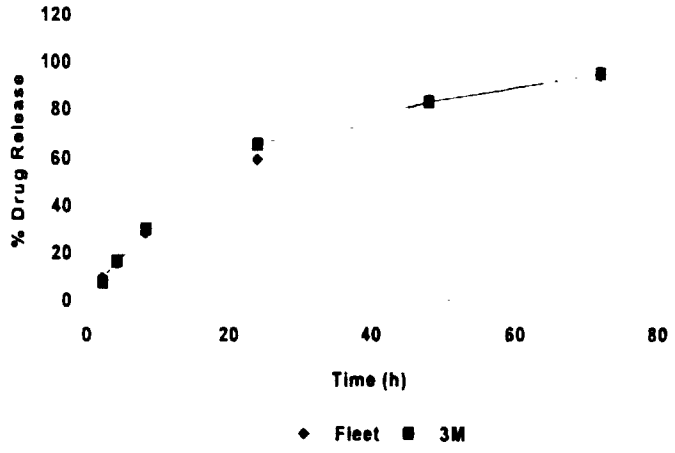
The sponsor submitted *in vitro* drug release data from batch PS2141 (n = 6), the batch most predominantly used in the pivotal clinical trials and a batch manufactured at (batch #3070585, n = 24) in a facsimile dated May 8, 1997.

The equivalence of the drug release between the clinical manufacturer and the proposed commercial manufacturer was tested by the following method. Release rates (slope of % drug released versus time) of each sample were calculated by taking the slope of % drug released versus time. The ratios of release rate of each commercial sample (n = 24) versus the release rate of each sample from the clinically tested batches (n = 6) were calculated. The resulting 144 ratios were rank ordered lowest to highest and according to Dr. Don Shiurmman, Division of Biometrics, FDA, the nonparametric 90% confidence interval on 6 vs. 24 samples can be calculated by using the 40th and 105th ordered samples. If the ratio in the rank order at the 40th position is greater than 75% and that at the 105th ordered position is less than 133.33% then equivalence between these two batches based on *in vitro* drug release profiles has been established.

After ordering the ratios of release rates, it was determined that the 40th ratio was 89.3% and the 105th ratio was 112.6%.

The mean drug release profiles of the batches used in the assessment of *in vitro* drug release equivalence are included in Figure 5.

Figure 5



Reviewer Comments:

1. *The proposed to-be-marketed formulation manufactured at the proposed commercial manufacturer was used in Study COL1620-002US, a multiple dose (twice a day) PK study. It should be noted that this is the only pharmacokinetic study in which twice a day dosing was used. Therefore, a between study comparison of the pharmacokinetic is not possible.*

2. *Since the 40th and 105th ordered ratios are 89.3% and 112.6%, respectively, it is concluded that equivalence has been established between the manufacturer of the clinically tested batches* [redacted] *and the proposed commercial manufacturer* [redacted].

E. Metabolism

The metabolism of progesterone delivered from Crinone™ is similar to that of endogenous progesterone. It should be noted that comparing the pharmacokinetics of progesterone after oral administration of micronized progesterone and the vaginal administration indicated that vaginal administration circumvents first pass metabolism of progesterone.

F. Protein Binding

The protein binding of progesterone delivered from Crinone™ in serum is similar to endogenous progesterone. It is reported that progesterone is approximately 96% bound to serum proteins and primarily to serum albumin (≈80%) and corticosteroid binding globulin (≈17%) and not appreciably bound to serum hormone binding globulin (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th ed., McGraw-Hill, New York, 1996, chapter 57, p 1429)

G. Special Populations

The pharmacokinetics of Crinone™ has not been assessed in subjects with renal or hepatic dysfunction or pediatric subjects.

H. Drug Interactions

No drug interactions have been assessed with Crinone™. However, potential drug interactions with progestins (progesterone and synthetic progestins), as reported by the sponsor are included in Table 11.

Table 11.

Precipitant Drug	Object Drug	Effect	Description
Aminoglutethimide	Medroxyprogesterone	↓ serum levels	unknown
Ethytoin, Mephenytoin, Phenytoin	Progestins	↓ serum levels	Induction of metabolism
Rifampin	Progestins	↓ serum levels	Induction of metabolism

Additionally, Crinone™ should be contraindicated with other vaginal therapy of any kind.

VIII. Pharmacodynamics/Safety

In Study COL1620-F04 a pharmacodynamic assessment of endometrial thickness in 20 subjects (23 enrolled) with premature ovarian failure receiving 45, 90 or 180 mg doses of Crinone™ was conducted. The mean (± SD) thickness of the endometria at Days 0 (pre-dose), 13 (estradiol only) and 24 (estradiol + progesterone) are included in Table 12 and intended to be illustrative of the changes (or lack thereof) in the endometria after estradiol alone treatment and estradiol plus progesterone (COL-1620). Additionally, histological evaluation of endometrial biopsy specimen were obtained on Day 24 from 21 subjects (23 enrolled) indicated that all 21 subjects had endometria characteristic of the secretory phase of the menstrual cycle.

Table 12. Mean±SD Endometrial Thickness (MM)

Dose	Day 0	Day 13 (Estraderm)	Day 24 (Estraderm + COL-1620)
45 mg (n=7)	3.8 ± 4.4	8.5 ± 1.8	7.2 ± 1.3
90 mg (n=7)	1.5 ± 0.8	8.6 ± 2.4	6.1 ± 1
180 mg (n=6)	3.4 ± 3.1	6.6 ± 2.1	5.6 ± 2

Reviewer Comments:

1. *Vaginal application of COL-1620 at doses ranging from mg/dose every other day given concurrently with exogenous estrogen from day 15 to 27 induced a secretory transformation of all the endometrial biopsy specimens obtained on Day 24.*

2. *Although it is possible that the vaginally administered progesterone doses result in therapeutic levels of progesterone in the endometrium while not resulting in systemic progesterone levels, actual data illustrating this has not been submitted for review. Additionally, the clinical significance of this is unknown.*

IX. Labeling

Attachment 1 includes the sponsor's proposed labeling.

Reviewer Comments:

The **CLINICAL PHARMACOLOGY** section of the product label should be changed to the following text. The strike out text should be removed from the proposed label, the double underlined text are recommended additions to the proposed label and the small print are recommendations for the additions of tables to illustrate the pharmacokinetics of Crinone™.

Redacted 7

pages of trade

secret and/or

confidential

commercial

information

XI. Attachment 2 - Pivotal Pharmacokinetic Study Summaries

Study Number: 006112

Title: A comparative study of progesterone following the administration of two formulations to healthy postmenopausal female volunteers.

Objectives: To compare the pharmacokinetics of single doses of COL-1620 (4%, 45 mg and 8%, 90 mg) intravaginally and 45 and 90 mg progesterone in oil intramuscularly on 2 separate occasions.

Study Design: This was an open label, randomized, crossover study in healthy postmenopausal females.

Patients: Twenty healthy postmenopausal females were enrolled.

Formulation: The COL-1620 (4 and 8%) formulation used in this study are the to-be-marketed formulation. However, the manufacturer of this formulation [redacted] was not the proposed commercial manufacturer

Blood Collection: Samples were collected at 0 (predose), 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hours post-dose.

Analytical Methods: The assay methodology and validation are submitted for review.

Results

Pharmacokinetics

The mean (± SD) pharmacokinetic parameters and the relative bioavailability (f). The relative bioavailability was calculated by the ratio of AUC0-96 after administration of COL-1620 and AUC0-96 after IM administration of Progesterone oil.

Table 13.

	45 mg Doses		90 mg Doses	
	COL-1620	Progesterone (IM)	COL-1620	Progesterone (IM)
AUC0-24 (ng*h/ml)	173.66 ± 108.68	552.57 ± 128.94	208.88 ± 102.87	897.77 ± 187.77
AUC0-48 (ng*h/ml)	237.98 ± 186.83	723.75 ± 107.51	257.66 ± 120.09	1224.11 ± 175.12
AUC0-96 (ng*h/ml)	303.86 ± 291.38	839.31 ± 115.37	296.78 ± 129.90	1378.91 ± 176.39
f (%)	0.28		0.20	
Cmax (ng/ml)	13.15 ± 6.49	39.06 ± 13.68	14.87 ± 6.32	53.76 ± 14.88
Tmax (h)	5.6 ± 1.8	8.2 ± 6.4	6.8 ± 3.3	9.2 ± 2.7

The mean serum progesterone versus time profiles of the 45 mg progesterone doses of COL-1620 and IM progesterone oil are illustrated in Figure 6. Similarly, the 90 mg progesterone dose profiles are presented in Figure 7.

The mean serum progesterone versus time profiles of the 45 and 90 mg doses of the proposed to-be-marketed formulations of COL-1620 are illustrated in Figure 8.

Figure 6. 45 mg Progesterone Dose

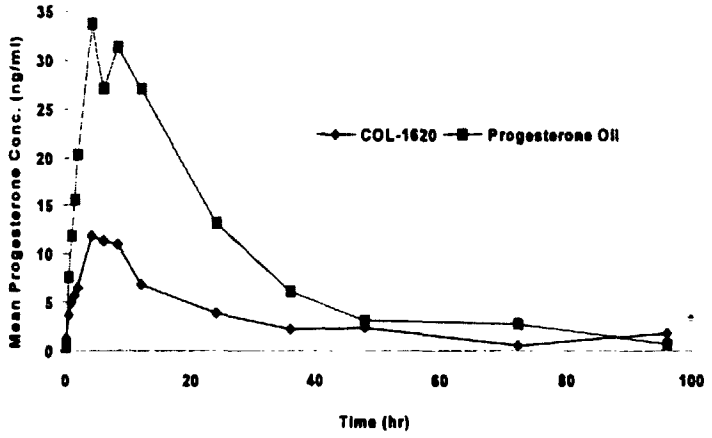


Figure 7. 90 mg Progesterone Dose

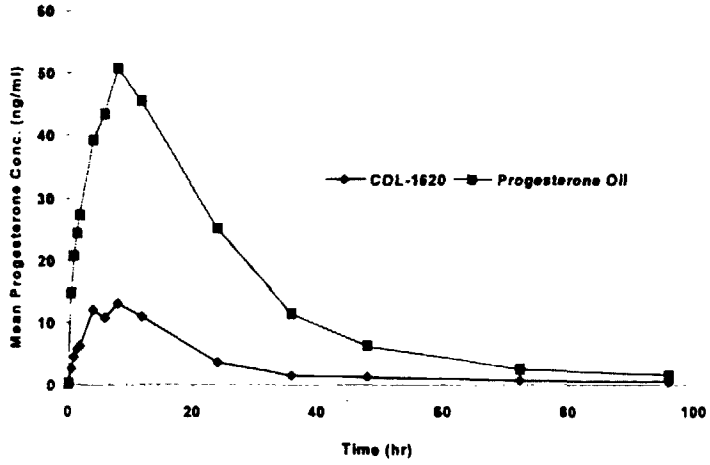
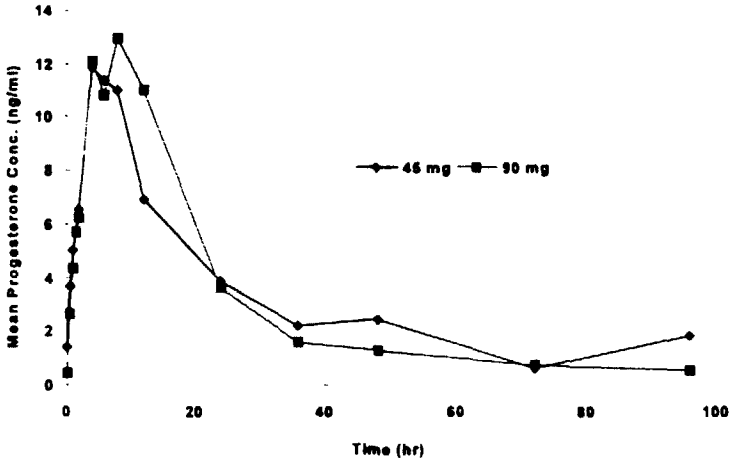


Figure 8. COL-1620 45 and 90 mg Progesterone Doses



Sponsor's Conclusion

1. Systemic plasma pharmacokinetic parameters demonstrated greater mean Cmax and mean AUC0-t with progesterone in oil injection when compared to the equivalent dose of COL-1620.

2. There was no statistically significant difference in mean Tmax at either dose level between the two formulations.

3. No clinically significant differences were noted between the two treatments at both doses when vital signs, ECGs, urinalysis, clinical chemistry, hematology and adverse events were monitored.

Reviewer Comments:

1. The methodology and validation of the assay used in this study are not submitted. Therefore, the confidence one can have in these data is limited.

2. I concur with the sponsor's conclusions.

3. Not only does dose proportionality not exist between the 45 and 90 mg doses of the proposed to-be-marketed COL-1620 formulations, there doesn't appear to be any statistically significant differences in AUC and Cmax between these dosage strengths.

Study Number: 005323

Title: A comparative study of progesterone following administration of two formulations to healthy postmenopausal female volunteers.

Objectives: To compare the pharmacokinetic profile and bioavailability of Crinone™ (progesterone vaginal gel) and Utrogestan® capsules (vaginal and oral).

Study Design: This was an open, randomized, parallel group study.

Patients: Eighteen normal healthy postmenopausal female volunteers were enrolled. The mean (SD) age (years), height (cm) and weight (kg) of the enrolled subjects were 53.7 (4.7), 159.7 (5.0) and 67.4 (11.1), respectively.

Formulation: The to-be-marketed 90 mg (8%) formulation of Crinone™ gel was used in this study. However, the manufacturer of the formulation used herein ([redacted]) is not the proposed commercial manufacturer [redacted]

Blood Collection: Samples for analysis of progesterone were collected 0 (predose), 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 72 and 96 h post dose.

Analytical Methods: The methodology and validation of the assay used to estimate serum progesterone levels are not presented for review.

Each serum sample (reference and test) was also assay by using . The validation of the assay used herein is included in Table 14.

Table 14 Assay Validation

LLQ	0.25 ng/ml		
Target Concentration	[redacted] ng/ml	[redacted] ng/ml	[redacted] ng/ml
Intra-assay Accuracy (%)			
Intra-assay Precision (% CV)			
Inter-assay Accuracy (%)			
Inter-assay Precision (%CV)			

Pharmacokinetic Methods:

Model-Independent Analysis

Pre-dose levels of progesterone were subtracted from post-dose levels of progesterone to account for endogenous levels. "Negative" progesterone levels (post-dose) were set to zero as indistinguishable from background. The pharmacokinetic parameters were generated from this analysis by the following methods;

Cmax and Tmax - data inspection
Elimination rate constant - linear least-squares regression of ln-transformed
AUC0-96 and AUC∞ - linear-trapezoidal method.

Model-Dependent Analysis

A two-compartment kinetic model was fit to the non-baseline corrected progesterone data and various rate constants (ka or k0*dose, k12, k21 and k10), apparent volume of distribution (Vd) and the baseline progesterone concentration (Cb).

Results

Pharmacokinetics

The pharmacokinetic parameters estimated from the assay methodology are included in Table 15.

Table 15. Pharmacokinetic Parameters by Method

Subject #	Cmax (nmol/L)	Tmax (h)	AUCt (nmol*h/L)	ke (h-1)	t½ (h)	ka (h-1)	k10 (h-1)	Vc (L)	Cb (nmol/L)
COL-1620 Vaginal (90 mg)	32 0±4 2	8.3±2 9	584 1±106 8	0 045±0 019	17 2±6.3	4 73±0 77	0 14±0.05	0 40±0 07	0 38±0 50
Utrogestan Vaginal (100 mg)	21 6±5 3	9.0±7 1	666 7±361 5	0.050±0 014	14 6±3 9	3.60±0 75	0 19±0.11	0 51±0 20	1 93±4 15
Utrogestan Oral (100 mg)	61 7±44 0	1.8±1 2	309 6±132.6	0 027±0.006	26.5±5.7	0.65±0.35	0 23±0 14	1 64±1.36	0 63±0 28

The serum samples were estimated by assay methods. The area under the serum concentration (AUC) of progesterone versus time profiles are included in Table 16.

Table 16.

	Subject #		
Utrogestan Oral (100 mg)	Mean ± SD	309.6 ± 132.6	20.3 ± 33 4
Utrogestan Vaginal (100 mg)	Mean ± SD	666.7 ± 361.5	765 7 ± 418 2
COL-1620 Vaginal (90 mg)	Mean ± SD	584 1 ± 106 8	480 4 ± 86 4

Figures 9 and 10 contain the progesterone concentration profiles as measured by the assay methods, respectively.

Figure 9 Mean (+ SD) Progesterone Levels: Method

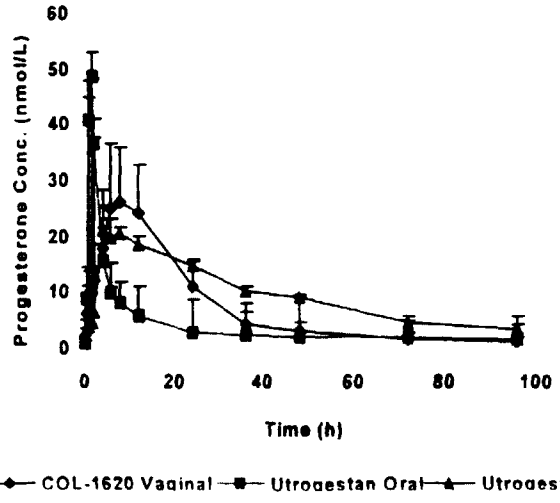
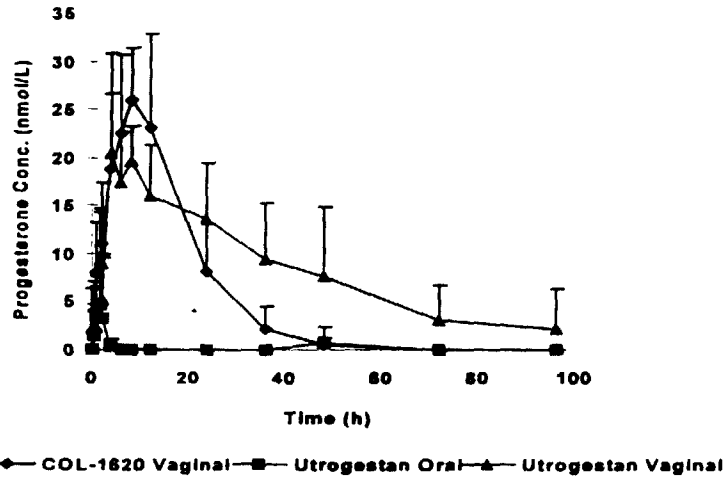


Figure 10. Mean (+ SD) Progesterone Levels: Method



Since 100 mg doses of Utrogestan (orally and vaginally) and only a 90 mg dose COL-1620 were used, dose normalized AUC from the Utrogestan given vaginally and COL-1620 given vaginally (estimated by are included in Table 17.

Table 17.

	AUC (ng*h/ml per mg dose)
Utrogestan vaginal	7.66 ± 4.18
COL-1620 vaginal	5.34 ± 0.96

Sponsor's Conclusions

1. With the assay methodology, the progesterone levels after oral administration were much less than either vaginal product.

2. COL1620 appeared to result in a faster absorption of progesterone than Utrogestan®, although the extent of absorption appeared to be similar between the two.

3. Utrogestan® vaginal formulation had at least six times more variability associated with Cmax and Tmax than COL1620. Thus, COL1620 may be associated with significant advantages in control of systemic progesterone concentrations as compared to intravaginal administration of Utrogestan®.

Reviewer Comments:

1. It appears from the results of this study that the method for estimating serum progesterone levels is not specific and the antibody used cross-reacts substantially with a hepatic metabolite of progesterone. Therefore, the assay should be used to more accurately estimate serum progesterone levels and pharmacokinetic parameters.

2. Due to the relatively high variability in the bioavailability of progesterone from the Utrogestan (100 mg) vaginal administration, the mean ± SD relative bioavailability of progesterone from the COL-1620 vaginal formulation compared the Utrogestan formulation is 111.12% ± 102.54 (range = %). From these data, it is concluded that the COL-1640 may provide a more consistent dose of progesterone compared to Utrogestan administered vaginally.

Study Number: COL1620-001US

Title: Pharmacokinetic Study of three dosage strengths of COL-1620 with natural progesterone.

Objectives: The primary objective was to assess the pharmacokinetic parameters of COL-1620 following single dose and following two different multiple dose regimens. The secondary goal of the trial was to determine the onset of steady-state with the multiple dose regimens.

Study Design: Partially randomized, open-label, controlled clinical study of three months in duration.

Subjects: A total of 62 post-menopausal subjects were randomized into one of three doses (45, 90 and 180 mg) progesterone gel. Sixty subjects completed the study ranging in age from . years.

Formulation: The formulation of COL1620 (8%) was not the proposed to-be-marketed formulation due to the use of Three doses of progesterone were administered 45 mg (COL1620 4%), 90 mg (COL1620 8%) and 180 mg (COL1620 8%).

Blood Collection: Samples for assessment of progesterone concentrations were collected at 0 (predose), 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72 and 96 h post-dose.

Analytical Methods:
The serum progesterone assays were performed by Using a commercially available *in vitro* solid-phase kit manufactured by The validation of the method is presented in Table 18

Table 18.

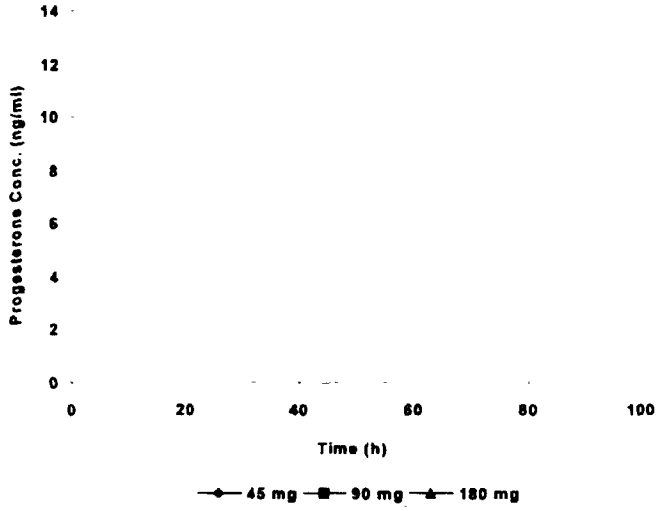
Sensitivity Limit	[redacted]ng/ml			
Accuracy	[redacted]%			
Target	LOW (≈1 ng/ml)	Medium (≈3 ng/ml)	High (≈15 ng/ml)	
Intraassay Precision (%CV)	[redacted]	[redacted]	[redacted]	
Interassay Precision (%CV)	[redacted]	[redacted]	[redacted]	
Specificity (% Cross reactivity)	Progesterone	100	17α-Hydroxyprogestone	3.4
	Androstenediol	ND	Medroxyprogesterone	0.3
	Corticosterone	0.9	Pregnane	ND
	Cortisol	0.03	5β-pregnan-3α-ol-20-one	0.05
	Danazol	0.006	5α-pregnan-3,20-dione	9
	11-Deoxycorticosterone	2.2	5β-pregnan-3,20-dione	3.2
	11-Deoxycortisol	0.01	Pregnenolone	0.1
	DHEA-SO_4	0.002	5-pregnan-3β-ol-20-one-sulfate	0.05
	20α-Dihydroprogesterone	0.2	Testosterone	0.1
	Estradiol	ND		

Results
Pharmacokinetics
The mean (± SD) pharmacokinetic parameters after single doses of 45, 90, 180 mg of COL-1620 are included in Table 19. The mean serum progesterone concentration versus time profiles after single vaginal doses of 45, 90 and 180 mg COL-1620 are illustrated in Figure 11.

Table 19. Single Dose Pharmacokinetic Parameters (mean ± SD, Tmax = median (range))

Dose	COL-1620, 45 mg	COL-1620, 90 mg	COL-1620, 180 mg
N	10	10	10
Tmax (h)	6 (4-8.1)	6 (1.5-12)	7.1 (4.1-12)
Cmax (ng/ml)	8.6 ± 3.3	11.2 ± 4.1	13.4 ± 6.1
Dose Norm. Cmax (ng/ml/ mg dose)	0.19 ± 0.07	0.12 ± 0.05	0.07 ± 0.03
AUC(0-t) (ng*h/ml)	162.1 ± 70.9	287.4 ± 115.4	316.4 ± 171.5
Dose Norm. AUC(0-t) (ng*h/ml/mg dose)	3.60 ± 1.58	3.19 ± 1.28	1.76 ± 0.95
T½ (h)	30.7 ± 10.0	41.1 ± 9.8	33.5 ± 26.5
Apparent Cl (L/h)	234 ± 111	288 ± 102	590 ± 239

Figure 11.



The mean progesterone concentration versus time profiles of the daily administration of 45, 90 and 180 mg multiple doses COL-1620 and administration of 45, 90 and 180 mg multiple doses of COL-1620 every other day are illustrated in Figures 12 and 13, respectively and the mean (± SD) pharmacokinetic parameters after multiple vaginal doses of 45, 90 and 180 mg COL-1620 administered by two dosage regimen, every day and every other day are included in Table 20.

Figure 12. Daily Administration of COL-1620

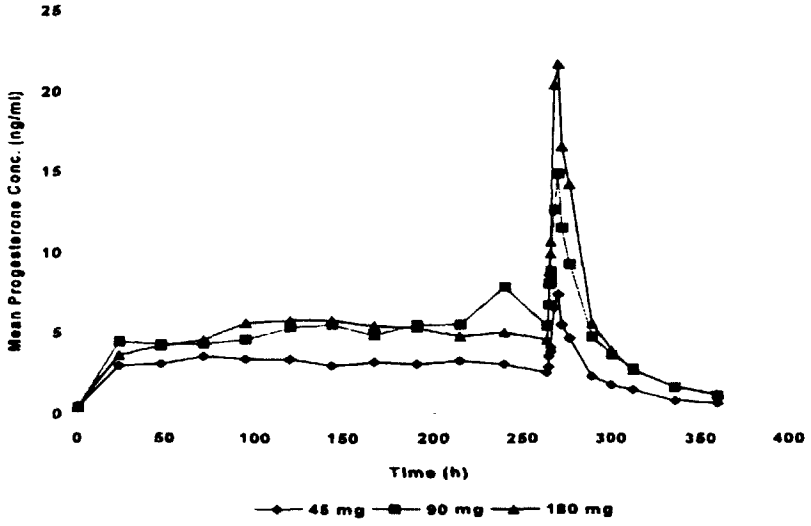


Figure 13. Administration of COL-1620 Every Other Day

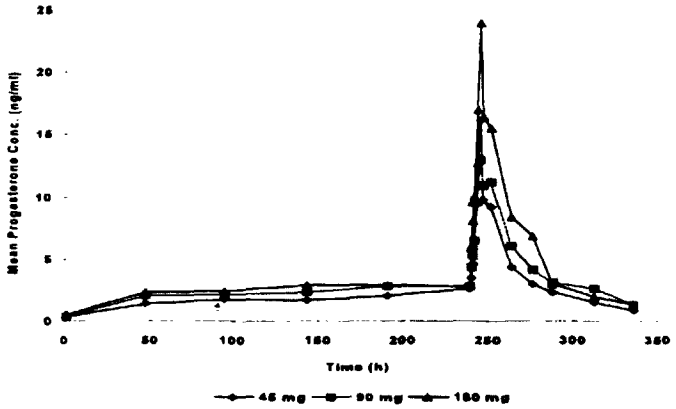


Table 20. Multiple Dose Pharmacokinetic Parameters (mean ± SD, Tmax = median (range))

Dose	COL-2620, 45 mg		COL-1620 90 mg		COL-1620 180 mg	
Dosing Regimen	Daily	Every other Day	Daily	Every other Day	Daily	Every other Day
N	10	10	10	10	10	10
Tmax (h)	6 (4-12)	6 (4-12)	6 (4-6)	6 (4-12)	6 (4-6)	6 (4-8)
Cmax (ng/ml)	7 72 ± 3.57	17.0 ± 15.0	16.0 ± 5.05	13.7 ± 3.58	22 7 ± 11.9	24.7 ± 17 4
Dose Norm. Cmax (ng/ml/mg dose)	0.172 ± 0.079	0.327 ± 0.224	0.177 ± 0.056	0.152 ± 0.040	0.126 ± 0.066	0.137 ± 0.096
Steady State AUCT (ng*h/ml)	104 ± 50	274 ± 297	212 ± 83	316 ± 136	297 ± 165	468 ± 360
Dose Norm. AUCT (ng*h/ml/mg dose)	2.31 ± 1.11	6.09 ± 6.59	2.36 ± 0.92	3.51 ± 1.51	3.30 ± 1 83	5.20 ± 4.00
T½ (h)	41 1 ± 19.4	47.4 ± 29.2	45.0 ± 34.7	39.1 ± 12.9	41 7 ± 20.7	51.1 ± 46.6
Cave Steady State (ng/ml)	4.44 ± 2.19	5.85 ± 6.28	8.99 ± 3.53	6.75 ± 2.82	12 8 ± 7 12	10.0 ± 7.84

Sponsor's Conclusion

1. The particular administration regimen selected (once daily versus once every other day) had little influence on systemic progesterone concentrations.

2. No significant changes in progesterone pharmacokinetic parameters were observed between single and multiple administration of COL-1620.

3. Under both single-dose and steady-state conditions, progesterone concentrations increased in proportion with the dose from mg; a further increase in dose (to 180 mg) resulted in less than proportional increases in systemic progesterone. It is likely that this disproportionality is due to specific characteristics of the formulation, and not to nonlinear systemic disposition of progesterone.

Reviewer Comments:

I concur with the sponsor's conclusions 1 and 2. However, since approval is sought only for the 90 mg dosage strength for use in ART the lack of dose proportionality between the 90 and 180 mg doses in not relevant for the approval of NDA 20-756.

Study Number: COL1620-002US

Title: Pharmacokinetic study of 90 mg strength of COL-1620 with natural progesterone, B.I.D. (Multiple-dose, open-label, single-center study)

Objectives: Assessment of pharmacokinetic parameters and steady-state levels of COL-1620, BID.

Study Design: This was an open-label, repeated-dose study. The study consisted of a 30-day screening period and a 12-day (23-dose) treatment period, with a follow-up evaluation conducted 4 days after the final dose.

Patients: Ten healthy, estrogenized, postmenopausal female subjects, ranging in age and weight from years (mean = 60) and 104 to 148 lbs. (mean=126) were enrolled.

Formulation: The to-be-marketed formulation of Crinone™ (8%) manufactured at the proposed commercial manufacturer was used in this study.

Blood Collection: Samples were collected prior to each dose (morning and evening) to assess steady-state and at 0 (predose), 0.5, 1.0, 1.5, 2, 4, 6, 8, 12,, 24, 36 ,48, 72 and 96 h after the last dose.

Analytical Methods: The serum progesterone assays were performed by Using a commercially available *in vitro* solid-phase kit manufactured by The validation of the method is presented in Table 21.

Table 21.

Sensitivity Limit	[redacted]ng/ml				
Accuracy	[redacted]%				
Target	LOW (≈1 ng/ml)		Medium (≈3 ng/ml)		High (≈15 ng/ml)
Intraassay Precision (%CV)	[redacted]		[redacted]		[redacted]
Interassay Precision (%CV)	[redacted]		[redacted]		[redacted]
Specificity (% Cross reactivity)	Progesterone	100	17α-Hydroxyprogestone	3.4	
	Androstenediol	ND	Medroxyprogesterone	0.3	
	Corticosterone	0.9	Pregnane	ND	
	Cortisol	0.03	5β-pregnan-3α-ol-20-one	0.05	
	Danazol	0.006	5α-pregnan-3,20-dione	9	
	11-Deoxycorticosterone	2.2	5β-pregnan-3,20-dione	3.2	
	11-Deoxycortisol	0.01	Pregnenolone	0.1	
	DHEA-SO4	0.002	5-pregnan-3β-ol-20-one-sulfate	0.05	
	20α-Dihydroprogesterone	0.2	Testosterone	0.1	
	Estradiol	ND			

Results

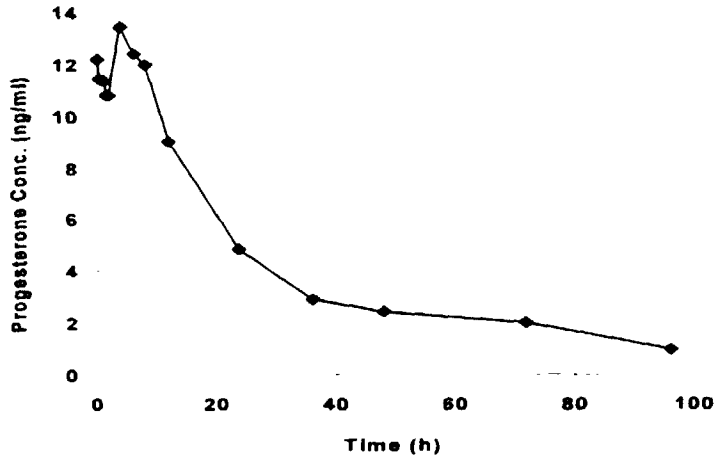
Pharmacokinetics

The individual and mean (± SD) pharmacokinetic parameters of progesterone after the last dose of a 12 day (23 dose) period are included in Table 22. Additionally, the mean serum progesterone concentration versus time profile after the final dose of COL-1620 is illustrated in Figure 14.

Table 22.

Subject #	Cmax (ng/ml)	Tmax (h)	AUC0-t (ng*h/ml)	λz (h-1)	# points in estimation of λz	t½ (h)
Mean±SD	14.57 ± 4.49	3.55 ± 2.48	389.8 ± 182.2	0.028 ± 0.006		25.91 ± 6.15

Figure 14 Mean Serum Progesterone Concentrations: Terminal Phase



Sponsor's Conclusions:

1. Upon attainment of steady state, the disposition of progesterone administered through COL1620 (8%) resulted in a relatively flat concentration-time profile for the first 12 hours following dosing, suggestive of zero-order release kinetics.

2. The average (± SD) steady state concentration was 11.6 ± 3.48 ng/ml.

Reviewer Comments:

The log trapezoid AUC0-τ for BID dosing of Crinone from this study was 138 72 ± 41.58 ng*h/ml.

Study Number: COL1620-003US

Title: Pharmacokinetic study of two dosage strengths of COL-1620 with natural progesterone (45 and 90 mg) - Effect of sexual intercourse.

Objectives: Assessment of the effect of sexual intercourse on the absorption of intra-vaginally administered COL-1620 during multiple dosing.

Study Design: This was a randomized, open label, repeated-dose study. The study consists of a 30-day screening period, a 12-day outpatient treatment period, and a one-day follow-up period. Patients were prohibited from having sexual intercourse prior to Day 5 of the treatment period and were required to have intercourse at least twice between Days 5 and 12.

Patients: 20 healthy females, ranging in age from years (mean = 59 years), in weight from lbs. (mean = 144 lbs.) were enrolled, 10 subjects per group.

Formulation: The proposed to-be-marketed formulations of COL-1620 (4% and 8%) were not used in this study, due to the use of

Blood Collection: Samples were collected pre-dosing on Days 1, 3, 5, 7, 9, 11 and 13 (end of study assessment) of the treatment period.

Analytical Methods: The serum progesterone assays were performed by Using a commercially available *in vitro* solid-phase kit manufactured by The validation of the method is presented in Table 23.

Table 23.

Sensitivity Limit	ng/ml				
Accuracy	%				
Target	LOW (≈1 ng/ml)		Medium (≈3 ng/ml)		High (≈15 ng/ml)
Intraassay Precision (%CV)					
Interassay Precision (%CV)					
Specificity (% Cross reactivity)	Progesterone	100	17α-Hydroxyprogestone	3.4	
	Androstenediol	ND	Medroxyprogesterone	0.3	
	Corticosterone	0.9	Pregnane	ND	
	Cortisol	0.03	5β-pregnan-3α-ol-20-one	0.05	
	Danazol	0.006	5α-pregnan-3,20-dione	9	
	11-Deoxycorticosterone	2.2	5β-pregnan-3,20-dione	3.2	
	11-Deoxycortisol	0.01	Pregnenolone	0.1	
	DHEA-SO4	0.002	5-pregnan-3β-ol-20-one-sulfate	0.05	
	20α-Dihydroprogesterone	0.2	Testosterone	0.1	
	Estradiol	ND			

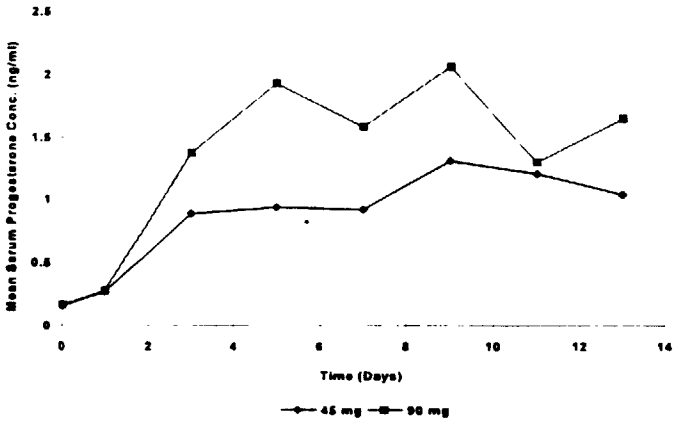
Pharmacokinetic Methods:
Blood samples on Days 3 and 5 are to assess the steady state trough levels of progesterone in the absence of sexual activity. These levels will be compared to those on Days 7, 9 and 11 during which time, patients were to engage in sexual intercourse at least twice (between Days 5 and 12).

Results

Pharmacokinetics

The mean trough serum progesterone levels from samples taken every other day are illustrated in Figure 15.

Figure 15.



Sponsor's Conclusion

1. No consistent pattern in the fluctuation of serum progesterone concentration from steady-state was demonstrated.

Reviewer Comments:

1. Only trough levels of progesterone were collected.

2. The frequency of the sexual intercourse by the patients included in this study is inconsistent and ranged from the "mandatory" 2 occurrences to a total of 8 sexual encounters from Days 5 to 12. The times of day of the sexual encounter in respect to dosing is not reported. The duration of each encounter is not reported. These extremely variable parameters may affect the degree of change from baseline leading to the inconsistency of change from baseline.

XII. Attachment 3 - Supportive PK/PD/Safety Study Summaries

Study Number: COL1620-F03

Title: Pharmacokinetic study of two progesterone formulations: COL-1620 versus Utrogestan® in post-menopausal women.

Objectives: to determine the pharmacokinetics, metabolism and the tolerance of COL-1620 (vaginal) and Utrogestan® (vaginal and oral) progesterone formulations after a single administration.

Study Design: This was a single-dose, open, randomized, crossover study. The duration of each period of treatment of 28 days during which the subjects received one patch of ESTRADERM TTS 50® on Days 1, 4, 8, 11, 15, 18, 22 and 25.

Study Subjects: Seven normal healthy women, aged 46 to 72 years, weighing from 55.4 to 83.0 kg and measuring from 150 to 171 cm.

Formulation: The formulation of COL-1620 used in this study is not the to-be-marketed formulation because of the use of list and the addition of mg

Blood Collection: Samples were collected at 8:00 A.M. on each of the two days prior to progesterone dosing and at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 18, 24, 30, 36, 42, 48 and 72 h post-dose

Analytical Methods:
Serum progesterone levels were estimated by To assure that the two main metabolites of progesterone, 5α-dihydroxyprogesterone and 5β-dihydroxyprogesterone do not interfere with the assay an method was employed. The samples were analyzed using method. The kit used was a commercial kit obtained from The method was a)

The following validation (Table 24) of the assay with and without extraction are presented for review and include the reproducibility of the standard curve.

Table 24.

Target (ng/ml)							
Without Extraction							
Mean ± SD	0.001	0.531 ± 0.016	0.934 ± 0.036	3.211 ± 0.113	9.069 ± 0.433	25.790 ± 1.091	50.822 ± 1.165
% CV		2.94	3.84	3.52	4.89	4.23	2.29
With Extraction							
Mean ± SD	0.011	0.480 ± 0.034	0.957 ± 0.080	3.210 ± 0.095	9.427 ± 0.742	25.585 ± 1.973	50.018 ± 2.390
% CV		7.13	8.39	2.96	7.87	7.71	4.78

Results
Pharmacokinetics
The pharmacokinetic parameters as measured at are included in Table 25 and 26, respectively. It should be noted that it appears that samples obtained from an individual subject were submitted to and not to both analytical sites. It is also unclear whether the data reported in the following tables is from extracted samples only.

Table 25. Mean (± SD) Progesterone Pharmacokinetic Parameters (samples analyzed at Cephac)

	COL-1620 (vaginal)	Utrogestan® (oral)	Utrogestan® (vaginal)
Cmax (ng/ml)	5 02 ± 3.09*	7.60 ± 8.08	3 50 ± 1 46
Tmax (h)	7 00 ± 3.69	2.33 ± 0.82	10 50 ± 12 93
AUC0-t (ng*h/ml)	114.00 ± 113.35 *	18.86 ± 17 27	103 79 ± 85 25

* normalized to 100 mg dose

Table 26. Mean (± SD) Progesterone Pharmacokinetic Parameters (samples analyzed at FRH)

	COL-1620 (vaginal)	Utrogestan® (oral)	Utrogestan® (vaginal)
Cmax (ng/ml)	7.24 ± 4.01*	7.11 ± 7.64	6.26 ± 2 20
Tmax (h)	6.67 ± 4.50	2.25 ± 0.99	11.17 ± 12 70
AUC0-t (ng*h/ml)	166.04 ± 123.26 *	19.05 ± 17 06	176.84 ± 143.39

* normalized to 100 mg dose

Sponsor's Conclusion

1. The rate of absorption of progesterone is decreased after vaginal administration compared to the oral administration.

2. The extent of absorption of progesterone after vaginal administration which is not different between COL-1620 and Utrogestan® vaginal formulations, is much higher than after treatment with the oral formulation.

3. The relative bioavailability of the three formulations is not modified at steady state. A significant difference was observed between the AUC0-t of the vaginal formulation and the oral formulation considering the [redacted] results. However, since this was not shown with the data and since the intersubject variability is high, any statistically significant conclusions of the comparative bioavailability of the three formulations tested is equivocal.

4. The study has also shown that after oral administration, the concentrations measured by direct are much higher than after measurements by illustrating the cross reactivity of the progesterone metabolites and subsequently that first pass metabolism is avoided after vaginal administration.

Reviewer Comments:

1. The progesterone pharmacokinetic parameters estimated from samples analyzed at are vastly different. The reason for this difference is unclear. There is no evidence that the same samples were sent to both labs for analysis, therefore the differences could be simply that different subjects were analyzed at each lab.

2. Additionally, cross-validation of the two analytical sites was conducted by sending the samples from two subjects to both sites where they were analyzed with and without extraction at (further substantiating Reviewer Comment #1). The results from this analysis show that levels estimated with extraction are generally lower than without extraction and that levels from these patients are generally higher at

3. The conclusions made by the sponsor herein are clouded by the uncertainty of the use of extraction in all the samples and the differences between the two analytical sites. It should be noted that a similar protocol was performed and has been submitted for review (005323). Therefore, the

results of this study can be considered supportive. Additionally, it was stated by Dr. Howard Levine, Columbia Research, that the analysis of progesterone concentrations used in this study is suspect and limited confidence can be placed in the data. Although, no scientific explanation for this was given.

Study Number: QCL/101

Title: An open label, randomized, parallel group, fixed dose, comparative study, to assess the effects of progesterone gel (COL 1620) in hysterectomized and bilaterally oophorectomized, or postmenopausal women receiving estrogen hormone replacement therapy.

Objectives: To identify, following 12 days of treatment, the dose of COL 1620 which leads to excretion levels of progesterone metabolites which most closely approximate those found secondary to physiological changes in normal premenopausal women during the mid-luteal phase of their cycle. To assess the tolerability of 6 applications of COL 1620 given at three dose levels for 12 days in postmenopausal women (hysterectomized or normal) receiving estrogen hormone replacement therapy.

Study Design: Two center, open-label, randomized, parallel group, dose finding study comparing three doses of COL 1620. Patients were randomly allocated one of the three different doses of COL 1620 in a double blind manner.

Patients: 53 patients were included in Study QCL/101 (45 evaluable) and all patients had a serum progesterone levels of <3 nmol/L and had a history of progestin intolerance.

Formulation: The formulation used in this study was NOT the to-be-marketed formulation and is included in Table 27, below.

Table 27.

	Crinone™ 4%		Crinone™ 8%	
Active Ingredients	mg/1.125g Dose	%w/w	mg/1.125g dose	%w/w
Progesterone				
Glycerin				
Hydrogenated Palm Oil Glyceride				
Carbomer-934P				
Polycarbophil				
Sorbic Acid				
NaOH				
Purified Water				

Blood Collection: No blood collections were made in this study and only renally excreted progesterone metabolites were assayed.

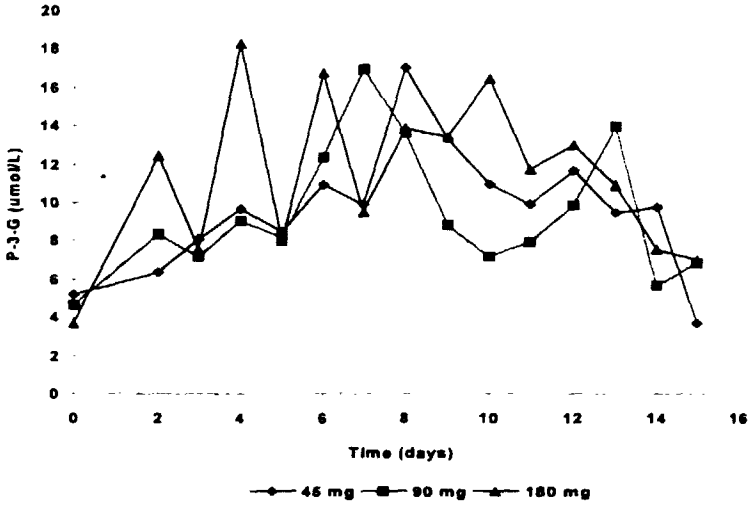
Analytical Methods: The pregnanediol-3α-glucuronide levels in urine were estimated by a However, the validation of this assay was not submitted for review

Results

Pharmacokinetics

The mean urinary excreted progesterone metabolite, pregnanediol-3α-glucuronide (P-3α-G) versus time profiles of the 45, 90 and 180 mg vaginally administered doses of COL-1620 are included in Figure 16.

Figure 16.



The mean change from baseline over Days 2 thru 14 and the statistical p-values comparing each dose are included in Table 28. Additionally, the only time point in which the p-value is <0.05 showing statistically significant differences between dosages is Day 2. These data are also reported in Table XX.

Table 28. Mean Changes from Baseline P-3α-G (µmol/L)

	45 mg	90 mg	180 mg	45 mg vs. 90 mg	45 mg vs. 180 mg	90 mg vs. 180 mg
Days 2 thru 14	5.77	4.41	8.20			
p-values				0.901	0.498	0.284
Day 2	1.54	3.67	8.73			
p-values				0.803	0.020	0.038

Sponsor's Conclusion

1. Mean/median levels of urinary P-3α-G increased 24 hours after application and were maintained above baseline during the application period.

2. There was little difference in the P-3α-G levels between dose groups, except at day 2 when the 180 mg dose group had a significantly greater than excretion level.

3. The study drug appeared better tolerated by patients in the 45 mg dosage group which is particularly important given the clinically documented history of progestin intolerance in these patients.

4. No serious adverse events were reported by any patient.

Reviewer Comments:

1. The validation of the P-3α-G in urine was not submitted. Therefore, the confidence one can have in these data is limited.

2. The to-be-marketed formulation does not contain the 2.0 mg of methylparaben that was included in the formulations used in this study. Therefore, the to-be-marketed formulation was not used in this study.

3. A significant increase in P-3α-G (progesterone metabolite) from baseline occurs with each dose (45, 90 and 180 mg) of COL-1620. However, no difference exists between the three doses in elevating renally excreted P-3α-G. The clinical significance of this elevation is unknown.

Study Number: Inveresk 010129

Title: A study to determine absorption of progesterone from COL-1620 after application to the penis.

Objectives: Determination of the extent of absorption of progesterone, if any, from the vaginal progesterone gel, COL-1620 (8%), when applied as a single dose of 90 mg to the penis.

Study Design: This was an open, single-dose study.

Patients: Ten healthy male subjects, aged 18-45, completed the study. The mean age of the subjects was 30.4±10.36 years, the mean height was 178.2±7.58 cm and the mean weight was 75.51±11.33 kg.

Formulation: 1.125 g of COL-1620 (8%) gel formulation (proposed to-be-marketed formulation) was administered by topical route to the penis. However, the formulation used herein was not manufactured by the proposed commercial manufacturer.

Blood Collection: Samples were collected for analysis of progesterone level at 0 (predose), 0.5, 1, 1.5, 2, 4, 6, 8 and 12 h post dose.

Analytical Methods: A monitoring method and a method were used to estimate serum progesterone levels. However, the validation of these assays was not presented for review.

Results

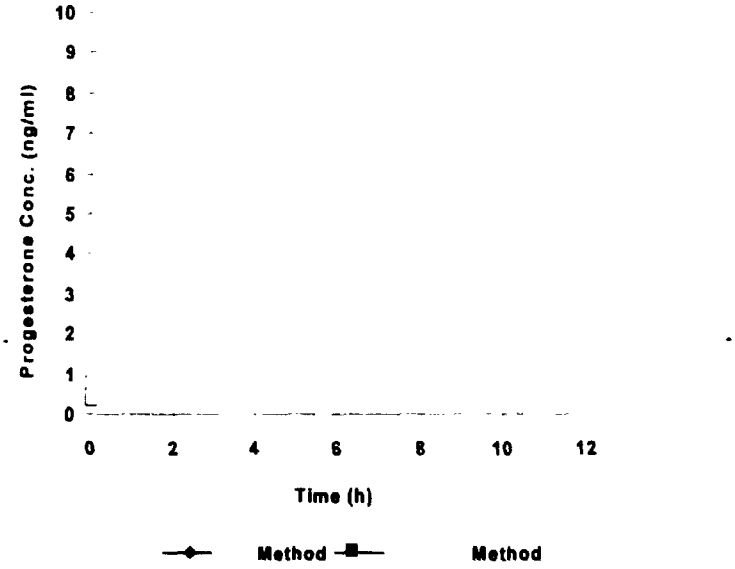
Pharmacokinetics

The bioavailability (AUC) of progesterone estimated by both methods are included in Table 29. Additionally, the serum concentration of progesterone versus time profiles from each method are included in Figure 17.

Table 29. AUC0-t (ng*h/ml)

Subject #	Method	Method
Mean ± SD	51 74 ± 31 64	47.57 ± 28 43

Figure 17.



Sponsor's Conclusion
Application of COL-1620 (8%) to the penis in normal male volunteers results in systemic absorption of progesterone.

Reviewer Comments:

1. I concur with the sponsors conclusion. However, the validation of the assays used herein are not submitted. Therefore, the confidence one can have in these data is limited.

2. Although, no clinically significant changes in safety values were recorded (data not shown), the clinical implication of repeated delivery of progesterone to sexual partners of females receiving COL-1620 is not discernable from this study and should be addressed by the reviewing medical officer(s).

Study Number: COL1620-F04

Title:. Endometrial effects of progesterone administered intravaginally using a polycarbophil base sustained-release preparation, Crinone™ (COL-1620).

Objectives: To evaluate the effects on the endometrium of estrogenized women suffering from premature ovarian failure (POF) of Crinone™, designed for transvaginal progesterone administration.

Study Design: A single-center, double-blind randomized, a parallel group, dose-finding study comparing 45, 90 and 180 mg doses of COL-1620.

Patients: Twenty three women with absent or inactive ovaries as a result of premature ovarian failure (POF), ovarian dysgenesis, prior chemotherapy or castration. Twenty women aged 25-41 years completed the study. These subjects were randomized to one of three dosage groups (45, 90 and 180 mg) as they entered the study.

Treatment: Exogenous estrogen was administered (x 28 days) by wearing 1 to 4 transdermal systems intended to deliver 0.1 mg of estradiol/system. On day 15 COL-1620 treatment was initiated and consisted of intra-vaginal applications **every other day** of a COL-1620 containing 45, 90 or 180 mg of progesterone.

Formulation: The formulations of COL-1620 (4% and 8%) used in this study are not the proposed to-be-marketed formulations and differ by the addition of and use of

Blood Collection: Blood samples were obtained at 8:00 A.M. on Days 0, 2, 6, 9, 13, 16, 20, 23 and 27.

Analytical Methods: It is stated in the submission that all hormones were assayed by using However, the methodology and validation of these is not submitted for review.

Results

Pharmacokinetics

Progesterone dosing was every other day on Days 15, 17, 19, 21, 23, 25 and 27. Samples for the assessment of progesterone concentrations were taken only at 8:00 A.M. on selected days. It should be noted that blood samples on Days 16 and 20 were ≈24 hours post dose while samples taken on Days 23 and 27 are ≈48 hours post dose. The mean progesterone concentrations at each sampling time are included in Table 30.

Table 30. Mean±SD Progesterone Levels (ng/ml)

Dose	Day 2	Day 6	Day 9	Day 13	COL-1620			
					Day 16	Day 20	Day 23	Day 27
45 mg	0.10±0.00	0.11±0.04	0.11±0.04	0.10±0.00	2.27±1.40	2.03±1.36	2.19±2.79	1.54±1.16
90 mg	0.14±0.06	0.13±0.06	0.14±0.07	0.12±0.06	5.63±3.03	4.65±1.49	3.90±2.62	3.51±3.87
180 mg	0.12±0.04	0.20±0.13	0.13±0.05	0.12±0.04	5.42±2.06	3.92±0.72	3.63±3.16	2.97±2.34

Exogenous estradiol was administered through one transdermal delivery system (0.1 mg/system) on Days 1, 4 and 25, two systems on Days 8, 19, 20 and 21, three systems on Days 15, 16, 17 and 18 and four systems on Day 11. The mean estradiol levels at each blood sample day are included in Table 31. Additionally, the follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels are included in Tables

32 and 33, respectively.

Table 31 Mean±SD Estradiol Levels (ng/ml)

Dose	Day 0	Day 2	Day 6	Day 9	Day 13	COL-1620			
						Day 16	Day 20	Day 23	Day 27
45 mg	20±8	77±11	143±75	138±402	402±123	397±109	251±123	223±104	106±71
90 mg	19±8	74±24	112±20	208±62	377±181	393±82	213±35	163±119	125±55
180 mg	25±23	110±105	150±97	295±228	546±230	421±99	299±87	184±94	86±52

Table 32. Mean±SD FSH Levels (IU/L)

Dose	Day 0	Day 2	Day 6	Day 9	Day 13	COL-1620			
						Day 16	Day 20	Day 23	Day 27
45 mg	67±30	49±13	31±12	31±11	25±6	26±10	15±11	11±8	11±8
90 mg	72±36	65±39	47±22	47±23	33±15	30±13	14±9	13±7	12±4
180 mg	55±20	42±21	35±17	32±18	23±12	22±15	13±10	10±6	10±6

Table 33 Mean±SD LH Levels (IU/L)

Dose	Day 0	Day 2	Day 6	Day 9	Day 13	COL-1620			
						Day 16	Day 20	Day 23	Day 27
45 mg	50±16	19±6	14±4	14±4	26±8	22±11	13±11	8±6	6±4
90 mg	33±12	21±11	19±11	19±7	24±11	21±15	10±6	8±5	4±2
180 mg	41±25	18±7	19±5	18±6	19±12	17±8	9±5	8±7	5±2

Pharmacodynamics

The histological evaluation of endometrial biopsy specimen obtained on Day 24 from 21 subjects indicated that all 21 subjects had endometria characteristic of the secretory phase of the menstrual cycle. The mean (± SD) thickness of the endometria at Days 0, 13 and 24 are included in Table 34 and intended to be illustrative of the changes (or lack thereof) in the endometria after estradiol alone treatment and estradiol plus progesterone (COL-1620).

Table 34 Mean±SD Endometrial Thickness (MM)

Dose	Day 0	Day 13 (Estraderm)	Day 24 (Estraderm + COL-1620)
45 mg (n=7)	3.8 ± 4 4	8.5 ± 1.8	7 2 ± 1.3
90 mg (n=7)	1 5 ± 0 8	8.6 ± 2 4	6.1 ± 1
180 mg (n=6)	3 4 ± 3 1	6 6 ± 2.1	5.6 ± 2

Sponsor's Conclusion

1 Vaginal application of COL-1620 every other day from day 15 to 27 induced a secretory transformation of all the endometrial biopsy specimen obtained on Day 24.

2. The low plasma progesterone levels and the pronounced endometrial effects observed suggest uterine selectivity of the effects induced by vaginal progesterone administration.

3. Every other day administration of COL-1620 is a convenient, safe and effective way to deliver progesterone in hormone replacement therapy, and that treatment efficacy is not likely to be hampered by relatively high plasma estradiol levels.

Reviewer Comments:

1. I concur with **Sponsor's Conclusion #**1.

2. Although it is possible that the vaginally administered progesterone doses result in therapeutic levels of progesterone in the endometrium while not resulting in systemic progesterone levels, actual data illustrating this has not been submitted for review. Additionally, the clinical significance of this is unknown.

3. The validation of the assay used to assess serum progesterone levels are not submitted for review. Therefore, the confidence one can have in these data is limited.

Study Number: COL1620-B01

Title:. Comparative clinical trial of histological effects an endometrium of Crinone™, a slow release vaginal progesterone preparation in menopausal women

Objectives: To determine the endometrial effects of 3 doses (45, 90 and 180 mg) of Crinone™ in menopausal women receiving oral estrogen.

Study Design: This was a single center, randomized, double-blind, parallel group, dose finding clinical trial.

Patients: Seventeen menopausal women, 13 had had a bilateral oophorectomy, and were ages 39 to 70 yrs.

Treatment: On "Visit 1", the subjects were initiated on exogenous estradiol therapy. The subjects were treated with exogenous estradiol for at least 12 days and then returned for "Visit 2". The subjects then returned for "Visit 3", 10 to 14 days after the onset of COL-1620 treatment.

Formulation: The COL-1620 (4% and 8%) are not the proposed to-be-marketed formulation and differ by the addition of and the use of

Blood Collection: One blood sample was collected on each visit; Visit 1 (day 1), Visit 2 (at least 12 days after Visit 1) and Visit 3 (from 10 to 14 days after onset of treatment).

Analytical Methods: The hormone levels were assessed by However, the validation of these assays was not presented for review.

Results

Pharmacokinetics

The mean progesterone, follicle stimulating hormone (FSH) and estradiol levels at each visit are included in Tables 35, 36 and 37, respectively.

Table 35. Mean±SD Progesterone Levels (ng/ml)

	Dose			p-value
	45 mg (n=5)	90 mg (n=6)	180 mg (n=6)	
Visit 1	0.40±0.10	0.47±0.10	0.55±0.37	0.66
Visit 2	0.60±0.4	0.50±0.24	0.42±0.04	0.67
Visit 3	2.20±2.70	2.50±3.61	0.98±0.65	0.60
p-value	<0.14	<0.034	<0.04	

Table 36. Mean±SD FSH Levels (IU/L)

	Dose			p-value
	45 mg (n=5)	90 mg (n=6)	180 mg (n=6)	
Visit 1	70.40±19.70	65.75±33.42	87.33±16.16	0.26
Visit 2	44.60±11.00	43.75±30.83	56.62±14.67	0.43
Visit 3	33.40±3.80	29.62±23.92	36.15±10.28	0.77
p-value	<0.08	<0.03	<0.03	

Table 37. Mean±SD Estradiol Levels (pg/ml)

	Dose			p-value
	45 mg (n=5)	90 mg (n=6)	180 mg (n=6)	
Visit 1	11.00±1.40	13.50±7.15	11.0±2.00	0.51
Visit 2	82.20±52.60	72.67±27.94	41.33±20.96	0.12
Visit 3	70.40±38.40	73.33±47.34	76.17±71.22	0.96

Pharmacodynamics
Histological assessment of endometrial biopsy at visit 3 was made. Of the 15 biopsy specimen; 8 exhibited secretory endometrium; 3 non-secretory and 4 were not assessable.

Additionally, an assessment of endometrial thickness at each visit illustrates the effect of exogenous estradiol alone (visit 2) and exogenous estradiol and progesterone (visit 3) was made and is included in Table 38.

Table 38. Mean±SD Endometrial Thickness (mm)

	Dose			p-value
	45 mg (n=5)	90 mg (n=6)	180 mg (n=6)	
Visit 1	2.56±0.98	3.70±1.87	2.03±1.24	0.15
Visit 2	4.82±2.32	7.25±3.11	6.41±2.21	0.42
Visit 3	5.06±1.70	5.45±2.11	8.85±1.65	0.41

Sponsor's Conclusion

1. Progesterone doses of 45, 90 and 180 mg (COL-1620) applied vaginally every other day antagonizes the proliferative effects of exogenous estradiol on the endometrium.

2. No significant differences could be observed between the three doses of progesterone.

3. No clinically significant adverse events could be related to the use of COL-1620 at the doses studied.

Reviewer Comments:

1. The validation of the used to assess hormone levels herein was not submitted for review. Therefore, the confidence one can have in these data is limited.

2. I concur with the sponsor's conclusions.