CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-701

MEDICAL REVIEW(S)

M100R2

Medical Officer's Original Summary of NDA 20-701

1. NDA 20-701
M.O. Review

Submission Date: July 23, 1997
Safety Update received: February 28, 1997
Review Completed: July 7, 1997

JUL 13 1997

Drug Name: Progesterone gel

Proposed Clinical Name: Crinone (COL-1620)

Chemical Name: pregn-4-ene-3,20-dione

Sponsor: Columbia Research, Inc.
100 No. Village Avenue
Rockville Centre, NY 11570

Pharmacologic category: Progesterone

Proposed Clinical Use: Secondary Amenorrhea

Dosage and Route of Administration: 45 mg and 90 mg vaginal suppositories

NDA Drug Class: 3S

Related Drugs: Micronized progesterone tablets, Progesterone in Oil and Water, Synthetic progestins

Related Reviews: NDA 20-756
Biopharm Review Dated:

2. Table of Contents: page(s)

3. Material Reviewed: Volumes 1.1, 1.2, 1.26-1.45

4. Chemistry/Manufacturing Controls: See Chemist review

5. Pharmacology/Toxicology: See Pharmacologist review

6. Clinical Background:

6.1 Amenorrhea is not a disease but a symptom and may be arbitrarily defined as the absence of menses for 6 months or longer. Primary amenorrhea is defined as the failure to initiate menses. Secondary amenorrhea is defined as the absence of menses for longer than 6 months in a woman who has previously had menstrual periods. The incidence of amenorrhea in a general obstetrical/gynecological practice occurs in less than 5% in most studies. Secondary amenorrhea encompasses a variety of distinct pathophysiological disturbances. One of them, hypothalamic amenorrhea (HA) leads to an arrest of ovarian function and in turn to amenorrhea through an arrest of the pituitary drive on the ovary. This latter phenomenon results from a lack of pituitary stimulation by gonadotropin releasing hormone (GnRH). Under these conditions, the unstimulated ovaries stop ovulating and producing progesterone (P) and estradiol (E2). The cause of the inhibition of GnRH secretion in HA has not been fully elucidated but is believed to result from neurogenic inhibitory influences triggered by stress and other mechanisms that converge on the basal hypothalamic region.

The clinical factors leading to HA often include regular involvement in activities combining strenuous physical exercise and mental stress. Another factor that has also been shown to interfere with GnRH production is an alteration in the lean/total body weight ratio. Decreases in body weight, particularly when associated with increases in the lean/total body weight ratio, are believed to play a pivotal role in the genesis of HA. Examples of types of women susceptible to being affected by HA include those who engage in activities such as jogging, ballet dancing, and diverse forms of nutrition restriction and peculiar alimentary practices. All inhibitory influences triggered by these mechanisms are believed to involve a common (and possibly final) endorphin-mediated pathway by which GnRH normally secreted by the median eminence neurons is inhibited.

The symptoms of estrogen deprivation associated with HA are similar to those commonly encountered in menopause, except for the classic lack of episodic disturbances in body heat control or hot flushes that are characteristic of menopause. However, these patients can manifest all the other symptoms of estrogen deprivation encountered in the menopause, such as vaginal and skin dryness and a variety of psychological and sleep disorders. If the estrogen deprivation is chronic, additional undesirable consequences can include a decrease in bone mass and a relative increase in cardiovascular risk compared to age-matches controls whose ovaries are functioning.

The appropriate treatment of secondary amenorrhea due to HA is dependent on a woman's desire to conceive. After an appropriate endometrial biopsy, progesterone or progesterone/estrogen are usually given in an effort to illicit withdrawal bleeding. When pregnancy is pursued, induction of ovulation is usually attempted. In all other patients with HA (those not interested in pregnancy), hormone replacement therapy (HRT) with estrogen and progesterone is recommended in order to prevent bone loss and cardiovascular risks associated with estrogen deficiency.

In this NDA, patients with a typical hormonal profile of HA, after 4 months of amenorrhea, were studied. The sponsor chose HA because it is a more extreme form of secondary amenorrhea, and patients are more easily defined biochemically. Conditions such as hyperprolactinemia, pituitary tumor and polycystic ovarian disease, which are more common causes of secondary amenorrhea, were excluded.

6.2 At present the only approved oral progestins are synthetic derivatives of C-19 and C-21 compounds, such as Norlutin(C-19) and Norlutate(C-19) and Provera [medroxyprogesterone acetate(C-21)]. These synthetic compounds can exert undesirable effects that are related to their effect upon the liver. Unfavorable effects associated with the use of oral progestins are alteration in the lipoprotein profile and the potential for partial (or total) impairment for the beneficial effects of the estradiol treatment on these lipoproteins.

Approved intramuscular progesterone is in the form of progesterone in oil. Formerly, there was a progesterone product in water, but it is no longer marketed. On May 13, 1997, Crinone (NDA-20-756) was approved for Assisted Reproductive Technology (or IVF).

6.3 At present, there are multiple clinical trials which are ongoing in Europe.

6.4 Human Pharmacology, pharmacokinetics, pharmacodynamics
Crinone contains naturally occurring progesterone in a polycarbophil-based gel to be administered intravaginally as either a 45 mg (4%) or 90 mg (8%) dose for the treatment of secondary amenorrhea. Its bioadhesive nature allows the progesterone to remain attached to the vaginal epithelial cells for 48-72 hours, allowing for slower delivery. The mean apparent terminal half-life varies depending on the dosing interval and is approximately 25-50 hours at steady state and 30-40 hours after a single dose. Near average steady-state levels, base on trough concentration, are achieved with one dosing interval (24 or 48 hours), depending on the dosing regimen as either once-every-day or once-every-other-day, respectively.

Following intravenous administration in human, progesterone exhibits a terminal elimination half-life of approximately 5 to 20 minutes. However, following administration of Crinone, the terminal half-life is prolonged to 25-50 hours, most likely reflective of relatively slow absorption. The kinetics of Crinone further exhibit a bi-exponential decline. Progesterone, known to be lipid soluble, distributes extensively to tissues and is primarily renally eliminated.

Progesterone circulates in the blood largely bound to serum proteins (approximately 96%), of which approximately 17% is bound to corticosteroid binding globulin (high affinity and low capacity), with the majority (80%) bound to albumin (low affinity an high capacity).

The metabolic process of progesterone has been published in the literature. In the ovary, progesterone is synthesized from cholesterol and the intermediate pregnenolone. Once progesterone is formed, it is then metabolized where the principle metabolic steps are the reduction of the double bond at C4 and the oxogroups at C3 and C20. Approximately 40 to 60% of progestin is metabolized to 5 alpha DHP and approximately 10% to 20 alpha DHP.

The most important metabolites that circulate in the human blood are 17 alpha-hydroprogesterone, 11-desoxycorticosterone(DOC) and 20-dihydroprogesterone. The transformation of progesterone into DOC (precursor to aldosterone) occurs mainly in the kidney, 20-dihydroprogesterone exhibits 25-50% of the progestational activity of progesterone.

The metabolite levels are substantially different when progesterone is dosed orally and

intravaginally. A cross-over study was performed in nine healthy female subjects administered either oral or intravaginal progesterone. The results conclude that all metabolite levels are much lower when progesterone is dosed intravaginally, than when dosed orally.

Progesterone undergoes both biliary and renal elimination. Following an injection of labeled progesterone 50 to 60% of the excretion of progesterone metabolites is via kidney, approximately 10% is via the bile and feces, the second major excretory pathway.

6.5 Other relevant background information

On December 20, 1993 a meeting was held between HFD-510 and Columbia Research, Inc. Agreement on study designs, efficacy parameters, and statistical analysis plans for Phase III studies of Crinone (from this point in the review Crinone will be referred to as COL-1620) for secondary amenorrhea and in vitro fertilization were reached. For secondary amenorrhea it was agreed that the primary comparison of interest is month one (estrogen replacement only) versus month two (estrogen and progesterone replacements) bleeding, and clinical bleeding will be defined as two pads of bleeding per day for two days. It was originally agreed that results with a confidence interval in the range of 80-100% would provide clinically meaningful evidence of efficacy. Ballet dancers and long-distance runners will be studied as representatives of the larger population of women who have progesterone deficiency for a variety of reasons; Ballet dancers and long-distance runners are a purer group, with defined biochemical deficiencies, than other groups with secondary amenorrhea. On April 19, 1994, it was agreed that studies should not be limited to long distance runners and ballerinas.

In a meeting held on October 27, 1995 with Dr. Lisa Rarick, it was agreed that the safety issues for progestins and progesterone are not the same and that the content of the label for COL-1620 should be based on findings in the clinical trials.

7 Description of Clinical Data Sources (both IND and non-IND)

Studies in this NDA were performed under IND submitted on June 30, 1992. Two protocol synopses for Phase III studies in IVF (2 phases) and secondary amenorrhea (2 studies) were provided on December 10, 1993. The development plan provided for two parallel, randomized, open-labeled studies of transvaginal administration of COL-1620 in secondary amenorrhea at two sites. Protocols 004US and 005US were initiated. Protocol 004US was prematurely terminated and study 009US was added at a third site. Each study sites were to recruit 60 patients into the study to obtain 25 evaluable patients in each treatment group.

The Safety Update:
The Safety Update was originally submitted on February 28, 1997 and contained safety information on NDA 20-701 and NDA 20-756. Safety information reviewed for NDA 20-701 contains information from four clinical trials (COL1620-006US, QCL/104,COL1620-GB01and COL1620-F02). Two other trials (COL1620-IT01 and COL1620-SW01) will not have safety data reviewed; they are double-blind studies and the blind can not be broken. These studies are quite dissimilar. Several studies are for one or two months; COL1620-GB01 is a six month study. The total number of treatment emergent adverse events (TEAEs) reported is 56 (74%) which is comparable to those seen in the ISS. The incidence of AE's are as follows: abdominal pain 21 (28%), pain 18 (24%), headache 17 (22%), breast enlargement 16 (21%), nervousness 16 (21%), somnolence 15 (20%), depression 14 (18%), perineal pain female 13 (17%) and nausea 12 (16%). Except for "pain", the most frequently report specific TEAEs were also among the most frequently reported specific TEAEs summarized in the ISS. Bleeding was noted in 17 patients. In only two patients was bleeding noted to be of a severe nature. In patients who prematurely withdrew from the studies, 9 were in the long term COL1620-GB01 and two were in the COL1620-IT01 study. The largest number of these patients withdrew due to vaginal discomfort/vaginal discharge and the rest withdrew due to the usual adverse effects associated with progesterones, i.e. appetite increase, somnolence, depression, headache, vaginal bleeding and skin disorder. One patient withdrew due to angina pectoris, which is unusual. There were no reported deaths. There were no clinically significant changes in vital signs, hematology, chemistry or urological parameters..

In summary, Safety Update data is consistent with that seen in the three clinical trials. Data presented will not require a change in the proposed labeling.

Clinical Studies:
8.1 Trial COL1620-004US
8.1.1 The objective of this study was to evaluate the safety and efficacy of intravaginally administered progesterone (COL-1620) at doses of 45 mg and 90 mg to induce withdrawal bleeding in a population of women of reproductive age who suffer from the type of secondary amenorrhea known as hypothalamic amenorrhea(HA).

8.1.2 Design
The study was designed as a three-month, single-center, parallel-group, randomized, open-labeled, multiple-dose study. At least thirty women with HA were to be randomized into each treatment group. Enrolled patients were to receive progesterone in a transvaginal delivery system (COL-1620) at doses of either 45 mg or 90 mg every other day during portions of the last two consecutive menstrual cycles of the three-cycles study period. In addition, all patients received Estraderm TTS 50 skin patches, for the transdermal delivery of estradiol, which were to be replaced every 3.5 days, during the

entire study period.

8.1.3 Protocol

Women suffering from hypothalamic amenorrhea (HA), a defined type of secondary amenorrhea characterized by the absence of ovarian function and the exclusion of other conditions such as hyperprolactinemia, pituitary tumor or polycystic ovarian disease (PCOD), were selected for participation in this study. Screening of baseline hormone levels was performed to ensure that only patients with the typical profile of HA were included in this study.

Inclusion Criteria:

- females of reproductive age (18-45 years) suffering from secondary amenorrhea due to HA which has been documented by a characteristic hormonal profile for low plasma FSH (0.0-6.2mU/mL), E_2 (< 50 pg/mL), LH (2-11 mU/mL), and prolactin (< 25 ng.mL) levels;
- patients must not have had withdrawal bleeding for at least a four-month period prior to entering the study;
- negative pregnancy test;
- no clinically significant findings on physical examination;
- normal Pap smear
- normal laboratory values (the Investigator could include patients with laboratory values outside the normal range if the values were not considered to be clinically significant);
- written informed consent to this study had to be given voluntarily;
- no vaginal medication or products could be used during the study period;
- serum progesterone concentration of < 2 ng/mL at screening.

Exclusion Criteria:

- women presenting with a history of uterine pathology such as uterine fibroids or a history of unresolved dysfunctional uterine bleeding (DUB);
- women who presented evidence of spontaneous ovulation during the course of the study [plasma progesterone (P) > ng/mL prior to P administration];
- women who showed an insufficient estrogenic stimulation (endometrial thickness < 5 mm) at Day 12, 13 or 14;
- patients who have had a hysterectomy;
- patients with current urogenital disease (including known HIV positive);
- patients with a history of allergic response to progesterone or related drugs or to the test product components
- use of an investigational drug within the last 90 days;
- use of ovarian hormonal treatment within the last 6 weeks;
- unable to comply with the protocol;

- presence of clinically significant disease that would interfere with the evaluation of the study.

8.1.3.2

Conduct of the Study
This study was conducted during three consecutive 28-day menstrual cycles. The effect of estrogen-only treatment on the menstrual bleeding pattern was evaluated using data from Cycle 1 and the withdrawal bleeding following estrogen and progesterone treatment was evaluated using data from Cycle 2 and 3. An endometrial biopsy was performed and evaluated at the end of Cycle 3.

Patients self-administered Estraderm TTS 50 every 3.5 days from Day 1 to Day 25 of all three cycles; patients self-administered COL-1620 every other day on Days 15-25 of Cycles 2 and 3. Finally, patients recorded menstrual bleeding and psychological symptoms on a daily basis in the patient dairy. Patient had five office visits (screening, before estrogen treatment on Day 12, 13 or 14 (Amendments, Section 4.12) of Cycles 1, 2 and 3 and on Day 24 of Cycle 3), during which information on bleeding pattern and psychological symptoms from the patient diary, adverse events, and concomitant medications was to be collected. In addition, each patient had two telephone interviews, after Day 25 of Cycles 2 and 3, respectively, during which information on bleeding patterns and psychological symptoms was to be collected.

At Visit 1, (before Cycle 1, Day 1) each patient was to be screened for compliance with inclusion and exclusion criteria. The screening was to include a medical history, smoking and alcohol use history, prior medication use history, gynecological history including gynecological treatments in the last six months and history of STD's, gynecological examination with swab and Pap smear, pregnancy test, transvaginal ultrasound to determine endometrial thickness, and a blood draw for determining biochemical profile and hormone levels. In addition, patients had a physical examination and measurement of vital signs. At screening, patients received Estraderm TTS 50 for Cycle 1 and a patient diary CRF. Patients with hormonal levels not in compliance with inclusion/exclusion criteria returned supplies to the investigator, and a screening log was to be kept.

At Visits 2 [Day 12, 13 or 14) of Cycle 1, patients had a pelvic ultrasound, reported adverse experiences and concomitant medications, and received Estraderm for Cycle 2. Patients with endometrial thickness of < 5 mm were excluded from the study.

At Visit 3 [Day 12, 13 or 14] of Cycle 2, patients has a pelvic ultrasound and blood collection for determination of hormonal levels, reported on adverse experiences and concomitant medications, and received COL-1620 for Cycle 2 and Estraderm for Cycle 3. Patients with endometrial thickness < 5 mm excluded from the study. On Visit 4 [Day

12, 13 or 14] of Cycle 3, patients had an ultrasound and blood collection for determination of hormonal levels. Patients were asked to report any adverse experiences and concomitant medications, and received COL-1620 for Cycle 3. Patients with endometrial thickness < 5 mm were excluded from the study.

On Visit 5 [Day 24 of Cycle 3] of Cycle 3, patients had a pelvic ultrasound and endometrial biopsy, a blood draw for biochemical profile and hormonal levels, a physical examination with measurement of vital signs, if determined by the investigator to be warranted, and were queried regarding adverse experiences and concomitant medications.

During the telephone interviews at the end of Cycle 3 (after Day 25), patients reported bleeding patterns and confirmed completion of the progesterone dosing.

All patients who completed Cycle 2 were considered evaluable and included in the analysis of efficacy. Protocol deviations were not used to exclude patients from the analysis population. Efficacy outcome variables included the bleeding pattern as the primary efficacy variable and the endometrial biopsy as the secondary efficacy variable. Bleeding was recorded by the patient in the patient diary on a daily basis as light, moderate or heavy, along with the number of pads/tampons used each day; bleeding was reported after six doses of COL-1620 to the investigator at the end of the study (after Day 25 of Cycles 2 and 3), respectively). Any bleeding (light, moderate or heavy) was defined as any bleeding on any day. Moderate to heavy bleeding was defined as bleeding which lasted for two or more days and which required two or more pads/tampons per day.

At Visit 5 (Day 24 of Cycle 3, the 10th day of exposure to progesterone in Cycle 3), an endometrial biopsy was obtained by aspiration (Pipelle). Tissue assays were performed by

8.1.3.3

In designing this study, it was proposed that the effect of treatment for COL-1620 be validated by requiring the lower 95% confidence limit for the observed success proportion to be within 10% of a true 90% success proportion. If the observed proportion is as high as 90%, this criterion could be achieved with 25 patients. If the observed proportion is as high as 95%, this criterion could be achieved with 13 patients. With an anticipated dropout rate of 15%, it was determined that at least 30 patients per treatment group should be enrolled to achieve a sample size of 25 at the end of Cycle 2.

There are two analysis populations, an intent-to-treat (ITT) and an efficacy (EFF) population. The ITT population consists of all patients who received at least one dose of the COL-1620 in Cycle 2 and who had an endometrial thickness $\geq$ 5 mm just prior to receiving COL-1620 at Visit 3 in Cycle 2. The EFF population consist of all ITT patients who received six doses of COL-1620, either in Cycle 2 or in Cycle 3. Efficacy

results are presented for the ITT population and are summarized in text for the EFF population since these results are similar.

Ninety percent and 95% confidence intervals were constructed for the proportion of patients with a successful bleeding pattern using approximations from the t-distribution. Confidence intervals were rounded to three decimals places. Histograms of each of the psychological symptoms (depression, moodiness and sleep disorders) are presented.

Summaries of all the hormone assays obtained throughout the study are presented. The following assays were only obtained at screening: LH, FSH, DHEAS, prolactin and testosterone. These assays were obtained to verify if the women's hormonal profiles were consistent with the inclusion and exclusion criteria (i.e. that they met the clinical profile for HA). For the remaining four visits, estrone and estradiol were assayed by to document proper estrogenization as an indicator of patient compliance with the study protocol; serum progesterone levels were also assayed by standard techniques to rule out the possibility that a patient might have ovulated on her own during the course of the study.

8.1.4 Results

This study, conducted between April 12, 1994 and January 11, 1995, was designed to assess the safety and efficacy of two doses (45 mg and 90 mg) of transvaginally administered progesterone-containing polycarbophil gel (COL-1620) in producing withdrawal bleeding in women with hypothalamic amenorrhea. Prior to beginning COL-1620 administration, patients had been estrogenized for six weeks by application of Estraderm TTS patches every three and one half days. Estraderm TTS application was to occur throughout the study. The study was prematurely terminated by the sponsor before all patients completed all three cycle because of poor estrogenization of patients and adhesion problems with the Estraderm TTS skin patches. Nevertheless, sufficient data were collected to allow efficacy analyses to be performed.

Fifteen patients were randomized to receive either 45 mg or 90 mg of COL-1620. Because the study was terminated before two patients in the 45 mg group and one patient in the 90 mg group received any study medication, the ITT population consisted of 13 patients in the 45 mg group and 14 patients in the 90 mg group. All percentages in subsequent analyses were calculated based on the ITT population.

In the 45 mg group, all 13 patients completed Cycle 2 of the study, and seven (54%) completed Cycle 3, and 10 patients in this group completed Visit 5, the last visit of the study. Three patients in this group (23%) withdrew when the study was terminated. In the 90 mg group, 12 of 14 patients (86%) completed Cycle 2, and eight (57%) completed Cycle 3, and nine patients in this group completed Visit 5. Five patients in this group (36%) withdrew from the study, one (7%) because of a protocol violation, and four (29%) when the study was terminated.

Demographically, all patients were Caucasian with the exception of one patient of Asian descent in the 90 mg group, and one patient of Hispanic descent in the 45 mg group. The mean age overall was 27.6 $\pm$ 0.8 years and the majority (14) of patients (52%) were from age 25 to 30. One patient was 36 years old. Mean height and weight of patients overall were 65 $\pm$ 0.6 inches and 122.7 $\pm$ 4.4 lbs, respectively. There were no meaningful differences between treatment groups in these demographic characteristics, although patients in the 45 mg group were slightly smaller and older, on average, than those in the 90 mg group.

There were no significant differences in the two groups with regard to alcohol and smoking use which might impact on the clinical outcome of this study.

With regard to medical and gynecological history at screening, eight patients (62%) in the 45 mg group and 12 patients (86%) in the 90 mg group had physical abnormalities. Most frequently, endocrine/metabolic abnormalities were reported in six patients in each group. Genitourinary system abnormalities were reported in 9 patients, six in the 90 mg group and three patients in the 45 mg group. CNS abnormalities were reported for seven patients, four in the 90 mg group and three in the 45 mg group.

At screening, nine patients (33%) reported having had at least one pregnancy (five patients (38%) patients in the 45 mg group and four (29%) in the 90 mg group). One patient in the 45 mg group (8%) had had a delivery. Sexually transmitted diseases (STD's) were reported in 3 patients, two in the 45 mg group and one in the 90 mg group.

The physical examination at screening revealed minor physical abnormalities with seven patients (54%) in the 45 mg group and three patients(21%) in the 90 mg group showing any abnormality. The most common abnormalities were related to the skin and lymph nodes, reported for four and three patients, respectively, in the 45 mg and 90 mg groups. Eye abnormalities were reported for four patients in the 45 mg group, and abnormalities of the ear, nose and throat were reported fro two patients in this group. In the 45 mg group, one patient had abnormalitiesof the cardiovascular system, and one patient had abnormalities in the musculoskeletal system. In the 90 mg group, one patient had endocrine/metabolic abnormalities, and one patient was hirsute. None of the reported disorders were felt to be clinically significant.

There were nine protocol violations which are summarized in the sponsor's table 3.0. This table will not be presented, but will be briefly summarized. One patient in the 45 mg group and eight patients in the 90 mg group violated the protocol. However, it is noted that 5 patients in the 90 mg group were protocol violators because they did not receive Estraderm or COL-1620 administration. Most of the protocol violators used the medication at the incorrect time, or misunderstood instructions. One patient had an endometrial thickness < 5 mm on Day 12, 13 or 14 and one patient used a topical vaginal

cream.

EFFICACY:

Panel A, from the sponsor, summarizes patients with successful bleeding. This table will not be reproduced because it is five pages long. Important points from this table are:

a) three patients in Cycle 1 had spotting prior to use of COL-1620, one in the 45 mg group and two in the 90 mg group; this spotting was recorded under "other symptoms" in the patient diary
b) In Cycle 2, 8/13 (62%) had withdrawal bleeding with the 45 mg dose, and 10/14 (71%) had withdrawal bleeding with the 90 mg dose;
c) In Cycle 3, 7/13 (54%) had withdrawal bleeding with the 45 mg dose and 8/10 (80%) had withdrawal bleeding with the 90 mg dose.

In Panel B, from the sponsor, any bleeding or spotting is shown for the cycle and day. Panel B comprises three pages and will be briefly summarized. Important points in this table are:

a) Patient number [redacted] (45 mg group) began spotted on days 11, 12 and 13 of cycle 1, while patient [redacted] (90 mg group) began spotting on Day 11 and patient 18 (90 mg group) began spotting on day 24 and 25.
b) During cycle one, only patient 18 in the 90 mg group was noted to have light bleeding.
c) After priming with Estraderm, patients with both dosages of COL-1620 were noted to have withdrawal bleeding from the 15th to the 28 day.
d) More patients reported moderate to heavy bleeding with the 90 mg dose than the 45 mg dose in Cycles 2 and 3. The duration of bleeding, as expected, was longer for some patients with the 90 mg dose.

Table I, Panel D from the sponsor, is the summary efficacy table for patients who received at least one dosage of COL-1620 with successful bleeding:

Table I
Panel D
Successful Menstrual Bleeding
ITT Population

Successful bleeding Pattern Description	Statistic	COL 1620 Dose 45 mg	90 mg
Total Number of Patients	Number	13	14
Light, Moderate, or Heavy	Number (%)	10 (77%)	11 (79%)
	90% lower C.I.	55.2%	58.4%
	95% lower C.I.	50.4%	54.0%

Note 77% of patients who received the 45 mg dose had some type of withdrawal bleeding and 79% had withdrawal bleeding with the 90 mg dose. The 95% C.I. is low for both dosages, primarily, because of the low number of patients evaluated.

The sponsor's Panel C is the EFF population. This table will not be reproduced. Panel C is composed of patients who received all six doses of COL-1620. Results are similar to those shown in Panel D. In the 45 mg group 10/13 (77%) patients in the 45 mg group had successful withdrawal bleeding, while 11/13 (85%) in the 90 mg group had successful withdrawal bleeding.

The intent-to treat endometrial biopsy results are shown in sponsor's Table 15.0. This table will not be reproduced, but will be summarized. The sponsor obtained an endometrial biopsy via Pipelle aspiration on day 24 of cycle 3 (10th day of exposure to progesterone). The biopsy tissue was immersed in formalin and paraffin and reviewed for conventional histological evaluation looking at signs of secretory transformation. In the textbook "Blaustein's Pathology of the Female Genital Tract" edited by Robert Kurman 4th Ed 1994, the author describes secretory endometrium in relationship to patients receiving hormone replacement therapy. Blaustein states "Histological changes in the endometria of women receiving replacement therapy include normal-appearing proliferative or secretory endometrium, mixed proliferative and secretory endometrium, abnormal secretory patterns, and atrophy. Secretory endometria can show variable secretory activity and may or may not display a predecidual change.....With low dose preparations the endometrium is atrophic or shows weakly secretory patterns that are not developed as fully as those seen in the normal luteal phase." With the above statements in mind, results are now presented for patients receiving COL-1620. Ten patients in the 45 mg group and

nine patients in the 90 mg group had endometrial biopsies. Of these, eight patients in the 45 mg group and nine patients in the 90 mg group had evaluable biopsies. Seven of eight patients (88%) in the 45 mg group and all nine patients (100%) in the 90 mg group had biopsy results supportive of a treatment effect (atrophic, secretory, menstrual, or "other") according to the sponsor. Two patients who had biopsies contained no endometrial tissue and were not evaluable. One patient in the 45 mg group had a proliferative endometrium, which is not suggestive of COL-1620 efficacy.

SAFETY

The number and percentage of patients in each treatment group who reported various adverse events (AEs) during the study are summarized by body system and preferred term in Table 16.0 This table will be briefly summarized. No serious adverse events were reported, and no patients discontinued from the study because of adverse events. In general, more patients reported AEs prior to, than after, first administration of COL-1620. Overall, 12 of 13 patients (92%) in the 45 mg group reported at least one AE prior to administration of COL-1620 (while patients were using Estraderm only), and 11 of 13 patients (85%) in this group reported at least one AE after beginning COL-1620. In the 90 mg group, 13 of 14 (93%) reported at least one AE prior to the administration of COL-1620 use, while eight of 14 patients (57%) in this group reported at least one AE after beginning COL-1620.

AEs reported by at least 15% of patients in either dose group, and percent change in the number of patients reporting these AEs following the first administration of COL-1620, were shown in Panel E(not reproduced). AEs reported most frequently prior to first administration of COL-1620 were the psychiatric disorders of emotional lability(mood swings), depression, and sleep disorder, followed by fatigue, bloating, nausea, vaginal discharge and headache. Before COL-1620 treatment, each of these AEs (except headache) was reported more frequently in the 90 mg group than in the 45 mg group, and each was reported less frequently after first administration of COL-1620 (except fatigue and bloating) in the 45 mg group. The frequency of emotional lability and depression decreased to zero, and the frequency of sleep disorder decreased to only one patient, after first administration of COL-1620. Fatigue, bloating (both decreasing in the 90 mg group only) nausea, vaginal discharge and headache decreased in frequency following COL-1620 administration as well. Most other AEs presented in Panel E also decreased in frequency following COL-1620 administration.

Most AEs were judged to be mild in severity. Two patients in the 45 mg group and 3 in the 90 mg group were judged to have moderate to severe AEs possibly related to the drug. Patient [redacted] had a severe headache which responded to aspirin, ibuprofen and bufferin. Patient [redacted] reported moderate headache prior to beginning COL-1620; this resolved after treatment. In the 90 mg group, patient 1 reported somnolence and fatigue prior to beginning COL-1620 and continued during treatment. This was judged to be moderate to severe and possibly related to the study drug. Patient 6 reported pruritus prior to beginning COL-1620, and moniliasis and pimples after taking COL-1620. The pruritus and moniliasis resolved, but the skin disorder remained to the end of the study. This was judged possibly drug related.

Of interest, the incidence of psychological symptoms (depression, mood swings and sleep disorders) according to the WHO Adverse Reaction dictionary, improved with treatment with COL-1620. The number of patients in each dose group reporting emotional lability and depression decreased to zero, while the number of patients in each dose group reporting sleep disorders decreased to one following the first administration of COL-1620.

Laboratory Measurements

Plasma hormonal profiles were used to assure that only patients with HA were enrolled into he study. This study was terminated because of adhesion problems with the Estraderm patches and poor estrogenization of the majority of patients in both dose groups. Nine of 13 patients (69%) in the 45 mg group and nine of 14 (64%) in the 90 mg group had serum estradiol concentrations below 40 pg/mL during at least one post-baseline visit. For this study, serum estradiol concentrations of at least 40 pg/mL were considered acceptable for HRT for hypothalamic amenorrhea, based on normal serum estradiol concentration of 40-45 pg/mL for women in the early follicular phase of the menstrual cycle.

Review of hematological measurements showed no outliers. Serum chemistry parameters were within normal limits except one patient with a total cholesterol of 209 mg/dL which is not clinically significant. Seven other abnormal laboratory values were judged to be clinically insignificant. Six patients were noted to have low WBC counts.

8.1.5 Reviewers comments and conclusion

In study COL 1620-004US the sponsor attempted to provide estrogen replacement via the Estraderm patch. There appears to have been significant problems with absorption and adhesion with Estraderm. Because of these adhesive problems, lower than expected estradiol levels were achieved, with probable inadequate estrogenization of the endometrium. The sponsor, therefore, terminated the study prior to completing all six doses of COL-1620. Data obtained shows that 10/13 (77%) patients in the 45 mg group and 11/14 (79%) had successful withdrawal bleeding in this study. Because of small numbers 95% CI are below 50%.

Endometrial biopsy material appear to support a progestational effect at the target organ. Evaluable biopsy material showed 88% to have a secretory effect in the 45 mg group and 100% in the 90 mg group. This endometrial data results were obtained with histological changes which included normal-appearing proliferative or secretory endometrium, mixed proliferative and secretory endometrium, and atrophy. This definition is consistent with those outlined by Kurman and Mazur in Blaustein's's Text of the Female Genital Tract, page 386, fourth edition, 1994. This definition of secretory endometrium is somewhat less stringent than other definitions, which may require a fully secretory endometrium. The rationale for not requiring a fully secretory

endometrium is that patients on hormone replacement therapy have a wide variety of changes that can be seen depending on the dosage, duration of use, whether a combined or sequential administration is use, and the time of the cycle when the biopsy is obtained.

There appears to be no significant safety problems in this study. Headaches were not a significant problem and psychological symptoms such as depression, mood swing and sleep disorders appear to have improved in most subjects.

8.1 Trial COL 1620-005US

8.1.1 The objective of this study was to evaluate the efficacy and safety of a transvaginally administered progesterone-containing polycarbophil-based gel (COL-1620) at doses of 45 mg and 90 mg in inducing withdrawal bleeding in a population of women of reproductive age who suffer from hypoestrogenic secondary amenorrhea. Women with diagnoses either of hypothalamic amenorrhea or premature ovarian failure(POF) were to be included in this study.

8.1.2
This study was a three-month, parallel group, randomized, open-labeled dose comparison trial comparing the effects of COL-1620 containing progesterone at doses of 45 mg or 90 mg administered every other day to women who were 18-45 years in age and who suffered from two well-defined subgroups of secondary amenorrhea: hypothalamic amenorrhea and premature ovarian failure. For each patient, the study period comprised three consecutive menstrual cycles of approximately 28 days each. Enrolled patients were to receive Premarin 0.625 mg per day for three cycles except days 27 and 28 of the third cycle. Patients were to receive progesterone in a transvaginal delivery system (COL-1620) at doses of either 45 mg or 90 mg every other day on Days 15-25 of the last two consecutive menstrual cycles.

Inclusion Criteria
Inclusion criteria are consistent with those of Study 004US except for the following:

- patients were allowed to use vaginal products for contraception (i.e., contraceptive foam, jelly, or cream), if used at least 6 hours before or after administration of progesterone gel, and vaginal infections, if used at least 48 hours before or after administration of progesterone gel (Protocol Amendment 1, December 22, 1994). Patients were allowed to use tampons (Protocol Amendment 1)
- willing to use condom or diaphragm contraception, or vaginal creams or jellies at least 6 hours before or after insertion of vaginal progesterone, unless (1) not sexually active, (2) sterilized (tubal), or (3) sexually active with a sterilized partner or female partner
- no hormonal medication during the past six weeks.

Exclusion Criteria

Exclusion criteria are identical to protocol 004 except for the following:

- patient with an endometrial thickness of ≥ 10 mm at baseline (Protocol Amendment 2; April 18, 1995);
- patients who bled (two or more pad/tampons for two or more consecutive days) at any time during the four months prior to entering the study were not to be enrolled in the study, and patients who bled (two or more pad/tampons for two or more consecutive days) at any time prior to taking COL-1620 in Cycle 2, were to be discontinued from the study (Protocol Amendment 2); and
- patient weight was to be appropriately based on the height and weight table as specified in Appendix D of the protocol (Amendment 2). Patients diagnosed with POF were exempt from meeting this weight criterion (Protocol Amendment 3; May 1995).

8.1.3.2

Conduct of the Study

This study was conducted in the same manner as Study 004 with the following exceptions. Premarin was to self-administered every day from Day 1 of Cycle 1 to Day 26 of Cycle 3 (instead of Estraderm 50). Each patient was scheduled for seven visits (instead of 5), and the sponsor conducted a more detailed psychological questionnaire (Profile of Mood States, POMS), which was used by the investigator to measure the level of emotional distress and depressive symptoms currently experienced. This was adjunctive information and is not included in this report.

Visits were essentially the same as in Study 004 with the exception that 7 visits were scheduled instead of 5. Visit 2 of study 005 was added. This visit included an ultrasound to determine endometrial thickness. Women with an endometrial thickness ≥ 10 mm were to be excluded from the study. In comparison, in study 004, the last interface with the investigator was a telephone conversation. In Study 005 this telecon was converted to visit 7. Endometrial biopsy material was performed at
and was evaluated in a blinded fashion by a pathologist at a central laboratory

Changes to the Study/Protocol Amendments

Five amendments were made to this protocol. These changes are:

1. The inclusion/exclusion criteria no longer required documentation of a low plasma estradiol concentration (<60 pg/mL) for inclusion into the study. This amendment also allowed use of tampons, or vaginal products for contraception if used at least six hours before or after administration of progesterone gel, and of vaginal medications prescribed by the Investigator for the treatment of vaginal infections, if used at least 48 hours before or after administration of progesterone gel.

2. Expanded the exclusion criteria to exclude women with an endometrial thickness of ≥ 10 mm at baseline, women who bled (two or more pads/tampons for two or more consecutive days) at any time during the four months prior to entering the study, and women who bled (two or more pads/tampons for two or more consecutive days) at any time prior to taking COL-1620 in Cycle 2. This amendment also specified maximum weight criteria for inclusion in the study.
3. Specified that women diagnosed with premature ovarian failure (POF) would be exempt from meeting the weight criteria outlined in the second protocol amendment.
4. Provided for additional efficacy analysis of withdrawal bleeding by including in the definition of withdrawal bleeding any bleeding experienced by patients subsequent to one or more doses of COL-1620.
5. Stated that endometrial biopsy tissue would be assayed by a pathologist at a central laboratory in a blinded fashion, in addition to the assays performed at Further, this amendment stated that only data obtained from this pathologist would be used for the secondary analysis of efficacy.

Reviewer's Comment
Overall, changes in the protocol helped to expand the inclusion criteria and provide for less exclusion in amendments 1, 2 and 3. Amendment 4 had the effect of biasing the efficacy result toward the sponsor by including, in the efficacy results, any withdrawal bleeding rather than withdrawal bleeding that occurred from days 15 to 25 of Cycles 2 and 3. The fifth amendment should have had the effect of providing a more independent reader of slides who was not affiliated with the processing institution.

8.1.3.3

The statistical analysis plan is essentially the same as in Study 004.

8.1.4 Results

This study, conducted between December 27, 1994 and December 29, 1995, was designed to assess the safety and efficacy of two doses (45 mg and 90 mg) of a transvaginally administered progesterone-containing polycarbophil-based gel (COL-1620) in producing withdrawal bleeding in women with hypoestrogenic secondary amenorrhea. Patients were estrogenized by oral administration of Premarin daily on Days 1-28 of Cycles 1 and 2, and Days 1-26 of Cycle 3. COL-1620 was administered every other day during Days 15-25 of Cycles 15-25. The primary efficacy parameter was successful bleeding after administration of COL-1620. Endometrial biopsy results served as the secondary measure of efficacy.

Thirty-three patients were enrolled into the study and were randomized to either the 45 mg treatment group (16 patients) or to the 90 mg group (17 patients) of COL-1620. All patients received Premarin.

Patient [redacted] (45 mg group) was not included in the ITT population due to a violation of the inclusion/exclusion criteria (progesterone level > 2 ng/mL at Day 14 of Cycle 2). Fifteen patients (100%) in the ITT population of the 45 mg group completed cycle 2, and 13 patients (87%) completed the study in the 90 mg group. Patient [redacted] (45 mg group) was discontinued after her first dose of COL-1620 during Cycle 3, due to a violation of the weight criteria specified in Protocol Amendment 2. Patient [redacted] (45 mg group) was lost to follow-up after Day 12, 13 or 14 of Cycle 3 (Visit 5). In the 90 mg group, 17 patients (100%) in the intent-to-treat population competed Cycle 2, and 16 patients (94%) completed the study. Patient [redacted] (90 mg group)withdrew from the study prior to Day 24 of Cycle 3 (Visit 6) because of patient desire (conflict with her new job).

Demographically, the racial distribution in the 45 mg group was similar to that of the 90 mg group: nine patients (60%) in the 45 mg group and nine patients (53%) in the 90 mg group were Caucasian, and six patients (40%) in the 45 mg group and eight patients (47%) in the 90 mg group were Black. Mean age (31.1 $\pm$ 1.9 and 31.0 $\pm$ 1.6 years in the 45 mg group and 90 mg group respectively) and the mean weight (144.5 $\pm$ 12.5 and 144.5 $\pm$ 17.2 lbs. in the 45 mg group and 90 mg group, respectively) were similar between the two treatment groups. The mean height was slightly greater in the 90 mg group than in the 45 mg group (64.8 $\pm$ 0.9 and 63.5 $\pm$ 0.5 inches, respectively).

Alcohol use was similar for the two groups. No smoking history is mentioned in this study.

With regard to medical and gynecological history at screening, eleven patients (73%) in the 45 mg group and 12 patients (71%) in the 90 mg group had a history of physical abnormalities at screening. In the 45 mg group, skin/lymph node abnormalities were most frequently reported, while in the 90 mg group gastrointestinal/abdominal and cardiovascular abnormalities were most frequently reported. Abnormalities of the CNS respiratory systems were also reported in both treatment groups.

At screening, seven patients (47%) in the 45 mg group and eight patients (47%) in the 90 mg group reported having had at least one pregnancy, and six patients (40%) in the 45 mg group and six patients (35%) in the 90 mg group has at least one delivery. Three patients (20%) in the 45 mg group and one patient (6%) in the 90 mg group had been sterilized, and five patients (33%) in the 45 mg group and three patients (18%) in the 90 mg group had prior gynecological surgeries (other than sterilization). One patient (7%) in the 45 mg group has a history of an STD.

The physical exam revealed four patients (27%) in the 45 mg group and five patients (29%) in the 90 mg group had at least one physical abnormality (not including scoliosis, galactorrhea, or hirsutism). The most common abnormalities in the 45 mg group were skin and lymph nodes disorders. In the 90 mg group, the most common disorder was related to the endocrine/metabolic system. None of these abnormalities are reported to have major clinical significance.

Seven patients (47%) in the 45 mg group and six patients (35%) in the 90 mg group had at least one protocol violation. The most frequent protocol violations were (in decreasing order): visit non-compliance (33% in the 45 mg group; 29% in the 90 mg group), study medication non-compliance (27% in the 45 mg group; 24% in the 90 mg group), and extension of estrogen only treatment in Cycle 3 (13% in the 45 mg group; 18% in the 90 mg group). Most of these violations included non-compliance with the Premarin and/or COL-1620 administration schedule, deviation from the visit schedule, use of vaginal medication within 48 hours of study drug administration, violation of the weight criteria outlined in Protocol Amendments 2 and 3 and extension of the time in which patients took Premarin only in Cycle 3.

EFFICACY:

Panel A, from the sponsor, summarizes patients with successful bleeding. This table is not shown due to it's extensiveness (5 pages). Important points from this table are:

a) Six patients, two in the 45 mg group, and 4 in the 90 mg group had bleeding during Cycle 1. Patient [redacted] in the 45 mg group had moderate to heavy bleeding after the fifteenth day of Premarin treatment; Patient [redacted] in the 90 mg group was noted to have moderate to heavy bleeding after the twentieth day of Premarin treatment. Additionally, patient [redacted] was noted to have light bleeding for most of cycle 1.

b) One patient ([redacted]) in the 45 mg group and 2 patients in the 90 mg group ([redacted]) had light bleeding during the period of premarin administration. Most patients in the 45 mg and 90 mg groups had withdrawal bleeding during the expected period of COL-1620 administration, from day 15 (shaded area) to day 25 with additional bleeding through day 28 and into cycle 3. More patients (7 moderate and 4 heavy) in the 90 mg group had moderate to heavy bleeding than occurred in the 45 mg group(3 moderate and 3 heavy).

c) In Cycle 3, several patients in both treatment groups were observed to have continued bleeding into cycle 3. This bleeding was noted to decrease over days 4 through 14, then recur with the administration of COL-1620 from days 15 to 25. As in Cycle 2, more patients experienced moderate to heavy bleeding in the 90 mg group(6 moderate and 6 heavy), while in the 45 mg group(5 moderate and 3

heavy) were observed to have moderate to heavy bleeding. For individual patients it appears the duration of bleeding was longer for the 90 mg group than the 45 mg group.

Table 2, Panel B, from the sponsor, is the summary table that shows patients who received at least one dose of COL-1620 with successful bleeding:

Table 2
Panel B
Successful Menstrual Bleeding
ITT Population

Successful Bleeding Pattern Description	Statistic	Treatment Group 45 mg	90 mg
Total Patients		15	17
Light, Moderate, or Heavy	n(%)	12(80%)	14 (82%)
	90% lower C.I.	61.2%	65.7%
	95% lower C.I.	57.1%	62.1%

Note 80% of patients in the 45 mg group experienced some type of withdrawal bleeding and 82% of patients in the 90 mg group experienced withdrawal bleeding. The 95% confidence intervals are low at 57.1% for the 45 mg group and 62.1% for the 90 mg dose.

Panel C (from the sponsor) was the EFF population, that is, a subgroup of patients in the ITT population who did not bleed prior to COL-1620 administration. This table will not be reproduced since the result are similar to the ITT population. Results showed 9/12 (75%) had withdrawal bleeding in the 45 mg group while 8/11 (73%) had withdrawal bleeding in the 90 mg group. Ninety-five percent confidence intervals were low (46.3% for the 45 mg group and 41.3% for the 90 mg group).

Baseline ultrasounds were preformed on patients at entrance into the study and during days 12, 13 or 14 of cycles 2 and 3. Endometrial thickness was to be at least 5 mm at entrance to the study. Ultrasound at day 24 of cycle 3 showed consistent endometrium thicknesses of 5 mm to 9 mm for both the 45 mg and 90 mg dosages. Endometrial biopsy material was obtained at Visit 6 (Day 24 of Cycle 3). Thirteen of 15 patients in the 45 mg group had endometrial biopsies. Of those 13 patients, 12 patients (92%) had an endometrial biopsy suggestive of a progestational effect due to COL-1620. Endometrial biopsy evaluation revealed one patient (8%) with early secretory endometrium, four patients (31%) with mid secretory endometrium, and seven patients (54%) with late

secretory endometrium. One patient (13%) had a proliferative endometrium, which is not suggestive of efficacy for COL-1620. In the 90 mg group, all 16 patients (100%) who underwent endometrial biopsies had results suggestive of a progestational effect due to COL-1620. Endometrial biopsy evaluation revealed two patients (13%) with atrophic endometrium, five patients (31%) with early secretory endometrium, three patients (19%) with mid secretory endometrium, and six patients (38%) with late secretory endometrium.

SAFETY

The number and percentage of patients in each treatment group who reported adverse events (AEs) during the study are summarized by body system and preferred term in Table 16.0 This table will not be reproduced. In the Intent-to-Treat population 15 (87% in the 45 mg group) and 17/17 (100% in the 90 mg group) had at least one adverse event prior to initiationing the use of COL-1620. No patient discontinued from the study because of adverse events, and there were no serious adverse events (SAEs). In the 90 mg group, Patient [redacted] had an AE (mass in the third ventricle of the brain, first reported on day 24 of Cycle 3), this AE was judged by the Investigator to be asymptomatic and consistent with a dermoid. The patient was not hospitalized, and no biopsy was scheduled. The Investigator judged this AE as not related to study drug. Table 3, Panel D is a summary of adverse events with an incidence of at least 15% in the ITT population. This Panel is abstracted from the sponsor's table 1.

Table 3
Panel D
Summary of Adverse Events with and Incidence of at Least 15%
ITT Population
(Abstracted from Table 16)

	COL-1620					
	45 mg			90 mg		
Adverse Event WHO Preferred Term	Before COL-1620	After COL-1620	Relative Change[1]	Before COL-1620	After COL-1620	Relative Change[1]
Total Patients	15	15		17	17	
Emotional Lability	6(40%)	4(27%)	-33%	8(47%)	6(35%)	-25%
Cramps (nos)	3(20%)	2(13%)	-33%	6(35%)	6(35%)	0
Headache	5(33%)	3(20%)	-40%	10(59%)	4(24%)	-60%
Fatigue	2(13%)	3(20%)	50%	5(29%)	4(24%)	-20%
Sleep Disorder	5(33%)	3(20%)	-40%	6(35%)	3(18%)	-50%
Depression	3(20%)	2(13%)	-33%	8(47%)	3(18%)	-63%
Upper Respiratory Tract Infection	2(13%)	2(13%)	-33%	3(18%)	3(18%)	0
Bloating	2(13%)	2(13%)	0	5(29%)	2(12%)	-60%
Nausea	2(13%)	1(7%)	-50%	4(24%)	1(6%)	-75%
Water Retention	1(7%)	0	-100%	3(18%)	1(6%)	-66%
Vaginal Discharge	0	1(7%)	N.D.[2]	3(18%)	0	-100%

[1]Percent Change in number of patients reporting AE with onset after first administration of COL-1620, compared to number of patients reporting AE with onset before first administration.
[2]N.D., not determined

Note, although the number of patients in the ITT population were small, most of the psychiatric disorders such as emotional lability (mood swings), depression and sleep disorders were improved with both dosages of COL-1620. Additional symptoms such as cramps, headache, fatigue, bloating and water retention were also improved.

Table 17 (not shown) reported the incidence of mild-moderate-severe treatment emergent AEs. In the 45 mg group five patients had a mild AE, five had a moderate AE, and four had a severe AE. Patients with the severe AEs were noted to have cramps, headache, vaginal dryness and urticaria. Patients with the severe headache and severe cramps were treated with medication and their symptoms resolved. Both events were judged to be possibly related to study drug. Additionally, the patient with the severe vaginal dryness was judged to be possibly related to study drug. In the 90 mg group, three patients had a mild AE, eleven had a moderate AE, and one had a severe AE. The one patient with the severe AE had a brain neoplasm which had been previously described. This was judged not to be drug related. No pattern of a greater frequency in AE's was noted with increasing dosage.

Minimal changes were reported in the hematological measurements from screening to Visit 6. The hemoglobin declined slightly, but was still within the normal range at visit 6. The WBC count also slightly decreased. Both changes in the hemoglobin and WBC counts were judged to be not clinically significant. There were mild changes in total protein and albumin in both treatment groups, these parameters remained well within the normal ranges and were judged not clinically significant.

Four patients had a vaginal abnormality at Visit 6 (white and /or yellow clumps in the vagina) which was not reported at Visit 1. This discharge was reported in two patients in the 45 mg group and two patients in 90 mg group. One patient was also noted to have a cervical polyp at Visit 6 which was not apparent at Visit 1.

Referring back to Panel D, although numbers are small as in the 004 study, it appears that there is a decreasing incidence in depression, mood swings (emotional lability), and sleep disorders in patients after administration of COL-1620 from Visit 1 to Visit 6.

8.1.5 Reviewer's comments/conclusions of study results:

In this randomized, open-labeled study(COL-1620-005US), the sponsor administered Premarin as the priming estrogen, in patients with HA or POF, who were randomized into this study. Satisfactory estrogenization of the endometrium was suggested via hormonal concentration at screening and subsequent visits. Ten patients in Cycle 1 had withdrawal bleeding prior to initiation of COL-1620 suggesting an initial low estrogen milieu which would be responsive to progesterone stimulation. Overall, this would have the effect of diminishing efficacy results of COL-1620. Results indicate that withdrawal bleeding in

the ITT population was achieved in 80% in the 45 mg group and 82% in the 90 mg group. Because of small sample size the 95% CI is low at 57.1% and 62.1% respectively for the 45 mg and 90 mg doses.

Endometrial biopsy, as defined by the sponsor, was efficacious in 92% of the 45 mg group and 100% in the 90 mg group. An argument could be made that a fully secretory endometrium is the best predictor of a complete progestational effect. However, adequate endometrial priming may not always be achieved with estrogen replacement therapy, therefore, various gradations of secretory endometrium may be the resultant effect in individualized patients. A more stringent definition of secretory endometrium was not described in the initial protocol for these studies. Therefore, as stated earlier, by definition in Blaustein's text, biopsy material data in this study supports a diagnoses of secretory endometrium.

There appears to be no significant safety problems in this study. As shown in Panel D most adverse effects appear to have improved slightly with COL-1620. Additionally, when summary table 18 (Vol 33 pages 117-118) is reviewed, it appears that the total number of patients with AE's, who received COL-1620, is reduced from 67% to 20% in the 45 mg group and from 76% to 12% in the 90 mg group, further suggesting an overall positive effect when HRT is administered.

8.1
Study COL-1620-009US

8.1.1 The objective of this study was to evaluate the comparative efficacy of a transvaginally administered progesterone (COL-1620) at doses of 45 mg and 90 mg in inducing withdrawal bleeding in a population of women of reproductive age who suffer from hypoestrogenic secondary amenorrhea (hypothalamic amenorrhea or premature ovarian failure).

8.1.2

This study was a two-site, three-month, parallel-group, randomized, open-label, dose-comparison trial comparing the effects of COL-1620 containing progesterone doses of 45 mg and 90 mg administered every other day to women who were 18-45 years of age and who suffered from two well-defined subgroups of secondary amenorrhea: hypothalamic amenorrhea and premature ovarian failure. The study was conducted at

between January 27, 1995 and December 29, 1995. For each patient, the study comprised three consecutive menstrual cycles of approximately 28 days each. Enrolled patients were to receive Premarin 0.625 mg/day for 3 cycles of 28 days consecutively, followed by

COL-1620 at doses of 45 mg or 90 mg every other day on Days 15-25 of the last two consecutive menstrual cycles.

Inclusion Criteria
Inclusion criteria are consistent with those of Study 004 and 005 except for the following:

- non-smoking females of reproductive age (18-45); and the additional inclusions shown in Study 005

Exclusion Criteria
Exclusion criteria are consistent with Study 005

8.1.3.2
Conduct of the Study
This study was conducted in the same manner as Study 005. The effect of estrogen-only treatment on the menstrual bleeding pattern was to be evaluated using data from Cycle 1 and withdrawal bleeding following estrogen and progesterone treatment was to be evaluated using data from Cycles 2 and 3. Premarin was self-administered every day from Day 1 of Cycle 1 to Day 28 of Cycle 3; patients were to self-administer COL-1620 in the morning of every other days on Days 15-25 of Cycles 2 and 3. An endometrial biopsy was to be evaluated at end of Cycle 3.

Six visits were scheduled and a telephone interview after Day 25 of Cycle 2 to assess withdrawal bleeding. Endometrial biopsy material was to be evaluated by
as in Study 005.

Changes to the Study/Protocol Amendments
Six protocol amendments were made during the three studies. For Study 009 all other amendments apply and the sixth (numbered 5 in this submission) relates only to study 009. The fifth protocol amendment (November 30, 1995) increased the number of patients enrolled in this study. This amendment specified the enrollment of approximately 80 patients in the study, so that a minimum of 30 patients would complete the study protocol in each COL-1620 dose group.

8.1.3.3

The statistical analysis plan was essentially the same as in Study 005 with the exception that at least 40 patients per dose group were enrolled in order to achieve a sample size of 25 at the end of Cycle 2 (anticipated dropout rate of 20%).

8.1.4 Results

This study, conducted between January 27, 1995 and December 29, 1995, was designed to assess the safety and efficacy of two doses (45 mg and 90 mg) of transvaginally self-administered progesterone (COL-1620) in producing withdrawal bleeding in women with hypoestrogenic amenorrhea. Patients were estrogenized by oral self-administration of Premarin daily on Days 1 through 28 of Cycles 1 and 2, and Days 1 through 26 of Cycle 3. COL-1620 was self-administered every other day during Days 15 through 25 of Cycles 2 and 3. The primary efficacy parameter was successful bleeding after the administration of COL-1620. Endometrial biopsy results served as the secondary measure of efficacy.

Seventy-three patients were enrolled into this study. Thirty-six were randomized to receive 45 mg COL-1620 and 37 were randomized to receive 90 mg of COL-1620. Of these patients, 35 in the 45 mg group and 37 in the 90 mg group received Premarin. The ITT population consisted of 34 patients in each dose group who received Premarin and at least one dose of COL-1620. Two patients in the 45 mg group and three patients in the 90 mg group withdrew from the study prior to receiving COL-1620 were not included in the ITT population. In the 45 mg group, all 34 ITT patients completed Cycle 2, and 32 patients (94%) completed Cycle 3. In the 90 mg group, all 34 ITT patients completed Cycle 2, and 30 patients (88%) completed Cycle 3.

Demographically, the two dose group were comparable with respect to race (94% and 88% Caucasian in the 45 mg group and 90 mg group, respectively, and 6% African-American in each group), age (mean 28.4 ± 1.3 and 27.6 ± 1.4 years in the 45 mg group and 90 mg group, respectively), weight (mean 119.1 ± 3.3 and 122.0 ± 3.1 pounds in the 45 mg group and 90 mg group, respectively), height (mean 64.9 ± 0.7 and 65.4 ± 0.5 inches in the 45 mg and 90 mg group, respectively), current alcohol use, and smoking history. Past smokers in the 45 mg group smoked more cigarettes on average per day before quitting (18.5) than did those in the 90 mg group (12.0).

With regard to medical history, the two doses were comparable. Twenty-three (68%) in the 45 mg group and 24 patients (71%) reported having abnormalities at screening. The most frequently reported abnormalities were endocrine/metabolic abnormalities (13 and 14 patients in the 45 mg group and 90 mg group, respectively).

With regard to the obstetrical and gynecological history, the two groups were comparable. Overall, 17 (25%) had at least one pregnancy. Seven (21%) in the 45 mg group and 10 (29%) in the 90 mg group had at least one pregnancy. Overall, 6 (9%) had one delivery, 3 in the 45 mg group and 3 in the 90 mg group. No patient had been sterilized. Nine patients (13%) had a history of an STD, 7 (21%) in the 45 mg group and 2(6%) in the 90 mg group.

Patients who withdrew from the study or who were protocol violators, were listed in sponsor's table 2.0. This table will not be reproduced, but will be summarized. Four patients in the 45 mg group withdrew from the study. Three withdrew because of patient desire, and the fourth patient was withdrawn as a protocol violator because of spotting in cycle 1, days 1, 2 and 3. Seven patients were withdrawn in the 90 mg group. One patient withdrew because of patient desire, one patient went on vacation and forgot her medication, one patient experienced an adverse event, one patient did not take her progesterone until Cycle 3, day 4, and three patients were protocol violators because of insufficient endometrial thickness (<5 mm) at days 12, 13 or 14 of cycles 2 or 3.

The medication history summary was not remarkable for prior medications. In the 45 mg group, one patient had taken fluoxetine hydrochloride, lithium, mesalazine, methylphenidate hydrochloride, and sertraline hydrochloride. These drugs were not seen in the 90 mg group, but as the reviewer, I do not feel this would be clinically significant as to the study outcome. In patients who took concomitant medications, analgesics and antibiotics (particularly metronidazole in the 45 mg group) were the predominant medications. Again, these medications are not clinically significant as to study outcome.

EFFICACY

Panel B, from the sponsor, summarizes patient with successful bleeding. This table is not shown due to its extensiveness(5 pages long). Important points from this table are:

a. Two patients in the 45 mg group were noted to have light bleeding. Two patients in the 90 mg group were noted to have light or moderate bleeding during the Premarin priming period.

b. In cycle 2, patient [redacted] had spotting on day 12 in the 45 mg group, and two patients had spotting on day 7 through 12. Most patients experienced significant bleeding between day 19 through 28. There appears to be no difference between the amount or quantity of bleeding in this cycle between the two dosages.

c. In cycle 3, in the 45 mg group, 7 patients experienced bleeding during days 1 through 14. Patients were noted to have moderate to heavy bleeding. In the 90 mg group, 8 patients have withdrawal bleeding during days 1 through 14. Patients were noted to have moderate to heavy bleeding. Most patients experienced withdrawal bleeding during days 15 thorough 25 as expected. There appears to be no difference in the days or amount of bleeding between the two dosages.

Table 4, Panel C, from the sponsor, is the summary table for the ITT patients and shows patients who received at least one dose of COL-1620 with successful bleeding:

Table 4
Panel C
Successful Menstrual Bleeding
ITT Population
(Abstracted from Table 14.0)

Successful Bleeding Pattern Description	Statistic	COL-1620 Dose 45 mg	90 mg
Total Number of Patients		34	34
Light, Moderate, or Heavy	Number (%)	28 (82%)	28 (82%)
	90% lower confidence limit	71.1%	71.1%
	95% lower confidence limit	68.9%	68.9%

Note 82% of patients experienced some type of withdrawal bleeding with both dosage groups. The 95% C.I. is approximately 69% for both dosages.

Panel D (from the sponsor), is the EFF population. This is a subgroup of patients in the ITT population who did not bleed prior to COL-1620 administration. This table will not be shown since results are very similar to the ITT population. In patients receiving the 45 mg dose, 32 patients were evaluable. Twenty-six of 32 had withdrawal bleeding (81%). For patients receiving the 90 mg dose, 30 patients were evaluable, 24(80%) had withdrawal bleeding. The 95% C.I. were 67.0% for the 45 mg dose, and 64.8% for the 90 mg dose.

At Visit 3 patients underwent an ultrasound. Endometrial thickness had to be > 5 mm or the patient was excluded from the study. Endometrial biopsies were performed at Visit 5. Biopsy was performed on 32 patients in the 45 mg group and 30 patients in the 90 mg group. Results of the endometrial biopsies are shown in sponsor's Table 15.0. This table will not be reproduced, but will be summarized. Summary biopsy specimens were evaluable in 29/31 (94%) in the 45 mg group and 29/29 patients(100%) in the 90 mg group. Results are as follows: biopsy material suggestive of a progestational effect in the 45 mg group included atrophic endometrium 4 (13%), 2 proliferative (6%), early secretory (19%), mid secretory 6 (19%), late secretory 13 (41%) and 1 other. Two patient (6%) showed no effect meaning, that a proliferative endometrium was established, but the endometrium was not converted to secretory. In the 90 mg group results showed an atrophic endometrium in 5 (17%), early secretory 1 (3%), mid secretory 7 (23%), late

secretory 16 (53%) and other 1 (3%). The "other " endometrium for both dosages contained no endometrial tissue, and was therefore, non-evaluable.

SAFETY

The number and percentage of patients in each treatment group who reported adverse events (AE's) during the study are summarized by body system and preferred term in the sponsor's table 16. This table will not be reproduced. Table 5, Panel E from the sponsor, will be reproduced because it shows the percentage of adverse events and is abstracted from table 16. In addition, this table also shows the adverse event by the preferred WHO term and whether there was any change in symptomatogy after administration of COL-1620.

Table 5
Panel E
Adverse events with an Incidence of at Least 15%
(Abstracted from Table 16.0)

	COL-1620 Dose					
	45 mg			90 mg		
Adverse Event WHO Preferred Term	Before COL-1620	After COL-1620	Relative Change[1]	Before COL-1620	After COL-1620	Relative Change[1]
Total Patients	34	34		34	34	
Cramps nos	5 (15%)	8 (24%)	60%	4 (12%)	11 (32%)	175%
Emotional lability	15 (44%)	10 (29%)	-50%	16 (47%)	8 (24%)	-50%
Depression	10 (29%)	10(29%)	0	13 (38%)	7 (21%)	-46%
Sleep Disorder	14 (41%)	7 (21%)	-50%	17 (50%)	8 (24%)	-53%
Headache	8 (24%)	6 (18%)	-25%	11 (32%)	6 (18%)	-45%
Fatigue	1 (3%)	5 (15%)	400%	3 (9%)	6 (18%)	100%
Bloating	8 (24%)	4 (12%)	-50%	3 (9%)	4 (12%)	33%
Weight Increase	5 (15%)	0	-100%	1 (3%)	0	-100%

[1]Percent change in number of patients reporting AE with onset after first administration of COL-1620, compared to number of patients reporting AE with onset before first administration.

As can be seen in Panel E most symptoms improved with Col-1620 administration. In this study, more patients experienced uterine cramps and fatigue with both doses, while bloating was increased with the 90 mg dose.

No patient died or reported serious adverse events during this study. One patient discontinued from the study because of an AE. Patient [redacted] (90 mg dose) reported continuous external vaginal itching, judged by the investigator to be severe and probably related to study drug which began on Day 18 of Cycle 2 (after two administrations of COL-1620) and lasted eight days. This patient also reported oozing of the study drug from the vagina, which was judged be be severe and definitely related to study drug. Both AE's resolved without sequelae.

Body systems in which AE's were most frequently reported include psychiatric disorders, body as a whole, central and peripheral nervous system, and gastrointestinal system. Referring back to Panel E it is easily seen, that the psychiatric disorders of sleep disorders, emotional lability, and depression are prominently reduced. Headache is also reduced. Most adverse events were judged by the investigator to be mild or moderate in severity. The only AE's judged by the investigator to be severe were cramps of nonspecific character (reported by 3 patients in the 90 mg group), migraine (reported by one patient in each group), influenza-like symptoms, vaginal discharge and genital pruritus (each reported by one patient in the 90 mg group), and syncope (reported by one patient in the 45 mg group). Overall, a higher proportion of patients in the 90 mg group (65%) than in the 45 mg group (47%) reported AE's that were judged by the investigator to be mild severity.

Seventeen laboratory values out of the normal range were reported for both dosage groups in blood samples obtained at screening though Visit 5. No patient in either group had laboratory values considered clinically relevant during the study. Although, nine patients were reported to have low hemoglobin and low WBC counts, these values were not considered clinically relevant and were not consistently associated with moderate or heavy bleeding. There were three increases in either the SGOT or SGPT and three decreases in the BUN; these values are not considered to be clinically relevant.

No patients developed new physical abnormalities during the study, and no differences in physical examinations results were between the two dose groups. No clinically relevant changes were seen in the vital signs. On final examination, one patient showed an improvement in her atrophic vaginitis at Visit 5, and one patient continued to have an ovarian cyst at Visit 5.

Referring back to Panel E, and consistent with the 004 and 005 studies, it appears that there is an improved incidence in depression, mood swings (emotional lability), and sleep

disorders with the use of COL- 1620 in patients after administration of COL-1620 and Premarin 0.625 mg/day from Visits 1 through 6.

8.1.5

In this randomized, open-labeled study (COL-1620-009US), the sponsor administered Premarin 0.625 mg/day as the priming estrogen in patients with HA or POF who were randomized in this study. Satisfactory estrogenization of the endometrium was suggested by ultrasound and hormonal concentration at screening and subsequent visits. Results indicate that in the 45 mg group and the 90 mg groups, withdrawal bleeding in the ITT population is achieved in 82% of patients. Two patients in the 45 mg group failed to achieve a secretory endometrium. Because of larger sample size than studies 004 and 005, the lower bound of the 95% CI is higher (68.9%) than in the other studies.

Endometrial biopsy supports efficacy of COL-1620. Endometrial biopsy was suggestive of a progestational effect in 94% of evaluable patients in the 45 mg group and 100% in the 90 mg group using the same criteria and reviewer as in study 005.

There appears to be no significant safety problems in this study. As shown in Panel E most adverse effects appeared to have improved slightly with COL-1620. Additionally, when summary table 18.0 (A's occurring after the start of COL-1620) is reviewed the total number of patients with at least one adverse event is decreased for both the 45 mg and the 90 mg dosages, suggesting a overall positive effect of HRT treatment. Of cause for some concern, is that in the 45 mg group two patients failed to convert a proliferative endometrium to secretory.

9 OVERVIEW OF EFFICACY

The sponsor conducted three-month, parallel, randomized, open-labeled, multiple dose studies in which 127 women in the ITT population were studied. All women had a well-defined diagnosis of hypothalamic amenorrhea or premature ovarian failure. Sixty-two women received 45 mg of COL-1620 and 65 women received the 90 mg COL-1620 every other day for 10 days after the uterus had been primed by either Estraderm or Premarin. The ITT population is shown in the following table with appropriate ninety-five percent CI.

Table 6
Summary Table of Efficacy for ITT Population

Studies	Number of Patients	Patients with Successful Bleeding N (%)	Lower 95% Confidence Limits
COL-1620-004US			
45 mg q.o.d.	13	10 (77%)	46.2%
90 mg q.o.d.	14	11 (79%)	49.2%
COL-1620-005US			
45 mg q.o.d.	15	12 (80%)	51.9%
90 mg q.o.d.	17	14 (82%)	56.6%
COL-1620-009US			
45 mg q.o.d.	34	28 (82%)	65.5%
90 mg q.o.d.	34	28 (82%)	65.5%
Overall			
45 mg q.o.d.	62	50 (81%)	68.6%
90 mg q.o.d.	65	53 (82%)	70.0%

Note the consistency of successful withdrawal bleeding between studies. The study population was homogenous between the studies, with the 009 study having more than double the number of patients as the 004 and 005 studies. The 80% rate of withdrawal bleeding is consistent with other progestational products such as oral Provera and oral micronized progesterone. The C.I. did not reach the sponsor's projected 80%. This is somewhat disappointing. However, it is noted that as the number of randomized patients increased in each study, the lower bound of the 95% C.I. also increased, thereby implying that with sufficient power the C.I. could have potentially reached 80%. These study populations, however, may be a more difficult population in which to produce withdrawal bleeding since all patients had low levels of endogenous estrogen and were anovulatory. Other patient populations, such as PCOD or hyperprolactemia patients, should had comparable or even higher rates of withdrawal bleeding since by definition, these patients have normal levels of endogenous estrogens.

The secondary efficacy variable is the production of a secretory endometrium with COL-1620 after priming of the endometrium with either Premarin or Estraderm on day 10 of the cycle. Results indicate, in the ITT population, that the 45 mg group produced a "progestational effect" in 52/55 patient (92%) while 4 patients (8%) had no effect (proliferative endometrium). In the 90 mg group, 54/55 (98%) produced an endometrium

that was classified as "progestational effect." There were no patients with proliferative endometrium at the higher dosage. The proliferative endometrium seen in one patient each in studies 004 and 005 and in two patients in the 009 study with the 45 mg dosage, is cause for some concern. In patients who might be receiving HRT for postmenopausal indications, complete transformation to a secretory endometrium is a necessity. Therefore, patients with irregular shedding, or significant unexpected bleeding may required an endometrial biopsy to rule out forms of hyperplasia. If this occurs, either changing the dosage to daily, or increasing the dosage to 90 mg every other day may be appropriate.

10 OVERVIEW OF SAFETY

Eighty-nine percent and 85% of the patients completed these studies in the 45 mg and 90 mg COL-1620 dose groups respectively. Seventeen patients discontinued prematurely; 7 (41%) were in the 45 mg dose group and 10 (59%) were in the 90 mg dose group. With both study dosages, approximately half of these discontinuations were due to the premature termination of study 004. No clear-cut dose-related trend in premature discontinuations was evident. No patient in the 45 mg group and one (2%) in the 90 mg group discontinued due to an AEs.

In the sponsor's summary table 14.1 (not shown) patients who received 45 mg q.o.d. had at least one treatment emergent adverse events (TEAE) with a maximum rating of mild, moderate, or severe at frequencies of 50%, 23%, and 10%, respectively, compared to corresponding frequencies of 48%, 22%, and 18% of patients who received 90 mg q.o.d.

Patients with TEAE's (i.e. adverse events that began or worsened after the first dose of COL-1620) with the strongest relationship to COL-1620 of $\geq$ 15% are shown in sponsor's summary Table 15.1 (not shown) by dose administered. For the 45 mg dose, the number of patients with a TEAE was 32 (52%). Cramps (nonspecific) were noted in 9 (15%) of patients, emotional lability 10 (16%), fatigue 8 (13%), sleep disorder 6 (10%), depression 6 (10%) and headache 10 (16%). With the 90 mg dose, TEAE's were noted in 38 (58%) of patients. Cramps (nonspecific) were reported in 17 (26%), emotional lability 9 (14%), fatigue 6 (9%), sleep disorder 5 (8%), depression 7 (11%), and headache 7 (11%). Other related AEs reported in the sponsor's table 15.1 with > 2% adverse events for either the 45 or 90 mg doses include bloating 6%-9%, pain 3%, eructation 3%, nausea 3%, myalgia 5%, insomnia 3%, nervousness 3%, upper respiratory tract infection 3%, acne 3% and genital pruritus 5%.

One patient discontinued use of COL-1620 with the 90 mg dose. She experienced a severe vaginal discharge and genital pruritus after exposure to the drug for 4 to 5 days. She improved after discontinuation of study drug.

There were no deaths in these studies. Overall, it can be stated that the adverse events seen with COL-1620 are not unexpected and are consistent with that of other progesterones. Some adverse events such as fatigue, somnolence, dizziness, nausea, breast tenderness, etc., seem to be lessened since the drug was given every other day for 5 days, and was given vaginally. More severe adverse events could be experienced as the dosage, daily use, or duration of treatment is extended. This was seen in patients treated in the IVF program who received treatment daily.

There is some concern and need for caution with the 45 mg dose. Four patients out of 52 (7.7%) had no transformation of the endometrium from proliferative to secretory. Patients receiving the 45 mg dose may need to be monitored more closely with endometrium biopsies or pelvic sonograms if they are receiving HRT for extended periods of time. These studies were only three months in duration, and prolonged use with Premarin 0.625 or higher, may produce an even higher incidence of no effect, which could lead to endometrial hyperplasia.

11 Labeling Review

1 Page (36)
Deleted
Labeling Revisions

12 Conclusions

The sponsor has demonstrated through three three-month, parellel-group, randomized, open-labeled, multiple-dose studies that Crinone is safe and effective in producing withdrawal bleeding and a progestational effect upon the endometrium. In patients receiving ERT for a prolonged period of time, the dosage of Crinone may have to be increased to 90 mg to protect against endometrial hyperplasia.

13 Recommendation

Approval with labeling revisions for a combined label for the indications of Assisted Reproductive Technology and Secondary Amenorrhea(after concurrence from all disciplines once reviews are completed). Prior to approval, the sponsor should commit to a Phase IV study to determine the rate of withdrawal bleeding in the usual targeted patient with secondary amenorrhea.

Phill H. Price, M.D.
July 7, 1997

Concur that application is approvable.
HJolson 7/13/97

This review is 38 pages with 3 pages of clinical investigators.

CC. IND/NDA
HFD-340
HFD-580 (NDA/IND)
HFD-580/PPrice/HJolson/WpFiles:20701mor.nda

Title: A Parallel, Randomized, Open-label Study of Transvaginal Administration of Natural Progesterone in Secondary Amenorrhea Using the Polycarbophil Base Sustained Release System, COL-1620

Study No: [redacted]

Product: COL-1620

Investigator: Michelle P. Warren, M.D.
St. Luke's/Roosevelt Hospital
New York, NY
Telephone: (212) 523-8930
Fax: (212) 523-8932

Sponsor: Howard Levine, Pharm. D.
Columbia Research Laboratories, Inc.
100 No. Village Avenue
Rockville Centre, NY 11570
Telephone: (516) 766-2660
Fax: (516) 766-2873

Prepared by: Quintiles, Inc.
P.O. Box 13979
Durham, NC 27703
Telephone: (919) 941-2888

Date of Study Initiation (First Patient Enrolled): 12 April 1994

Date of Study Completion (Last Patient Completed): 11 January 1995

Report Date: 18 December 1995 (Draft)
3 May 1996 (Final)

Title: A Parallel, Randomized, Open-Label Study of Transvaginal Administration of Natural Progesterone in Secondary Amenorrhea using the Polycarbophil Base Sustained Release System, COL-1620

Study No: COL1620-005US

Product: COL-1620

Investigator: Mona M. Shangold, M.D.
Hahnemann University Hospital
Philadelphia, PA
Telephone: (215) 762-6850
Fax: (215) 246-5250

Sponsor: Howard Levine, Pharm. D.
Columbia Research Laboratories, Inc.
100 North Village Avenue
Rockville Centre, NY 11570
Telephone: (516) 766-2660
Fax: (516) 766-2873

Prepared by: Quintiles, Inc.
P.O. Box 13979
Research Triangle Park, NC 27709-3979

Date of Study Initiation (First Patient Enrolled): 27 December 1994

Date of Study Completion (Last Patient Completed): 29 December 1995

Report Date: 26 April 1996

Title: A Parallel, Randomized, Open-Label Study of Transvaginal Administration of Natural Progesterone in Secondary Amenorrhea using Polycarbophil Base Sustained Release System, COL-1620

Study No: COL1620-009US

Product: COL-1620

Investigators: Michelle P. Warren, M.D.
St. Luke's Roosevelt Hospital
New York, NY
Telephone: (212) 523-8930
Fax: (212) 253-8932

Beverly M.K. Biller, M.D.
Massachusetts General Hospital
Boston, MA
Telephone: (617) 726-3872
Fax: (617) 726-5905

Sponsor: Howard Levine, Pharm. D.
Columbia Research Laboratories, Inc.
100 North Village Avenue
Rockville Centre, NY 11570
Telephone: (516) 766-2660
Fax: (516) 766-2873

Prepared by: Quintiles, Inc.
P.O. Box 13979
Durham, NC 27703
Telephone: (919) 941-2888

Date of Study Initiation (First Patient Enrolled): 27 January 1995

Date of Study Completion (Last Patient Completed): 29 December 1995

Date of Report: 26 April 1996