

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-276

MEDICAL REVIEW

**Medical Officer's Review of NDA 21-276
Original Submission**

I.- GENERAL INFORMATION

NDA submission number: 21-276

Applicant identification:

Name

Address and telephone number

Parke-Davis Pharmaceutical Research
2800 Plymouth Road
Box 1047
Ann Arbor, Michigan 48106-1047
734/622-5000

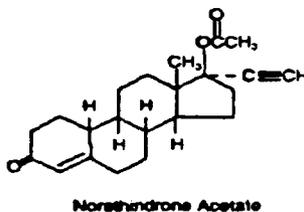
Submission/review dates

Date of submission	June 30, 2000
CDER stamp date	July 03, 2000
Date submission received by reviewer	August 30, 2000
Date review begun	September 05, 2000
Date review completed	5/16/2001

Drug identification

Generic name: Norethindrone acetate (NEA) and ethinyl estradiol (EE)
Proposed trade name: Estrostep™
Chemical name (17-alpha)-17-(acetyloxy)-19-norpregna-4-en-20-yn-3-one and 17 alpha-19-norpregna-1,3,5(10)-traien-20-yne-3, 17diol

Chemical structure:



Pharmacologic Category: Oral contraceptive

Dosage form: 21 or 28 day pack, one tablet per day
5 days white triangular tablet with 1 mg NEA and 20 mcg EE
7 days white square tablets with 1 mg NEA and 30 mcg EE
9 days white round tablets with 1 mg NEA and 35 mcg EE
+/- 7 days brown round tablet with 75 mg ferrous fumarate, USP

Route of Administration oral tablets

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

II.- INDEX

I. General Information:	Page	1
Drug identification		1
II Index		3
III Executive Summary		6
Recommendations		6
Summary of Clinical Findings		6
IV Proposed indication and usage		7
Proposed dosage and administration		7
Related drugs		8
Materials reviewed		8

VI Chemistry/Manufacturing Controls		14
VII Animal Pharmacology /Toxicology		14
VIII Statistical Review		14
IX Microbiology		14
X Human Pharmacology/ Pharmacodynamics		14
XI Human Clinical Experience		14
XII Overview of Medical Studies		14
Introduction		14
Indication acne. Rational		15

XIII	Phase 3 Studies:	Page	18
	Study 376-403		18
	Study Objective		18
	Investigators		18
	Protocol overview		20
	Study schedule and phases		20
	Subject selection		21
	Treatment Regimen		26
	Efficacy Parameters		27
	Safety parameters		29
	Study Results		30
	Demographic		30
	Efficacy analysis		33
	Safety analysis		34

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

XIV	Study 376- 404	Page	38
	Investigators		38
	Protocol overview		40
	Study Results		41
	Demographic		41
	Efficacy analysis		44
	Safety analysis		45
XV	Summary		50
	Demographic characteristics		50
	Overview of Efficacy		54
	Quality of Life		55
	Overview of Safety		56
	Serious Cases		59
	Narratives of Serious Cases		61
	Pregnancy		64
XVI	Considerations of Risk Benefit analysis		66
	Comparison of intermenstrual bleeding		66
	Comparison of other adverse events (ovarian cysts)		66
	Comparison of contraceptive efficacy		66
	Potential for premature epiphyseal closure in postmenarcheal adolescents taking oral contraceptives		67
	Literature quotations		68
	Reviewer comments on risk-benefit		68
XVII	Summary and Evaluation		69
XVIII	Pediatric Waiver		70
XIX	Medical Review of Label		71
XX	Recommendations		124

III. EXECUTIVE SUMMARY

Recommendations

The application is approvable, depending upon the sponsor's acceptance of revised labeling

Summary of Clinical Findings

A. Brief Overview of Clinical Program

Two identically designed but separate clinical studies were conducted in the United States by Parke-Davis in support of efficacy and safety for the acne indication. These studies were randomized, double-blind, placebo-controlled and multicenter. There were 1031 subjects enrolled (i.e. signed a consent form) (ages 13-49), of which 593 who met the inclusion/exclusion criteria were randomized, and 403 completed the study. The study compared the approved Estrostep® (297 subjects randomized, 213 completed) and a placebo (296 randomized, 190 completed), after administration over 6, four-week cycles, for the acne indication.

B. Efficacy

In study 403, the Estrostep® group demonstrated, in the Intent-To-Treat population (ITT), a statistically significant decrease in lesion counts for comedones and for total lesion counts but not for inflammatory lesion counts. After 6 cycles, the difference from baseline for Estrostep® over placebo was 6 for comedones, while for total lesion counts, the Estrostep® effect over placebo was 8 lesions. The results for the third lesion count, inflammatory lesions, were not statistically significant.

On Facial Global Assessment, no Estrostep® treated subject in the ITT population, or in the PP population, reached an Investigator Global Assessment of absent (no residual acne lesions) by the end of the study. The percent of Estrostep® treated subjects who were graded as "absent and/or minimal" at study end (16%) was statistically significantly different from the placebo-treated group (7%). The difference over placebo at study end was 9%.

In study 404, the Estrostep® group demonstrated, in the Intent-To-Treat population, a statistically significant decrease in Total lesion counts as well as for comedones and for inflammatory. At the end of the study, the difference from baseline over placebo was 3 for total lesion counts, 6 for comedones, and 9 for inflammatory lesions. In this study, the results obtained in the PP population were supportive of efficacy but of similarly lacking in robustness

On Facial Global Assessment, the percent of Estrostep® treated subjects (19%) who were graded as "absent and/or minimal" at study end was statistically significantly different from the placebo-treated group (7%). The difference over placebo at study end was 11%.

The difference in effect of Estrostep® over placebo for the pooled population from both studies was as follows: a reduction of 9 for total lesion count, 6 for comedones, and 3 for inflammatory lesions.

C. Safety

The pattern and frequency of adverse events reported during these two studies was consistent with those reported when Estrostep® was studied for oral contraception.

D. Dosing

Dosing was identical to the dosage approved for Estrostep® when used as an oral contraceptive.

IV. PROPOSED INDICATION & USAGE SECTION

The label proposed by the Sponsor includes the following:

INDICATIONS AND USAGE

[REDACTED]

Estrostep® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

[REDACTED]

Estrostep® is indicated for the treatment of moderate acne vulgaris in females, [REDACTED] years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications.

[REDACTED]

Oral contraceptives are highly effective. Table II lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

Proposed Dosage & Administration section

The label proposed by the sponsor includes the following:

[REDACTED]

The timing of initiation of dosing with Estrostep® for acne should follow the guidelines for use of Estrostep® as an oral contraceptive. Consult the DOSAGE AND ADMINISTRATION section for oral contraceptives.

Dosage and Administration for 21-Day Dosage Regimen

To achieve maximum contraceptive effectiveness, Estrostep® 21 must be taken exactly as directed and at intervals not exceeding 24 hours. Estrostep® 21 provides the patient with a convenient tablet schedule of "3 weeks on—1 week off." Two dosage regimens are described, one of which may be more convenient or suitable than the other for an individual patient. For the initial cycle of therapy, the patient begins her tablets according to the Day-1 Start or Sunday-Start regimen. With either regimen, the patient takes one tablet daily for 21 consecutive days followed by one week of no tablets.

- A. Sunday-Start Regimen:** The patient begins taking tablets from the top row on the first Sunday after menstrual flow begins. When menstrual flow begins on Sunday, the first tablet is taken on the same day. The last tablet in the dispenser will then be taken on a Saturday, followed by no tablets for a week (7 days). For all subsequent cycles, the patient then begins a new 21-tablet regimen on the eighth day, Sunday, after taking her last tablet. Following this regimen of 21 days on—7 days off, the patient will start all subsequent cycles on a Sunday.
- B. Day-1 Start Regimen:** The first day of menstrual flow is Day 1. The patient places the self-adhesive day label strip that corresponds to her starting day over the preprinted days on the tablet dispenser. She starts taking one tablet daily, beginning with the first tablet in the top row. The patient completes her 21-tablet regimen when she has taken the last tablet in the tablet dispenser. She will then take no tablets for a week (7 days). For all subsequent cycles, the patient begins a new 21-tablet regimen on the eighth day after taking her last tablet, again starting with the first tablet in the top row after placing the appropriate day label strip over the preprinted days on the tablet dispenser. Following this regimen of 21 days on—7 days off, the patient will start all subsequent cycles on the same day of the week as the first course. Likewise, the interval of no tablets will always start on the same day of the week.

Tablets should be taken regularly at the same time each day and can be taken without regard to meals. It should be stressed that efficacy of medication depends on strict adherence to the dosage schedule.

Related Drugs

[Redacted]			
NDA	20,130	Estrostep	Oral contraceptive for acne
NDA	20,681	Ortho Tri-cyclen*	O. C. for acne

* This NDA is listed here because it is a similar oral contraceptive which has been approved for the acne indication

MATERIAL REVIEWED

NDA volumes reviewed: 1.1-1.49

Other documents reviewed applicable to this review:

NDA 20,130 Estrostep
NDA 20,681 Ortho Tri-cyclen

[Redacted]

Amendments reviewed:

Submission	Type	Dated	Submission	Type	Dated
------------	------	-------	------------	------	-------

Submission	Type	Dated	Submission	Type	Dated
000	Original	6/30/00	006	SU	11/17/00
001	NC	9/6/00	007	BM	12/20/00
002	NC	9/14/00	008	NC	12/20/00
003	BM	10/9/00	009	BM	1/30/01
004	BM	11/7/00	010	BM	2/22/01
005	BM	11/10/00			

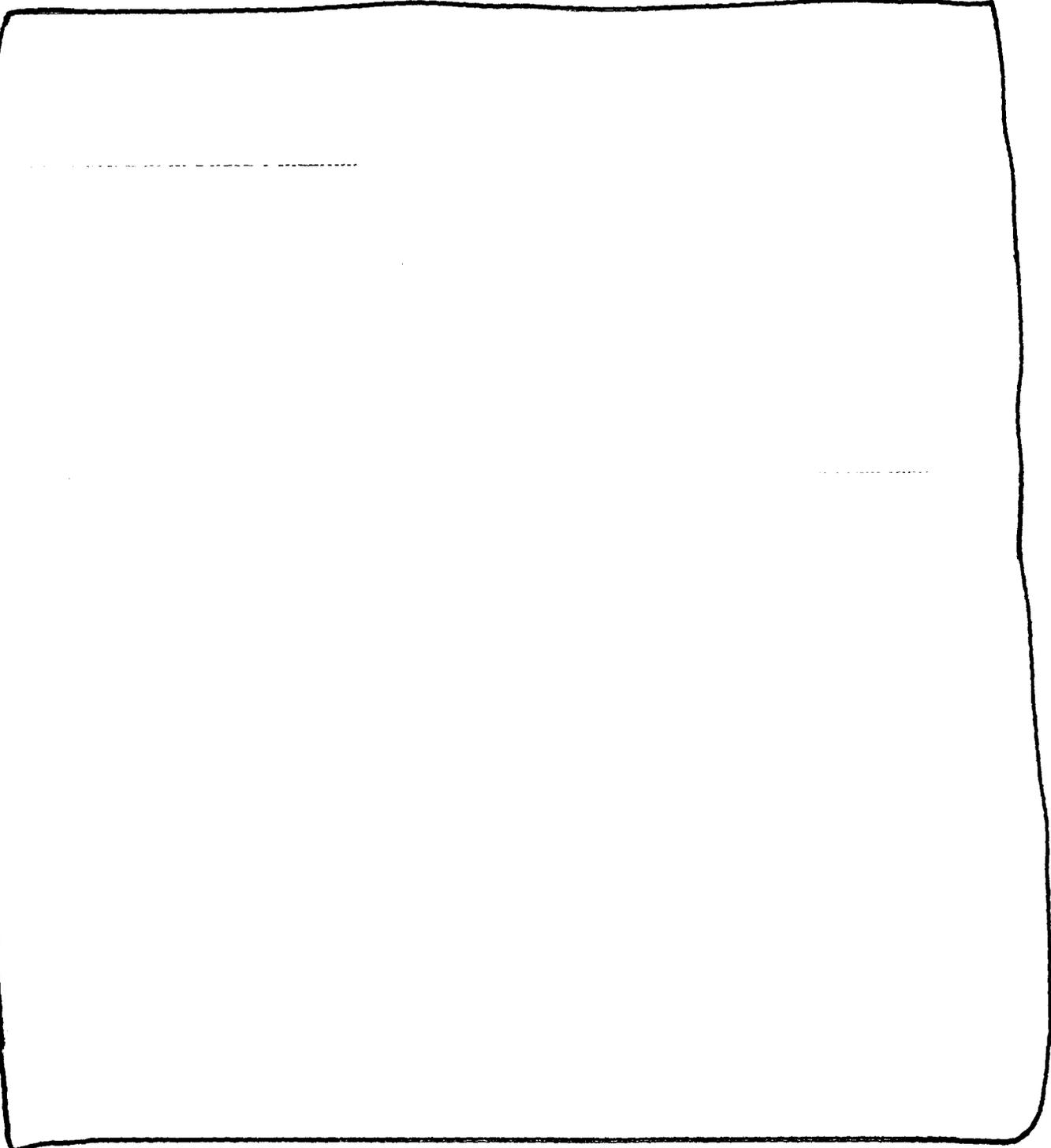
APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

V.- REGULATORY BACKGROUND

Studies in support of the acne indication in this NDA were conducted under [redacted] which was submitted 4/22/98.

The following have been important interactions with the Agency relating to [redacted]



3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

[Redacted]

VI.-CHEMISTRY/MANUFACTURING CONTROLS : No new data is being supplied.

VII.-ANIMAL PHARMACOLOGY/TOXICOLOGY: No new data is being supplied.

VIII.-STATISTICAL REVIEW: See Statistical review.

IX.-MICROBIOLOGY : No new data is being supplied.

X.-HUMAN PHARMACOKINETICS/PHARMACODYNAMICS: see Biopharm review.

XI.-HUMAN CLINICAL EXPERIENCE:

Foreign experience: There is no foreign experience since the drug has never been approved outside the U.S.

Post-Marketing Experience

The drug product has not been approved for the acne indication and therefore there is no postmarketing experience for the acne indication.

XII.-OVERVIEW OF CLINICAL STUDIES

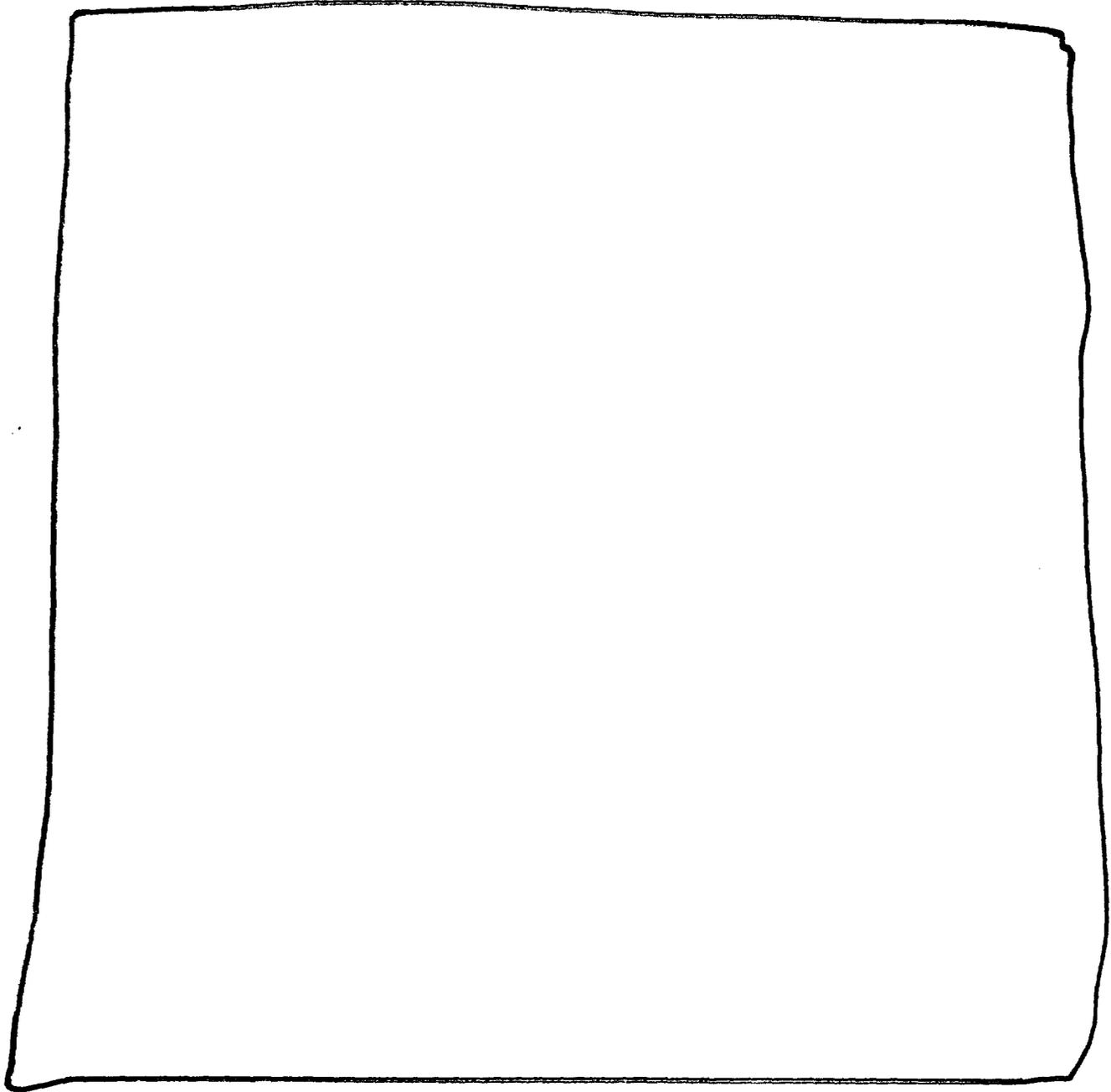
Introduction

The Clinical studies provided in this submission are as follows:

Protocol	Description	Number of subjects (Active /placebo)		
		Enrolled	Randomized	Completed
376-403	Efficacy and safety and pharmacokinetics	476	298 (150/148)	188 (102/86)
376-404	Efficacy and safety	550	295 (147/148)	215 (111/104)

These studies were conducted with the formulation currently marketed for oral contraception.

[Redacted]



Indication Acne

Rationale:

Sponsor hypothesizes the following concepts:

- Acne vulgaris, while most common in adolescence and young adulthood, is also prevalent in middle aged adults and can lead to lifelong scarring. Acne is the end result of a process initiated by androgenic stimulation of sebum production.
- The characteristic adolescent onset of acne is due to the pubertal rise in androgen

secretion that triggers a rise in sebum production. In susceptible individuals, the surface keratin is more viscous and traps sebum within the sebaceous follicle where it serves as a culture medium for bacteria. This secondary bacterial infection leads to the classic inflammatory lesions seen in acne vulgaris. If untreated, these inflammatory lesions can lead to permanent scarring. Nearly all of the currently available acne treatments target the lesions that form as a result of increased sebum production rather than the underlying androgen secretion. These treatments include topical cleansers, such as benzoyl peroxide; systemic antibiotics; and topical retinoids, such as Accutane. While these agents are useful in the treatment of acne, they do not address the underlying androgen production, and thus may not be completely successful in all individuals.

- Oral contraceptives reduce androgen levels by 2 mechanisms. They suppress gonadotropin secretion, decreasing ovarian androgen secretion and they increase the concentration of sex hormone binding globulin (SHBG), reducing the amount of free androgen available. Previous uncontrolled studies indicated a role for oral contraceptives in the treatment of acne. In 1997, however, results from a placebo-controlled trial was published demonstrating the efficacy of an oral contraceptive containing 35 mcg EE and triphasic norgestimate in the treatment of acne. This improvement in acne was associated with a rise in SHBG and a fall in free testosterone concentration. This study was used to support a New Drug Application (approved on December 31, 1996) for the treatment of acne in women 15 years in age and above, providing an important addition to the anti-acne armamentarium.
- Since oral contraceptives containing Norethindrone acetate, such as Estrostep®, have a similar effect to norgestimate on free testosterone and SHBG, sponsor predicts a similar impact on acne lesion counts and should be applicable to younger postmenarcheal girls. There has been speculation based on in vitro data, that norethindrone acetate (NA) may be more "androgenic" than norgestimate. Clinical studies indicate, however, that norethindrone acetate does not counteract the estrogen-mediated rise in SHBG and subsequent decrease in free testosterone.
- A post approval pharmacokinetic study assessed the impact of 3 cycles of Estrostep® on serum androgens (free testosterone) and sex hormone binding globulin (SHBG), a hepatic indicator of relative estrogenic versus androgenic activity (Protocol 376-397, RR 774-00376, Dec 2, 1997). This study indicated that following multiple-dose administration of Estrostep®, serum SHBG levels increase 2 to 3-fold and free testosterone concentrations decrease 45% to 64%, indicating minimal androgenic activity. Based on these results, Parke-Davis/Warner-Lambert requested and received approval from the Reproductive Division of the FDA to include the term "minimal androgenicity" in the package insert for Estrostep® along with the SHBG and free-testosterone data. One of the primary adverse effects of androgens is their role in promoting acne, particularly in younger women. Acne is the end result of a process initiated by androgenic stimulation of sebum production.

The characteristic adolescent onset of acne is due to the pubertal rise in androgen secretion that triggers a rise in sebum production. In susceptible individuals, the surface keratin is more viscous and traps sebum within the sebaceous follicle where it serves as a culture medium for bacteria. This secondary bacterial infection leads to the classic inflammatory lesions seen in acne vulgaris. If untreated, these inflammatory lesions can lead to permanent scarring.

- Estrostep® is the first estroprophasic oral contraceptive combining low dose phasic ethinyl estradiol (20, 30, and 35 mg for 5, 7, and 9 days, respectively) with a constant low dose of norethindrone acetate (1 mg), that raises SHBG and lowers free testosterone. Girls as young as age 14 were included in this study because this is the age where 93% of girls are already menstruating, thus reducing the possibility of treating pre pubertal girls.

Reviewer comment: these concepts are presented by the sponsor as a discussion of rationale for conducting the studies. The inclusion of the sponsor's discussion in the review does not constitute concurrence with using any of these statements in promotional or marketing materials.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

XIII.- STUDY 376-403

TITLE OF STUDY: Efficacy and Safety of Estrostep® in the Treatment of Moderate Acne Vulgaris: A 6-Month Randomized, single dose, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study (Protocol 376-403)

INVESTIGATORS: 22 Active investigators were recruited for 18 sites:

Protocol	Investigator	IRB
376-403-01	John E. Wolf, Jr., MD Baylor College of Medicine Department of Dermatology 6560 Fannin, Scurlock Tower, Ste. 802 Houston, TX 77030	Baylor College of Medicine One Baylor Plaza Houston, TX 77030-3498 Approval 5/18/99
376-403-02	David Rodriguez, MD International Dermatology Research, Inc 8370 West Flagler Street, Ste 200 Miami, FL 33144	Concordia Research Laboratories, Inc. 7 East Frederick Place Cedar Knolls, New Jersey 07927 Approval 7/20/98
376-403-03	Jim Leyden, MD University of Pennsylvania Hospital 36th & Spruce Streets Philadelphia, PA 19104	University of Pennsylvania Com Studies Involving Human Beings 133 South 36 th Street/3246 Philadelphia, PA 19104
376-403-04	Alan Shalita, MD Wei-Li Lee, PhD (Co-PI) SUNY Health Science Center Dept. of Dermatology 450 Clarkson Avenue, Box 46 Brooklyn, NY 11203	SUNY IRB 450 Clarkson Ave. Brooklyn, NY 11203 Approval 1/22/99
376-403-05	Joseph Daddabbo, MD Michael Noss, MD (Co-PI) Hill Top Research Inc 7720 Montgomery Road Cincinnati, OH 45236	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 8/5/98
376-403-06	Charles Zugerman, MD Chicago Center for Clinical Research 515 North State Street, Suite 2700 Chicago, IL 60610	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 1 7/8/98
376-403-07	David Portman, MD Mark Bechtel, MD (Co-PI) Columbus Center for Women's' Health Res. 5965 East Broad Street, Suite 110 Columbus, OH 43213	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 7/8/98
376-403-08	David Fivenson, MD Linda Stein, MD (Co-PI) Henry Ford Hospital Department of Dermatology 2799 W. Grand Blvd Detroit, MI 48202	Henry Ford Hlth Sys.Human Rights Com. CFP-1 2799 W. Grand Blvd. Detroit, MI 48202 Approval 6/2/98

Protocol	Investigator	IRB
376-403-09	J. Michael Maloney, MD Cherry Creek Dermatology 3535 Cherry Creek North Drive, Suite 207 Denver, CO 80209	Western IRB 3535 Seventh Ave. SW Olympia, WA 98508-2029 Approval 8/27/98
376-403-10	Geoffrey Redmond, MD Center for Health Studies, Inc Five Commerce Park Square 23200 Chagrin Blvd – Suite 325 Cleveland, OH 44122	Biomedical Research Institute of America 3110 Camino del Rio South A215 San Diego, CA 92108-3831 Approval 7/9/98
376-403-11	Gloria Bachmann, MD Gary Ebert, MD (Co-PI) Robert Wood Johnson Medical School – Ob/Gyn.Dept 125 Paterson Street New Brunswick, NJ 08901	UMDNJ 675 Hors Lane Piscataway, NJ 08854 Approval 9/17/98
376-403-12	Allan Kayne, MD Virginia Mason Medical Center 1100 Ninth Avenue, Mailstop GB-CRP Seattle, WA 98101	Virginia Mason Research Center IRB 1000 Seneca Street Seattle, WA 98101 Approval 8/4/98
376-403-13	Sewon Kang, MD Clinical Pharmacology Unit Univ. of Michigan 1500 E. Med Center Dr, Room 1910 Taubman Ann Arbor, MI 48109-0314	Stephen Gebarski, M.D. Com. for Clinical Research & Investigation Involving Human Beings 1500 E. Medical Center Drive Ann Arbor, MI 48109-0605 Approval 7/2/98
376-403-14	Steven Drosman, MD Medical Center for Women's Clinical Res. 5920 Friars Road, Suite 101 San Diego, CA 92108	Western IRB 3535 Seventh Ave. SW Olympia, WA 98508-2029 Approval 7/28/98
376-403-15	Gary Vicik, MD Hill Top Research, Inc. 12401 Olive Blvd, Suite 100 St Louis, MO 63141	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 7/8/98
376-403-16	Eileen Brady, MD Lovelace Scientific Resources 2441 Ridgecrest Drive, SE Albuquerque, NM 87108	Lovelace Institutional Review Board Lovelace Respiratory Research Institute 2425 Ridgecrest Drive, SE Albuquerque, NM 87108 Approval 3/1/99
376-403-17	Charles P. Hudson, MD 1020 Professional Blvd, Suite B Evansville, IN 47714	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 3/10/99
376-403-18	James Simon, MD Women's Health Research Center 14201 Laurel Park Drive, Suite 104 Laurel, MD 20707	Western IRB 3535 Seventh Ave. SW Olympia, WA 98508-2029 Approval 4/7/99

The study began with the first dose of study medication on September 11, 1998, and ended with the last subject observation on February 1, 2000. Randomization codes were released on

March 30, 2000. One site, 003, did not randomize any subjects and that site was terminated early by the sponsor.

The following outside laboratories/contract research organizations were contracted for the following duties:

- [REDACTED] analyzed blood samples obtained for the efficacy and safety parameters;
- [REDACTED] performed the norethindrone (N) and ethinyl estradiol (EE) analyses;
- [REDACTED] performed the analyses for the androgens.
- [REDACTED] performed data management activities, statistical analyses and writing of research report.

[REDACTED] supplied the clinical trial supplies.

OBJECTIVES

The objectives of this study were to assess the efficacy and safety of Estrostep® compared with placebo in the treatment of moderate acne vulgaris at study exit.

DESIGN

This is a double-blind, placebo-controlled, parallel group, 2 arm, multicenter study to assess the efficacy and safety of Estrostep® in the treatment of moderate acne vulgaris for 6 months.

Randomization was one to one, to Estrostep® or to placebo.

Protocol overview:

Study Schedule and Phases

Sponsor planned to screen subjects identified as potential candidates for inclusion and exclusion criteria, within 6 weeks prior to randomization. Initial acne ratings were to be performed at the screening visit in the menstrual cycle immediately preceding randomization. If there was a delay in randomization, the acne rating would be repeated and could be done at the randomization visit.

Study medication was to be started in relationship to onset of menses as is standard practice with oral contraceptives. The first tablet was to be taken on menstrual cycle day 1, 2, 3, 4, 5, or 6, with day 1 being the first day of menstrual bleeding. Tablets would then be taken once a day until the 28-day treatment cycle is completed. The first tablet of the following cycle would be started on the day following completion of the previous cycle. Accordingly, the first tablet of

each of the 6 study medication cycles would begin on the same day of the week.

SUBJECT SELECTION

Inclusion Criteria:

Female subjects of any race, aged 14 to 49 years, ≥ 1 year postmenarche, with a baseline menstrual cycle ≤ 42 days were eligible for randomization to the double-blind phase of the study if they also had (vol12, page 103, Appendix A.2):

- Moderate facial acne with 20 to 100 comedones and 20 to 65 inflammatory lesions (papules or pustules) and no more than 5 nodules who had not responded to topical antiacne therapy;
- A negative urine pregnancy test at the randomization visit;
- A normal pelvic examination with a normal or reactive/reparative Pap smear within the previous 6 months. If a subject was ≤ 18 years of age, and had never been sexually active, both the pelvic examination and the Pap smear could be omitted.
- Discontinued prior to randomization: (1) hormonal injections for ≥ 6 months, (2) systemic retinoids for ≥ 3 months, (3) oral contraceptives or hormonal implants, androgens or antiandrogens for ≥ 2 months, (4) topical or systemic antibiotics, corticosteroids, anti-inflammatories, DHEA and topical acne treatments for ≥ 4 weeks except for soaps or cleansers;
- Agreed to use an effective method of non-hormonal contraception unless has had bilateral ovariectomy or tubal ligation, or male partner has had vasectomy
- Agreed to avoid any topical or systemic acne treatment other than provided as part of the study and to use sunscreen of SPF 15 or greater. Cosmetics, moisturizer, and facial cleanser may have been used if they were non-comedogenic.

Exclusion Criteria

Subjects could not enter the double-blind treatment phase of the study if any of the following applied:

- Smokers over the age of 35 pregnant or nursing.
- Other significant facial skin disease for which topical treatment would be required during the study or which could obscure acne ratings.
- Evidence of significant endocrinopathy such as marked hirsutism as defined by questionnaire, or by rapid progression of androgenic signs or other reason to suspect severe androgen excess.

- Testosterone levels >150 ng/dL or DHEA-S >600 µg/dL (at sites where androgens were measured).
- A history of thromboembolic, cerebrovascular, or coronary artery disease; documented or suspected malignancy of the breast or reproductive organs; moderate or severe migraine associated with oral contraceptives.
- Jaundice associated with pregnancy or prior oral contraceptive use.
- Undiagnosed abnormal vaginal bleeding.
- Hepatic adenomas or carcinomas.
- Iron storage disease.
- Significant concomitant disease such as: uncontrolled hypertension, diabetes mellitus, hyperlipidemia, liver disease, renal disease, history of alcoholism as reported by the subject within the previous 3 years, current acute or chronic gallbladder disease, and history of retinal thrombosis or undiagnosed visual change.
- Any other contraindication to estrogen/progestin therapy.

Screening Phase

During the screening phase subjects were to be assessed for study eligibility as described under inclusion and exclusion criteria, and an initial acne rating was to be performed. If a subject was eligible but did not complete screening procedures in time to be randomized within 30 days of her screening visit, she might still be admitted but a second acne lesion count was to be performed and would be considered the baseline determination. If at this second rating, lesions were fewer or greater than specified in the entry criteria, the subject would be ineligible. If a subject had fewer acne lesions than required to meet the inclusion criteria, she could be re-examined in a subsequent cycle. If acne was insufficiently severe on a second lesion count, the subject would be ineligible. If acne was cystic or more severe than permitted by lesion count, this subject could not be re-screened.

Visit 1, Screening – Screening procedures could be performed at one or more visits.

- Medical history and Subject Informed Consent
- Acne rating (lesion count)
- Marked hirsutism screen
- Fasting blood collection for CBC, chemistry profile, lipids, and pregnancy (hCG)
- Vital signs - weight, height, blood pressure, heart rate
- Pelvic exam and Pap smear. If subject is under 18 years of age, a blind Pap could be substituted for the standard Pap and pelvic examination may be omitted if, in the opinion of the examiner, the introitus will not permit comfortable speculum and bimanual exam. Results

of a pelvic exam and Pap smear done within the previous 6 months could be used if pelvic exam was normal and Pap results were normal or reactive/reparative.

- Recent and current medication
- Breast exam and mammogram for women ≥ 40 years of age. Results of a breast exam and mammogram done within the previous 18 months could be used if the results were normal or considered not clinically significant if abnormal.

Clinic Visits

Subjects would be seen for randomization on menstrual Cycle Day 1, 2, 3, 4, 5, or 6, then once during each of study Cycles 1 to 5, and 3 times in the sixth (final) study cycle.

Visit 2 – Randomization

- Date of onset of last menstrual period and urine pregnancy test
- Acne specific quality of life questionnaire and impact of acne on daily activities assessment
- Predose blood collection for androgens: SHBG, DHEA-S, free and total testosterone at sites selected for androgen sampling
- Predose blood collection for assay of EE and N
- Dispense study medication

Visits During the Double-Blind Phase

A clinic visit would occur once in each of Treatment Cycles 1 through 5 and 3 times during Cycle 6. For Cycles 1 through 5, one visit should occur during treatment Cycle Days 17 to 24. For Cycle 6, a visit should occur during Cycle Days 1 to 7, 8 to 14, and 18 to 21.

Visits would be titled as follows:

- Visit 3 Cycle 1, Treatment Cycle Days 17 to 24
- Visit 4 Cycle 2, Treatment Cycle Days 18 to 21
- Visit 5 Cycle 3, Treatment Cycle Days 17 to 24
- Visit 6 Cycle 4, Treatment Cycle Days 17 to 24
- Visit 7 Cycle 5, Treatment Cycle Days 17 to 24
- Visit 8 Cycle 6, Treatment Cycle Days 1 to 7
- Visit 9 Cycle 6, Treatment Cycle Days 8 to 14
- Visit 10 Cycle 6, Treatment Cycle Days 18 to 21 (Termination visit)

At the clinic visits, the following information would be collected and procedures performed:

- Acne assessment: lesion count and global assessment: at each visit
- Blood pressure: at Visits 3, 4, 5, 6, 7, and 10
- Date of onset of last menstrual period: at Visits 4, 5, 6, 7, and 10
- Dispense study medication: at Visits 3, 4, 5, and 6

Two study medication cards would be given at Visit 2 and one card at Visits 3, 4, 5, and 6. This will ensure that the subject always has one extra medication card in case she cannot come for a scheduled visit.

- Dispense subject dose record: at Visits 3 and 7:
- Review compliance with subject by checking current and returned tablet card; collect previous cycle tablet card if completed; review concurrent medications, adverse events: at all visits
- Blood collection for androgens: SHBG, DHEA-S, and free and total testosterone at sites selected for androgen sampling, collect subject dose record, blood collection for assay of EE and N at Visit 4
- Acne specific quality of life questionnaire and impact of acne on daily activities assessment: at Visit 5
- Urine pregnancy test if menses is late or if pregnancy is suspected

In addition at Visit 10 or at the early termination visit:

- Subject self-assessment, quality of life questionnaire
- Subject's weight and heart rate
- Fasted blood collection for CBC, chemistry, lipids, and pregnancy test
- Blood collection for androgens (sites selected for androgen sampling)
- Blood collection for assay of EE and N
- Collect subject dose record
- Collect medication card or provide container for subject to mail medication card to clinic if Visit 10 (final visit) occurs before Cycle Day 21.
- At the final visit, each subject will be given 2 Estrostep® sample packs if she wishes to stay on Estrostep® so that she may continue medication while waiting for a prescription from her own physician.

**APPEARS THIS WAY
ON ORIGINAL**

Timetable of Visits and Procedures:

Study Phase Clinic Visit Number	Screening		Double Blind Treatment							
	V-1 ^a	V-2 Cycle 1 (1)	V-3 Cycle 1 (17-24)	V-4 Cycle 2 (18-21)	V-5 Cycle 3 (17-24)	V-6 Cycle 4 (17-24)	V-7 Cycle 5 (17-24)	V-8 Cycle 6 (1-7)	V-9 Cycle 6 (8-14)	V-10 Cycle 6 (18-21)
Study Cycle (Cycle Days)										
Medical History	X									
Hirsutism Screen	X									
Pelvic Exam/PAP ^b	X									
Vital Signs ^c	H, w, B, r		B	B	B	B	B			w, B, r
Acne Lesion Count	X		X	X	X	X	X	X	X	X
Global Assessment			X	X	X	X	X	X	X	X
Pregnancy Test, hCG ^d	Serum	urine								Serum
Hematology, Chemistry	X									X
Lipids	X									X
Medication Dispensed		X	X	X	X	X				
Medication Collected				X	X	X	X			X
Dose Record Dispensed			X				X			
Dose Record Collected				X						X
Concurrent Medication	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Androgens ^e		X		X						X
Plasma for EE/N		X		X						X
Quality of Life		X			X					X
Impact on Daily Activities		X			X					X
Subject Self-Assessment										X

- Screen procedures may require more than one visit.
- Unless performed previously within protocol requirements
- h = Height; w = Weight; B = Blood pressure; r = Heart rate.
- May be done at any time if pregnancy suspected; do if subject is amenorrheic
- At sites selected for androgen sampling

Prohibited/Allowable Medications or Precautions

The use of any medication known to interfere with the contraceptive efficacy of NA/EE or any medication suspected to interfere with steroid metabolism, or that affects acne severity, was prohibited during the study; these included:

- Sex hormones (estrogens, progestins, androgens) including topical or vaginal administration and hormonal contraceptives other than the study medication;
- Anti-androgens including spironolactone, flutamide, and finasteride;
- Tetracycline and derivatives such as minocycline and doxycycline;
- More than 2 courses of not more than 14 days of any antibiotic such as erythromycin and [redacted] which might influence acne severity;
- DHEA;
- Hepatic enzyme inducers (e.g., barbiturates, phenytoin, carbamazepine, ethosuximide, primidone, rifampin, troglitazone); or
- Anti-inflammatory medications, which might affect acne severity such as ibuprofen.

Use of ibuprofen was prohibited. Only subjects with 6 or more consecutive days of treatment with ibuprofen were excluded from the per-protocol population.

Any other medication required for the subject's well-being was allowed at the discretion of the investigator as long as it did not affect acne severity. Medications such as acetaminophen and decongestants, as well as non-comedogenic moisturizer, cleanser, and cosmetics were allowed. All concurrent medications were recorded on the appropriate case report form (CRF) (Appendix A.3). Medication names were coded electronically using a modified World Health Organization dictionary that uses a combination of generic and brand names.

Study Drug Compliance

Compliance was to be based on the number of tablets taken during the first 21 days of a cycle. If less than 18 tablets were taken in a cycle, the subject was to be considered non-compliant for that cycle. If a subject is non-compliant in two consecutive cycles or any three cycles, the subject is considered non-compliant for the overall study. The number of days on study treatment will be the difference between the date of first dose and the date of last dose of study drug. Compliance will be summarized by displaying counts of compliant versus non-compliant subjects in each treatment group at each cycle and overall.

Number of Subjects (total and for each treatment): 298 (Estrostep®, 150; placebo, 148)

TREATMENT REGIMEN

Qualifying subjects were randomized to one of two treatment groups:

- Estrostep® (1 mg NA/20 mg EE for 5 days; 1 mg NA/30 mg EE for 7 days; 1 mg NA/35 mg EE for 9 days; ferrous fumarate for 7 days)
- Matching placebo for 21 days and ferrous fumarate for 7 days - according to a randomization schedule prepared by the Parke-Davis Biometrics Department.

Subjects were instructed to take 1 tablet each day from a 4-week medication card. Neither subject nor investigator were to know which group a subject was in. The subject would contact the site when her menses begins, so that a clinic visit could be scheduled within 6 days following the onset of menstruation. At this visit, study medication would be dispensed and medication would be started. A sticker indicating the day of the week the first tablet is taken would be placed on each tablet card to guide the subject since all subsequent cycles would start on the same day of the week at 28-day intervals. When a card is completed, the subject would begin medication from a new card on the following day.

In the event tablets are missed, the subject was to take them as described in the patient package insert with some modification:

- if 1 tablet is missed, it should be taken as soon as the subject remembers. If she remembers the day after the tablet should have been taken, 2 tablets should be taken on that day.
- If 2 tablets are missed during the first 3 weeks of that medication cycle, each should be taken as an extra tablet on 2 consecutive days.
- If 3 tablets are missed, 2 should be taken on consecutive days but the third not made up.

Whenever a subject reports a missed tablet, backup contraception should be reviewed and reinforced. If it appears that there is a substantial risk of pregnancy, the subject should be counseled accordingly and a pregnancy test performed as soon as a positive result would be expected.

If a subject missed more than 3 tablets (not counting the tablets for Cycle Days 22-28) in 2 consecutive or any 3 cycles she would be considered non-compliant, and should be withdrawn from the study.

Test Product, Dose and Mode of Administration, Batch Number:

Estrostep® Test product: CI-376 Administration: once a day (QD) oral administration (P.O.):

- 1 mg NA/20 mg EE [lot # CJ0190298, CJ0630399, CJ1110898] for 5 days;
- 1 mg NA/30 mg EE [lot # CJ0200298, CJ0640399, CJ1120898] for 7 days;
- 1 mg NA/35 mg EE [lot # CJ0210298, CJ0650399, CJ1130898] for 9 days) for 21 days
- followed by 75 mg ferrous fumarate (lot # CJ0270398, CJ0660399) for 7 days

Placebo Tablets: Administration: QD oral administration of tablets, Placebo tablets

- 1 mg/20 mcg [lot # CM1371297] for 5 days
- 1 mg/30 mcg [lot # CM1381297] for 7 days
- 1mg/35 mcg [lot # CM1391297]) for 21 days
- followed by 75 mg ferrous fumarate (lot # CJ0270398, CJ0660399) for 7 days

Duration of Treatment: Six, 28-Day cycles

Randomization tables: These are listed in appendix A.5, vol. 12, page 259

EFFICACY PARAMETERS:

Primary Efficacy Parameters

Primary efficacy was to be measured in the Intent-to Treat population (ITT) at study exit, with Last Observation Carried Forward (LOCF) for those subjects with missing dose.

Lesion counts: Change from baseline to study exit in total number of acne lesions, inflammatory lesions and comedones. To demonstrate efficacy, the change from baseline in lesion counts for Estrostep® treated subjects had to be significantly greater when compared to placebo in at least 2 of the 3 lesion categories.

In addition, the Facial Acne Global Assessment at study exit had to be supportive of the lesion counts data. The Facial Acne Global Assessment used in the study had 7 responses as shown below.

Sponsor used the following scale:

Absent: Subject has no noticeable acne even on careful inspection.

Minimal: Subject does not give immediate visual impression of having acne but careful inspection may reveal a few lesions. (Subjects in this category may have a few comedones and a few small inconspicuous papules that have minimal erythema. There may be small amount of pigmentation, but no appearance of pustules, nodules, or cysts.)

Mild: Subject has slightly noticeable acne but it appears mild. (Subjects in this category may have a few to several comedones and a few papules that have mild erythema. There may be some pigmentation and a few small, inconspicuous pustules, but no nodular or cystic appearing lesions. Most of the face appears clear.)

Mild to Moderate: Subject has noticeable acne but it appears mild to moderate. (Subjects in this category may have several comedones and a few to several papules most of which have mild erythema. There may be a fair amount of pigmentation and a few pustules or more prominent papules. There are no nodular or cystic appearing lesions. As much as 20% of the facial area may be involved.)

Moderate: Subject has definitely noticeable acne, but it appears moderate. (Subjects in this category may have several to many comedones and several papules most of which have moderate erythema. There may be pigmentation, several pustules and some large prominent papules, but no nodular or cystic appearing lesions. Up to half of the facial area may be involved.)

Marked: Subject gives strong visible impression of inflammatory acne with many conspicuous inflammatory lesions. (Subjects in this category may have numerous comedones and many inflammatory lesions that are conspicuously erythematous. There may be a few to several nodular or cystic appearing lesions. More than half of the facial area may be involved.)

Severe: Subject gives the appearance of extensive papulopustular and nodular acne. (Subjects in this category may have many inflammatory lesions with severe erythema and may have many nodular to cystic appearing lesions some of which may be suppurative or hemorrhagic with purulent drainage. Most of the facial area may be involved.)”

In the primary analysis the combined response category of absent or minimal was compared to the combined response category of mild, mild to moderate, moderate, marked, or severe for each treatment group.

The response of absent was compared to all other combined responses (i.e., minimal, mild, mild to moderate, moderate, marked, or severe).

Secondary Efficacy Parameters

- Lesion counts: Change in lesion counts from baseline to each follow-up visit
- Facial Acne Global Assessment at each follow-up visit
- Self-Assessment of Facial Acne at study exit
- Total and free testosterone, sex hormone binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEA-S) level changes from baseline to study exit at selected study sites

Pharmacokinetic Data

Sponsor has measured plasma ethinyl estradiol (EE) and norethindrone (N) concentrations and these data are contained in a separate research report, RR 764-03375. Biopharmacology has prepared a separate review of this report.

ENDPOINTS AND ANALYSIS

Population definition:

Sponsor studied efficacy in per-protocol, intent-to-treat, and modified -intent-to-treat populations, defined as follows:

- ITT population: all randomized subjects who received at least 1 dose of study medication and who had a valid baseline lesion count assessment
- per-protocol population: subset of the ITT population who had no major protocol violations
- MITT population: all randomized subjects who received at least 1 dose of study medication.

Reviewer comment: In the communications prior to submitting the NDA, there was agreement of the Sponsor with the Agency that the ITT population would include all patients who had been randomized and who had been dispensed medication. When the NDA was submitted, the Sponsor's definition of ITT was stated as in the preceding paragraph. However, upon request by the Agency, the Sponsor clarified that all randomized patients had been dispensed medication and all were included in the MITT population for analysis. A review of the data confirmed that all randomized patients had been included in the MITT, including those for whom it was not known with certainty whether they had taken even one dose of medication. The difference between the sponsor's ITT and MITT population was whether or not they also had a baseline evaluation. The preferred Agency's definition for ITT corresponds best, in this instance, with the Sponsor's definition of MITT. The number of MITT subjects was almost identical to ITT, and so were the results for both.

A last observation carried forward (LOCF) approach was used to complete missing efficacy data; if there were no post-baseline efficacy data, baseline values were carried forward. Values for missing baseline lesion count assessments in the MITT population were imputed using the first available post-baseline lesion count.

Safety parameters:

A urine pregnancy test was performed at the randomization visit (Visit 2) before starting any study medication, at any time during the study if a pregnancy was suspected, and if a subject developed amenorrhea while on study medication. In addition, a serum pregnancy test was

performed at the end of treatment. If a woman became pregnant during the study, she was withdrawn from treatment and from the study. Although pregnancies were captured on adverse event case report forms, they were not considered adverse events (AEs) in this study.

Sponsor planned to repeat any clinically significant abnormal value that were noted until the abnormality resolved or a reason for the abnormality was determined.

All subjects randomized to receive study medication were assessed for adverse events. Serious adverse events (SAE) were reported directly and immediately (within 24 hours) to the study monitor. SAEs were events that resulted in any of the following:

- Death;
- Life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect; and
- Medically significant event (includes laboratory abnormalities).

STUDY RESULTS

Demographic characteristics:

Table 403-1 Baseline Demographic Characteristics - Intent-to-Treat Population

	Placebo N = 148	Estrostep N = 150	Total N = 298
Age, yr.			
Mean (SD)	23.96 (7.49)	24.99 (7.92)	24.48 (7.71)
Median (Min, Max)			
Age Category, yr. N (%)			
13-15 ^a	22 (15%)	21 (14%)	43 (14%)
16-17	12 (8%)	13 (9%)	25 (8%)
18-21	32 (22%)	21 (14%)	53 (18%)
22-29	45 (30%)	51 (34%)	96 (32%)
30-39	31 (21%)	39 (26%)	70 (23%)
40-49	6 (4%)	5 (3%)	11 (4%)
Race, N (%)			
White/Caucasian	98 (66%)	100 (67%)	198 (66%)
Black	25 (17%)	18 (12%)	43 (14%)
Asian	5 (3%)	5 (3%)	10 (3%)
Hispanic	17 (11%)	20 (13%)	37 (12%)
Other	3 (2%)	7 (5%)	10 (3%)
Smoking Status, N (%)			
Never Smoked	103 (70%)	102 (68%)	205 (69%)
Past Smoker	23 (16%)	25 (17%)	48 (16%)
Current Smoker	22 (15%)	23 (15%)	45 (15%)
Body Mass Index, kg/m ²			
Mean (SD)	24.85 (5.45)	25.18 (5.53)	25.01 (5.48)
Median (Min, Max)			

^a 2 subjects less than 14 years of age were protocol exceptions

SD = Standard Deviation

Reference Appendices: C.6.1, C.10.1, C.11.1, and C.12.1

Table 403-2 Baseline Clinical Characteristics - Sponsor's ITT

	Placebo N = 148	Estrostep N = 150	Total N = 298
Total Lesion Count			
Mean (SD)	75.28 (30.35)	77.02 (26.46)	76.16 (28.43)
Median (Min, Max)	[REDACTED]		
Inflammatory Lesion Count			
Mean (SD)	29.74 (10.45)	29.28 (10.51)	29.51 (10.47)
Median (Min, Max)	[REDACTED]		
Total Comedones			
Mean (SD)	45.55 (25.30)	47.74 (22.85)	46.65 (24.08)
Median (Min, Max)	[REDACTED]		

Reference Appendices: C.6.1, C.10.1, C.11.1, and C.12.1
SD = Standard Deviation

Subject Evaluability:

Table 403-3 Number of Subjects

	Total ^b	Placebo	Estrostep
Screened (signed consent)	476 ^c		
Randomized	298	148	150
Modified Intent-to-Treat Population	298	148	150
Intent-to-Treat Population	298	148	150
Per-Protocol Population	221	104	117 (58%)
Safety	282	148	151 ^a
Completed study ^d	188	86	102

a: this number is derived from data given by the sponsor in vol. 12, table 14, page 155

b: the total in this table is derived from the addition of the placebo and Estrostep® columns as supplied by the sponsor

c: this number is from sponsor's Appendix C.4, in vol. 12, page 281

d: from table c.4, vol. 12, page 28

From Appendix C.5, vol. 12, page 282

Table 403-4 Number of Subjects Randomized/Completed by Study Site

Center	Investigator	No. Randomized			No. Completed		
		Total	Placebo ^a	Estrostep®	Total	Placebo	Estrostep®
001	J Wolf	3	1	2	1	0	1
002	D Rodriguez	7	3	4	3	2	1
003	J Leyden	0			0		
004	A Shalita, W Lee	7	4	3	4	2	2
005	J Daddabbo, M Noss	3	1	2	2	0	2
006	C Zugerman	15	8	7	10	5	5
007	D Portman, M Bechtel	10	4	6	9	3	6
008	D Fivenson, L Stein	8	4	4	5	2	3
009	J Maloney	131	64	64	93	41	45
010	G Redmond	32	16	16	22	12	10
011	G Bachmann, G Ebert	1	0	1	1	0	1
012	A Kayne	16	8	8	10	6	4
013	S Kang	7	4	3	2	2	0
014	S Drosman	31	16	15	11	5	6
015	G Vicik	8	4	4	4	1	3
016	E Brady	6	4	2	0		
017	C Hudson	8	4	4	7	3	4
018	J Simon	5	3	2	4	2	2
Total		298			188		

From appendix c.1, vol. 12, page 287

a : numbers for the placebo and Estrostep® columns are taken from Appendix E.4, vol. 15 page 1065

Reviewer comment: as a result of the uneven enrollment, three centers included the greatest majority of subjects: centers 009, 010 and 014, with 131, 32 and 31 enrolled subjects. It is of interest that the proportion of subjects who completed the study was much greater in some centers, such as 007 (9 of 10), 017 (7 of 8), 018 (4 of 5) while at other centers less than half of the subjects completed the study: 001 (1 of 3), 013(2 of 7), 014(11 of 31) 016 (0 of 6)

Table 403-5 Subject Exclusions

	Placebo N=148	Estrostep® N=150
Excluded from MITT population for:		
No study medication	0	0
Excluded from ITT population for:		
No baseline assessment data	0	0
Excluded from Per-Protocol population for:		
Lesion counts were too high at screening	2	6
Lesion counts were too low at screening	7	4
Inadequate washout	3	5
Withdrawn before Cycle 3	23	16
Non-compliant with study medication during last 3 cycles	3	1
Substantial use of prohibited concurrent medications	6	1

Reference: Appendix A.6 and C.5

Table 403-6 Reasons for withdrawal from the study

	(randomized) Placebo (148)	Estrostep® (150)
Early Withdrawal	62 (42%)	48 (32%)
Lack of compliance	4 (3%)	3 (2%)
Lack of efficacy	8 (5%)	3 (2%)
Adverse event	4 (3%)	13 (9%)
Other/Administrative*	41 (28%)	29 (19%)
Withdrew consent	4	5
Moved away	4	3
Lost to follow up	13	3
Scheduling difficulty	0	2
Sponsor requested termination	7*	2
Lost medication.	1	0

From Appendix C.4, Table 3 page 44, vol 12 and from Response to additional data request, supplied by sponsor in submission 2000-12-20A

*sponsor submitted greater detail about patients terminated for administrative reasons, as shown later on Table S-7 and S-8, on pages 52 and 53.

Table 403-7 Reported number of subjects compliant with medication, by cycle

	Placebo(N=148)	Estrostep® (N=150)
Intent-to-Treat Population		
Cycle 2 (V-4)	124	134
Cycle 3 (V-5)	120	127
Cycle 4 (V-6)	109	121
Cycle 5 (V-7)	98	112
Cycle 6 (V-10)	86	97
Per Protocol Population	Placebo(N=104)	Estrostep(N=117)
Cycle 2 (V-4)	101	117
Cycle 3 (V-5)	104	116
Cycle 4 (V-6)	98	110
Cycle 5 (V-7)	87	102
Cycle 6 (V-10)	78	88/

Appendix C.9.2

Prior Medications

The treatment groups were balanced in respect to prior medications. The most frequently used medications prior to study in the Estrostep® group were tetracycline (3%), clindamycin (2%) and tretinoin (2%) and in the placebo group were benzoyl peroxide (3%), minocycline (2%), tetracycline (2%), and tretinoin (2%). A complete summary of prior medications is located in Appendix C.7.1 for the intent-to-treat population and in Appendix C.7.2 for the per-protocol population.

Concurrent medications

The most frequently used concurrent medications for the intent-to-treat population were (acetaminophen), ibuprofen, multivitamins, (albuterol), acetylsalicylic acid, and (Table 13, Appendix C.8.1). was used by 19 (13%) subjects in the Estrostep® treatment group and 16 (11%) subjects in the placebo group. There were no meaningful differences between the treatment groups. Similar results were reported for the per-protocol population (Appendix C.8.2).

Table 403-8 Most Frequently Used Concurrent Medications-Intent-to-Treat Population

Medication	Placebo N = 148	Estrostep N = 150
Ibuprofen	13 (9%)	14 (9%)
Multivitamins	14 (9%)	14 (9%)
Acetylsalicylic acid	6 (4%)	3 (2%)

Reference: Appendix C.8.1.

EFFICACY ANALYSIS

The following analyses were discussed and concurred between the clinical and statistical reviewers. The supporting efficacy endpoint result are fully explained in the statistical review and will not be repeated here. The overall outcomes for lesion counts and for investigator's global evaluation are as follows:

Table 403-9. Summary of analysis of effectiveness of Estrostep® over placebo *

403 Evaluation ▽	Per Protocol N= 101 Estrostep® / 86 Placebo				ITT N=150 Estrostep® / 148 Placebo			
	Mean of % reduction from baseline		Mean change from baseline		Mean of % reduction from baseline		Mean change from baseline	
Lesion Type ▽	%	p	N	P	%	P	N	p
Inflammatory	5.9	.4409	1.6	.4290	8.3	.0645	2.2	.0515
Baseline mean			30/30				29/30	
Comedones	13.8	.1937	7.7	.1525	14.5	.0187	6.6	.0197
Baseline mean			48/44				41/40	
Total	9.3	.1845	9.3	.1501	10.6	.0169	8.7	.0118
Baseline mean			78/74				70/69	

▽ % Minimal or Better 13.9% .019
21%/8%

9.0% .021
16%/7%

Reviewer comment: In study 403, the Estrostep® group demonstrated, in the Intent-To-Treat population (ITT), a statistically significant decrease in lesion counts for comedones and for total lesion counts but not for inflammatory lesion counts. After 6 cycles, the difference from baseline for Estrostep® over placebo was 6 for comedones, while for total lesion counts, the Estrostep® effect over placebo was 8 lesions. Yet, the magnitude of these effects, after 6 months of treatment, is fairly small. The results for the third lesion count, inflammatory lesions, were not statistically significant. The results of the Per-Protocol population (PP) were smaller than for ITT population and did not support the efficacy seen in the ITT population. The mean of percent reduction in lesion counts from baseline for Estrostep® over placebo, paralleled the decrease in lesion counts, and was in the range 8% for inflammatory lesions, up to 14% for comedones. For the PP population, the range was 5 -13% and it did not reach significance.

On Facial Global Assessment, no Estrostep® treated subject in the ITT population, or in the PP population, reached an Investigator Global Assessment of absent (no residual acne lesions) by the end of the study. The percent of Estrostep® treated subjects who were graded as "absent and/or minimal" at study end (16%) was statistically significantly different from the placebo-treated group (7%). The difference over placebo at study end was 9%.

Safety:

Sponsor reported no deaths occurred during study and only 1 subject experienced any serious adverse events (SAEs). Overall, there were no unexpected differences between treatment groups in adverse events, associated AEs, serious AEs, or AEs resulting in withdrawals. One Estrostep-treated subject experienced 2 SAEs that were rated moderate in intensity and unrelated to treatment by the investigator. Less than half (42%) of the subjects experienced an AE, less than a quarter (20%) experienced an associated AE, and 6% withdrew due to an AE. Seven placebo-treated subjects became pregnant while on study. The majority of clinical laboratory values remained in the same category (i.e., low, high or normal) at study exit as they were at baseline indicating few if any treatment related effects. There were no clinically significant changes in blood pressure or weight.

Table 403-10 Overview of Adverse Events - Randomized Subjects

	Placebo N (%)	Estrostep® N (%)
Subjects with Adverse Events		
All	51 (34%)	74 (49%)
Associated	19 (13%)	39 (26%)
AEs by Maximum Intensity		
Mild	18 (35%)	31 (42%)
Moderate	31 (61%)	35 (47%)
Severe	0	8 (11%)
Missing	2 (4%)	0
Serious Adverse Events		
All	0	1 (1%)
Associated	0	0
Deaths	0	0
Withdrawals due to AEs		
All	4 (3%) ^a	13 (9%)
Associated	4 (3%)	13 (9%)

^a Four additional withdrawals were due to unintended pregnancy which is not considered an AE (see

Table 403-11 The Most Frequently (≥5%) Occurring All and Associated Adverse Events – Randomized Subjects

Adverse Event	Placebo N (%)		Estrostep® N (%)	
	All	Associated	All	Associated
Infection	17 (11%)	0	20 (13%)	0
Metrorrhagia	3 (2%)	2 (1%)	14 (9%)	14 (9%)
Flu Syndrome	7 (5%)	0	13 (9%)	0
Nausea	2 (1%)	2 (1%)	12 (8%)	11 (7%)
Accidental Injury	3 (2%)	0	10 (7%)	0
Headache	5 (3%)	3 (2%)	9 (6%)	4 (3%)
Migraine	0	0	8 (5%)	6 (4%)

Reference: Appendix C.27

Table 403-12 Withdrawals Due to All and Drug-Related Adverse Events

Adverse Event	Treatment	Subject No.	Study Day of Onset/Resolution	Outcome ^a	Drug-Related
Abdominal Pain	Estrostep	014-107	9/11	Recovered	Yes
Alopecia	Estrostep	014-386	79/cont	Not yet recovered	Yes
Depression	Placebo	009-441	78/80	Recovered	Unknown
Dizziness	Estrostep	009-578	8/11	Recovered	Yes
Emotional Lability	Estrostep	010-425	2/22	Recovered	Unknown
Emotional Lability	Estrostep	014-122	55/cont	Not yet recovered	Unknown
Leg Cramps	Placebo	014-347	10/13	Recovered	Unknown
Migraine	Estrostep	009-313	54/cont	Not yet recovered	Yes
Migraine	Estrostep	009-325	15/17	Recovered	Unknown
Migraine	Estrostep	014-379	111/111	Recovered	Yes
Nausea	Estrostep	010-311	1/8	Recovered	Unknown
Nausea	Estrostep	014-384	3/19	Recovered	Yes
Nervousness	Placebo	014-348	22/82	Recovered	Yes
Peripheral Edema	Placebo	009-315	19/33	Recovered	Unknown
Rash	Estrostep	013-339	7/cont	Not yet recovered	Unknown
Vomiting	Estrostep	006-266	8/9	Recovered	Yes
Vomiting	Estrostep	010-489	20/20	Recovered	Yes
Weight Gain	Estrostep	014-122	55/cont	Not yet recovered	Unknown

Cont. = Continuing

Reference: Appendices B.3.2, C.33 and F.2

^a At subject withdrawal

Withdrawals Due to Adverse Events (376-403)

Subject 266 at Site 006, (Protocol 376-403), a 28-year-old white female with no significant medical history, was randomized to Estrostep. The subject experienced nausea on Day 5 and vomiting on Day 8. On Day 9, study medication was discontinued due to the vomiting. The nausea and vomiting resolved. The investigator considered these events to be related to the study medication.

Subject 313 at Site 009, (Protocol 376-403), a 26-year-old white female with no significant medical history, was randomized to Estrostep. She experienced a migraine headache on Day 54. Study medication was discontinued on Day 76 as a result of the migraine headache, which was considered ongoing. The subject came in for a final visit on Day 77. The investigator considered this event to be related to the study medication.

Subject 315 at Site 009, (Protocol 376-403), a 33-year-old American Indian female with no significant medical history, was randomized to placebo. The subject experienced bloating of the hands and feet on Day 19 and an increase in acne on Day 21. Study medication was discontinued on Day 30 and she recovered from the bloating of the hands and feet on Day 33. The investigator considered the relationship of these events to the study medication as unknown.

Subject 325 at Site 009, (Protocol 376-403), a 27-year-old white female with a history of migraine headaches, was randomized to Estrostep. The subject developed a migraine headache on Day 15 for which she took aspirin. Study medication was discontinued on Day 15 and she recovered by Day 17. The investigator considered the relationship of this event to the study medication as unknown.

Subject 441 at Site 009, (Protocol 376-403), a 32-year-old white female with a history of depression and premenstrual syndrome, was randomized to placebo. On Day 78 she experienced an exacerbation of her depression. Study medication was discontinued on Day 78 and the exacerbation of the depression resolved by Day 80. Concomitant medications included fluoxetine HCl. The investigator considered the relationship of this event to the study medication as unknown.

Subject 578 at Site 009, (Protocol 376-403), a 33-year-old white female with no significant medical history, was randomized to Estrostep. The subject experienced nausea and dizzy spells on Day 8. Study medication was discontinued on Day 11 and the nausea and dizzy spells resolved by Day 11. The investigator considered these events to be related to the study medication.

Subject 311 at Site 010, (Protocol 376-403), a 29-year-old black female with no significant medical history, was randomized to Estrostep. The subject experienced nausea on Day 1. On day 8 the study medication was discontinued and the nausea resolved. Concomitant medications included vitamins A, C, and E, multivitamin, and calcium. The investigator considered the relationship of this event to the study medication as unknown.

Subject 425 at Site 010, (Protocol 376-403), a 24-year-old white female with no significant medical history, was randomized to Estrostep. The subject experienced moodiness on Day 2. Study medication was discontinued on Day 21 and the moodiness resolved by Day 22. The investigator considered the relationship of this event to the study medication as unknown.

Subject 489 at Site 010, (Protocol 376-403), a 15-year-old black female with no significant medical history, was randomized to Estrostep. On Day 20, the subject experienced vomiting and the study medication was discontinued. The vomiting resolved on Day 20. Concomitant medications included naproxen sodium, ibuprofen, and acetaminophen. The investigator considered this event to be related to the study medication.

Subject 339 at Site 013, (Protocol 376-403), a 31-year-old white female with no significant medical history, was randomized to Estrostep. The subject experienced a rash and itching on her arms and legs on Day 7. On Day 12 the study medication was discontinued and the rash cleared significantly. Concomitant medication included cetirizine HCl that was started on Day 22 to treat the rash and itching. The investigator considered the relationship of this event to the study medication as unknown.

Subject 107 at Site 014, (Protocol 376-403), a 28-year-old white female with a history of asthma,
MOR NDA 21-276

was randomized to Estrostep. The subject developed abdominal cramps and breakthrough bleeding on Day 9. On Day 11 the study medication was discontinued and the abdominal cramps resolved. Concomitant medications included albuterol and salmeterol. The investigator considered these events to be related to the study medication.

Subject 122 at Site 014, (Protocol 376-403), a 29-year-old white female with no significant medical history, was randomized to Estrostep. The subject experienced mood swings and weight gain on Day 55. Study medication was discontinued on Day 105. Concomitant medications included multivitamins. The investigator considered the relationship of these events to the study medication as unknown.

Subject 347 at Site 014, (Protocol 376-403), a 29-year-old white female with no significant medical history, was randomized to placebo. On Day 10 the subject developed bilateral leg cramps which were treated with aspirin. Study medication was discontinued on Day 10 and the leg cramps resolved on Day 13. The investigator recorded the relationship of this event to the study medication as unknown.

Subject 348 at Site 014, (Protocol 376-403), a 30-year-old black female with no significant medical history, was randomized to placebo. The subject developed irritability on Day 22. Study medication was discontinued on Day 46 and the irritability resolved by Day 82. The investigator considered this event to be related to the study medication.

Subject 379 at Site 014, (Protocol 376-403), a 23-year-old black female with no significant medical history, was randomized to Estrostep. On Day 111, the subject developed a migraine headache that was treated with acetaminophen. Study medication was discontinued on Day 111 and the migraine resolved. The investigator considered this event to be related to the study medication.

Subject 384 at Site 014, (Protocol 376-403), a 22-year-old Hispanic female with no significant medical history, was randomized to Estrostep. On day 3 the subject reported nausea and the study medication was discontinued. The nausea resolved by Day 19. The investigator considered this event to be related to the study medication.

Subject 386 at Site 014, (Protocol 376-403), a 23-year-old white female with no significant medical history, was randomized to Estrostep. The subject experienced mild hair loss on Day 51 that increased in severity to moderate on Day 79. Study medication was discontinued on Day 98. The investigator considered this event to be related to the study medication.

Laboratory Measurements

Change from Baseline for Clinical Laboratory Measurements

There were no clinically significant shifts (Appendix C.34) or mean changes (Appendix C.35) from baseline to study exit in laboratory parameters as determined by the medical monitor.

Proportion of Subjects with Possibly Clinically Significant Laboratory Parameters at Study Exit

At study exit, 63 (21%) subjects (Estrostep®, 32; placebo, 31) had laboratory parameter values that were possibly clinically significant (Appendices A.7, C.36 and F.4). Only 3 parameters included more than 1% of subjects receiving Estrostep. The most common of these parameters, triglycerides (values > 200 mg/dL), occurred in 8% of Estrostep-treated subjects and in 3% of placebo subjects. Elevations in triglycerides are expected with oral contraceptive use and not of clinical concern at the levels observed. Low values of high density lipoprotein cholesterol were observed for 3% of subjects in each treatment group, and did not represent a significant change from baseline values for these subjects.

Increases or decreases from baseline of white blood cells to values outside the reference range occurred for 5% of subjects receiving Estrostep® and 2% of subjects receiving placebo. Of these only one subject (002-249) in the Estrostep® group had changes that appeared clinically significant. This subject withdrew early from the study on Study Day 111 due to lack of efficacy. Although her platelet and white blood cell counts had decreased to 96 K/mm³ and 3 K/mm³, respectively, at study exit, she was asymptomatic and had reported no adverse events during the study. A repeat blood draw was not done and no additional follow-up information is available at this time.

Other parameters that included ≤1% Estrostep® treated subjects were considered not clinically meaningful.

Blood Pressure and Weight

No clinically significant changes in blood pressure (Appendices C.37) or weight (Appendix C.38) were observed in either treatment group.

XIV .-STUDY 376-404

TITLE OF STUDY: Efficacy and Safety of Estrostep® (CI-376) in the Treatment of Moderate Acne Vulgaris —A 6-Month Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study (Protocol 376-404)

INVESTIGATORS: 22 active investigators were recruited for 19 sites:

Center	Investigator	IRB
376-404-01	Terry Jones, MD J and S Studies, Inc 4309 Wellborn Road Bryan, TX 77801	Western IRB 3535 Seventh Ave. SW Olympia, WA 98508-2029 Approval 8/4/98
376-404-02	Janet Hickman, MD Ed. and Research Foundation, Inc 2602 Langhorne Road Lynchburg, VA 24501	IRB for the Ed. and Research Foundation, Inc 2602 Langhorne Rd. Lynchburg, VA 24501 Approval 10/13/98
376-404-03	David Pariser, MD Virginia Clinical Research, Inc. 601 Medical Tower Norfolk, VA 23507	Western IRB 3535 Seventh Ave. SW Olympia, WA 98508-2029 Approval 6/25/98

Center	Investigator	IRB
376-404-04	Joseph Jorizzo, MD Wake Forest University of Medicine Department of Dermatology Medical Center Boulevard Winston-Salem, NC 27157	Clin. Research Practices Com. of Wake Forest University School of Medicine Medical Center Blvd. Winston-Salem, NC 27157 Approval 7/23/98
376-404-05	Leonard Swinyer, MD Dermatology Research Center 3920 South 1100 East, No. 310 Salt Lake City, UT 84124	Western IRB 3535 Seventh Ave. SW Olympia, WA 98508-2029 Approval 8/20/98
376-404-06	Frank Dunlap, MD Hill Top - Argus Research, Inc 7042 E. Broadway Tucson, AZ 85710	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 7/22/98
376-404-07	Janet Roberts, MD Dermatology Specialists NorthWest 2222 NW Lovejoy, Suite 419 Portland, OR 97210	RCRC 4009 Banister Lane Austin, TX 78704 Approval 7/6/98
376-404-08	Richard Berger, MD Hill Top Research Inc. 223 Highway 18, Suite 203 East Brunswick, NJ 08816	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 10/7/98
376-404-09	Stephen Kraus, MD Georgia Clinical Research Center 5671 Peachtree Dunwoody Road Atlanta, GA 30342	Western IRB 3535 Seventh Ave. SW Olympia, WA 98508-2029 Approval 6/29/98
376-404-10	Michelle Warren, MD Sloane Hospital for Women 16 East 60th Street New York, NY 10022	Columbia Presbyterian Medical Center IRB 630 West 168 th St. New York, NY 10032 Approval 11/2/98
376-404-11	Richard Derman, MD University of Illinois at Chicago Dept. of Obstetrics & Gynecology 1919 West Taylor St, Room 525 Chicago, IL 60612	Office of Protection of Research Subjects 311 D Administrative Office Building Chicago, IL 60612 Approval 10/16/98
376-404-12	Melanie Lewitt-Appell, MD Scott Touger, MD (Co-PI) Hill Top Research Inc 516 Brookwood Blvd. Birmingham, AL 35209	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 7/15/98
376-404-13	Richard Newman Sherman, MD SPQR 4937 Hearst St. Suite 2L Metairie, LA 70001	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 7/8/98

Center	Investigator	IRB
376-404-14	Regina Hamlin, MD Hill Top Research Inc 6079 N. Fresno Street, Suite 101 Fresno, CA 93710	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 7/8/98
376-404-15	Sidney Rosenblatt, MD Ronald W. Cotliar, MD(Co-PI) Irvine Clinical Research Center 16259 Laguna Canyon Road Irvine, CA 92618	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 7/8/98
376-404-16	John Humeniuk, MD Hill Top Med Quest Research 562 A Memorial Drive Ext Greer, SC 29651	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 3/10/99
376-404-17	Ken Takegami, MD Adult & Pediatric Dermatology 504 N. Jackson Tullahoma, TN 37388	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 4/14/99
376-404-18	John Goodman, MD Hill Top Research, Inc. 2051 45 th St., Suite 200 West Palm Beach, FL 33407	Schulman Associates IRB 10 Knollcrest Dr., Suite 200 Cincinnati, OH 45237 Approval 4/14/99
376-404-19	Suzanne Barbier, MD Women's Clinical Research Center 3216 NE 45 th Place, Suite 100 Seattle, WA 98105	Western IRB 3535 Seventh Ave. SW Olympia, WA 98508-2029 Approval 5/20/99

Protocol overview

The protocol for this study was identical to that of Study 403 except it did not include tests for hormone levels

Study Medication:

Lot Number NA/EE 1 mg/20 mcg CJ1110898	CJ0190298 CJ0630399
NA/EE 1 mg/30 mcg	CJ0200298 CJ0640399 CJ1120898
NA/EE 1 mg/35 mcg	CJ0210298 CJ0650399 CJ1130898
Ferrous Fumarate 75 mg	CJ0270398 CJ0660399
Placebo 1 mg/20 mcg	CM1371297
Placebo 1 mg/30 mcg	CM1381297
Placebo 1 mg/35 mcg	CM1391297

STUDY RESULTS

Demographic characteristics

Table 404-1 Baseline Demographic Characteristics Sponsor's ITT

	Placebo N = 147	Estrostep N = 146	Total N = 293
Age, yr.			
Mean (SD)	23.88 (7.38)	23.55 (7.13)	23.71 (7.24)
Median (Min, Max)	[REDACTED]		
Age Category, yr	N (%)		
14-15	23 (16%)	17 (12%)	40 (14%)
16-17	10 (7%)	18 (12%)	28 (10%)
18-21	30 (20%)	30 (21%)	60 (20%)
22-29	52 (35%)	59 (40%)	111 (38%)
30-39	28 (19%)	16 (11%)	44 (15%)
40-49	4 (3%)	6 (4%)	10 (3%)
Race,	N (%)		
White/Caucasian	104 (71%)	102 (70%)	206 (70%)
Black	21 (14%)	20 (14%)	41 (14%)
Asian	2 (1%)	13 (9%)	15 (5%)
Hispanic	17 (12%)	10 (7%)	27 (9%)
Other	3 (2%)	1 (1%)	4 (1%)
Smoking Status,	N (%)		
Never Smoked	106 (72%)	108 (74%)	214 (73%)
Past Smoker	24 (16%)	14 (10%)	38 (13%)
Current Smoker	17 (12%)	24 (16%)	41 (14%)
Body Mass Index , kg/m²			
Mean (SD)	25.60 (6.24)	24.42 (6.67)	25.01 (6.47)
Median (Min, Max)	[REDACTED]		

Reference Appendices: C.6.1, C10.1, C11.1, and C12.1

SD = Standard Deviation

Table 404-2 Baseline Clinical Characteristics Sponsor's ITT

	Placebo N = 147	Estrostep N = 146	Total N = 293
Total Lesion Count			
Mean (SD)	69.22 (24.38)	70.24 (24.95)	69.73 (24.62)
Median (Min, Max)	[REDACTED]		
Inflammatory Lesion Count			
Mean (SD)	29.19 (10.06)	29.65 (8.69)	29.42 (9.39)
Median (Min, Max)	[REDACTED]		
Total Comedones			
Mean (SD)	40.03 (19.70)	40.59 (21.90)	40.31 (20.79)
Median (Min, Max)	[REDACTED]		

SD = Standard Deviation

Reference Appendices: C.6.1, C10.1, C11.1, and C12.1

Subject Evaluability:

Table 404-3 Number of Subject

	Total	Placebo	Estrostep
Screened	555		
Randomized	295	148	147
Modified Intent-to-Treat Population	295	148	147
Intent-to-Treat Population		147	146
Per-Protocol Population	222	112	110
Safety		148	147
Completed study ^a	215	104	111

Reference: Appendix A.6 and C.5

a: from Appendix C.4

b: the total in this table is derived from adding the placebo and Estrostep® columns

Table 404-4 Number Of Subjects Randomized/Completed by Study Site

Center	Investigator	No. randomized			No. Completed		
		Total	Placebo	Estrostep®	Total	Placebo	Estrostep®
Site Number	Investigator						
376-404-01	Terry Jones,	20	9	11	18	9	9
376-404-02	Janet Hickman,	6	4	2	4	3	1
376-404-03	David Pariser,	35	18	17	27	14	13
376-404-04	Joseph Jorizzo,	9	5	4	3	1	2
376-404-05	Leonard Swinyer	17	7	10	13	5	8
376-404-06	Frank Dunlap	8	4	4	7	4	3
376-404-07	Janet Roberts	29	14	15	24	11	13
376-404-08	Richard Berger	0			0		
376-404-09	Stephen Kraus	14	7	7	5	2	3
376-404-10	Michelle Warren	49	25	24	35	16	19
376-404-11	Richard Derman	24	12	12	20	9	11
376-404-12	Melanie Lewitt-Appell & Scott Toger	31	15	16	20	10	10
376-404-13	Richard N Sherman	8	4	4	7	3	4
376-404-14	Regina Hamlin	26	13	13	21	11	10
376-404-15	Sidney Rosenblatt & Ronald W. Cotliar	3	2	1	0		
376-404-16	John Humeniuk	7	4	3	4	2	2
376-404-17	Ken Takegami	4	2	2	3	2	1
376-404-18	John Goodman	2	1	1	1	0	1
376-404-19	Suzanne Barbier	3	2	1	3	2	1
Total		295			215		

From List of Investigators PD 376-404 Appendix C.1

Reviewer comment: the number of subjects enrolled per center is very uneven. Interestingly, some centers had very few dropouts while others had large numbers of dropouts