Clinical Review

1. Introduction and Background

1.1 Established and Proposed Trade Name of Drug, Drug Class, Applicant's Proposed Indication(s), Dose, Regimens, Age Groups

Angeliq is a combination hormone product containing the estrogen, estradiol (E_2), and the progestin, drospirenone (DRSP). The applicant initially proposed — indications for women with an intact uterus, including:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause
2. Treatment of vulvar and vaginal atrophy.

The proposed regimen is a single daily oral tablet. The applicant requests approval of — doses:

Adult women are the target population, including women older than 65 years old.

1.2 State of Art for Indications

A variety of combination hormone products are available in the U.S. for the same indications. Similar products include Ortho-Prefest, Activella, Femhrt, Prempro and Premphase. All are one-a-day oral formulations. Like Angeliq, Ortho-Prefest and Activella contain a daily dose of E_2 1 mg. Femhrt contains ethinyl estradiol as its estrogen component. Prempro and Premphase use conjugated estrogens as their estrogen component.

The skin patch, Combipatch, also provides E_2 in combination with a progestin. In addition, estrogens and progestins are also available individually and used in a variety of combinations for menopausal symptoms.

Although only approved for menopausal symptom indications and osteoporosis prevention, E/P therapy has been widely used off-label to prevent coronary heart disease and Alzheimer's disease, based primarily on observational data. However, the recent results of two large clinical trials showed an increase, not a decrease, in coronary heart disease in women using Prempro, a popular form of E/P therapy for menopause symptoms.[1,7]

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[7] Grady D, et al. Cardiovascular disease Outcomes during 6.8 years of hormone therapy -Heart and Estrogen/Progestin Replacement Study follow-up. *JAMA* 2002;288:49-66.

1.3 Important Milestones in Product Development

Table 1, adapted from the applicant's submission, summarizes major regulatory events.

Table 1. Regulatory Milestones in Product Development

Date	Regulatory Event
February 12, 1997	Industry meeting ([redacted] ; DRSP/ethinyl estradiol(EE)). Sponsor told that showing bioequivalence with Estrace will allow Estrace indications; estradiol, estrone and estrone sulfate should be evaluated.
July 25, 1997	IND 53,842 (DRSP/ E_2) submitted to FDA
August 11, 1998	Meeting to discuss the single- versus multiple-dose bioequivalence studies for DRSP and E_2 tablets and whether the studies presented were sufficient for the Human Pharmacology and Bioavailability/Bioequivalence portion of the NDA (Item 6)
December 8, 1998	Teleconference to discuss questions regarding the August 11, 1998 meeting with the Division. Small substudy or 24-hour urine calcium excretion is acceptable; study drug-drug interactions in patients on digoxin in the pivotal trials if the trials enroll women on digoxin; efficacy for prevention of osteoporosis may be supported by European study.
March 24, 2000	Teleconference to discuss the use of drug in older women, the need to measure serum potassium and electrocardiograms (EKGs) in future studies, and the FDA's request that Berlex conduct a NSAID drug interaction study that could be submitted as part of the 4-month safety update during the NDA review cycle.
June 14, 2000	Division informed Berlex that bioequivalence data were sufficient (via phone contact)
January 24, 2001	Pre-NDA meeting. A risk management section suggested for the clinical section of the NDA

Also of significance for Angeliq was the related approval of Yasmin, a combination oral contraceptive containing DRSP 3 mg and ethinyl estradiol 0.03 mg. The primary clinical concern that arose during review of Yasmin was the potential for electrolyte disturbances in women exposed to DRSP. Before approving Yasmin, the FDA evaluated extra safety data, including the potassium data from the endometrial protection trial that the applicant is presenting as the pivotal trial for the Angeliq NDA. Yasmin was approved on May 11, 2001 with the Phase IV commitments to

- Educate patients and providers about the hyperkalemia risks
- Set up a surveillance program to look for inappropriate prescribing patterns
- Submit case report summaries of all patients who have clinical events that might be caused by hyperkalemia.
- Set up a protocol to evaluate pregnancy exposures

1.4 Other Relevant Information

Angeliq is not approved or marketed elsewhere. There are pending applications in the United States, Holland, and Australia.

1.5 Important Issues with Pharmacologically Related Agents

Unlike other progestins, DRSP is chemically related to the antimineralocorticoid spironolactone. Spironolactone can cause serious electrolyte problems, particularly hyperkalemia, in susceptible people. DRSP has seven times the antimineralocorticoid potency of spironolactone, making DRSP 3 mg roughly equivalent in antimineralocorticoid potency to spironolactone 25 mg. Therefore there is potential for hyperkalemia, especially in women who have other risk factors for hyperkalemia.

Since 1995, there has been increasing concern that certain progestins may be "thrombogenic". Oral contraceptives containing the newer progestin desogestrel and gestodene may be associated with a higher incidence of venous thromboembolism than oral contraceptives containing older progestins. The suspected increase in risk is too small to detect in the clinical trials designed for marketing approval. The studies detecting increased risk have been observational studies. In general, the odds ratios have been small and there has been demonstrable prescription bias, making interpretation difficult. Nonetheless, most of the observational evidence has supported a small increased risk, prompting the European Agency for the Evaluation of Medicinal Products to release the following information for women in September 2001:

"Women using a combined oral contraceptive containing desogestrel or gestodene with 30 ug of ethinylestradiol ... have a small increased risk of venous thromboembolism compared to women using combined oral contraceptives containing levonorgestrel with less than 50 ug of ethinylestradiol.

While in users of such levonorgestrel containing products the frequency of venous thromboembolism is estimated to be about 20 case per 100,000 women-years of use, it is estimated to be about 30 to 40 cases per 100,000 women-years of use of desogestrel or gestodene containing products with 30 ug of ethinylestradiol."

In the U.S., oral contraceptives containing desogestrel contain the following statement on the label:

"Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate two-fold increased risk, which corresponds to an additional 1–2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this two-fold increase in risk."

There is no approved product containing gestodene in the U.S.

2. Significant Findings from Chemistry, Animal Pharmacology and Toxicology

2.1 Pharmacology

Nonclinical studies showed that DRSP is a progestin with antiandrogenic and antimineralocorticoid activities, but no estrogenic, androgenic or glucocorticoid activity. DRSP showed antimineralocorticoid properties in both *in vivo* and *in vitro* assays. According to the FDA pharmacology reviewer, there were no preclinical signals to suggest that DRSP was an unusually thrombogenic progestin, and there were no QT prolongation signals in the animal studies.

2.2 Chemistry

There were no chemistry issues. For further details, the reader is referred to the review by the FDA chemist.

3. Human Pharmacokinetics and Pharmacodynamics

3.1 Pharmacokinetics

Bioequivalence Data:

To prove efficacy, the applicant showed bioequivalence of E_2 in Angeliq to E_2 in Estrace. The biopharmaceutical reviewer reviewed the bioequivalence trials, summarized here.

Berlex presented two bioequivalence studies to support bioequivalence. The first study was a single dose, open-label, randomized, two-period, crossover study in which 36 postmenopausal women received two Estrace 2 mg tablets or two of the Berlex E_2 2 mg tablets. Estrone and E_2 were evaluated. The study showed bioequivalence between the Berlex E_2 and Estrace, by AUC and Cmax for E_2 and free estrone.

The second study was a multiple-dose, open-label, two-period, crossover study in which 36 postmenopausal women took study drug for 13 days. Women received either Estrace 2 mg each day (as two, 1 mg tablets), or E_2 2 mg + DRSP 4 mg per day (as two tablets, each containing 1 mg E_2 and 2 mg DRSP). The study showed bioequivalence for E_2, free estrone, and estrone sulfate based on AUC and Cmax.

Dissolution data linked the Berlex product containing E_2 alone to the combination product.

PK Properties of Angeliq:

The liver converts E_2 to various forms, including estrone and estrone sulfate. Estrogens undergo a continuous enterohepatic recirculation, during which they are altered in the liver, secreted in the bile and then reabsorbed in the small intestine. Most estrogens circulate bound to SHBG and

albumin, and only unbound estrogens are active. E_2, estrone, estriol and the sulfate and glucuronide conjugates are secreted in the urine.

The E_2 in Angeliq has PK parameters similar to those of related E/P products, as seen in Table 2.

Table 2. Comparison of E_2 PK Parameters of Other Oral E/P Products after Single Dose Administration.

Product	AUC24 (pg-h/ml)	T max (hr)	Cmax (pg/ml)
Angeliq with 1 mg DRSP	339	4.8 ± 4.4	43.8 ± 10.0
Activella	N.A.	6.8 ± 2.9	34.6 ± 10.8
Ortho Prefest	424	7	39.3

The half-life of DRSP 1 mg combined with EE 1 mg is 42.3 ± 21.3 hours. The two main metabolites of DRSP are formed without the cytochrome P450 system and are not active. DRSP excretion is slightly higher in the feces than the urine. The pharmacokinetics of DRSP are dose proportional within the dose range of 1-4 mg.

Based on *in vitro* and *in vivo* studies, DRSP is unlikely to inhibit the metabolism of drugs that use cytochrome P450 enzymes at clinically relevant doses. Conversely, drugs that affect cytochrome P450 enzymes are unlikely to affect the metabolism of DRSP because DRSP is only a minor substrate for P450 enzymes. A drug-drug interaction study with omeprazole and DRSP 3 mg did not show an interaction with cytochrome P450 enzymes 2C19 or 3A4. A drug-drug interaction study with simvastatin did not show a clinically significant CYP 3A4 inhibition with DRSP 3 mg.

Based on a multiple dose crossover PK study (Report AP01), there is no PK interaction between DRSP and E_2. The presence of either DRSP or E_2 did not influence the AUC, Tmax, or $t_{1/2}$ of the other component. The doses studied were DRSP, 1 mg and 4 mg, and E_2, 1 mg and 2 mg.

The effects of mild to moderate renal insufficiency on DRSP PK were studied in a group of 28 women exposed to DRSP 3 mg daily for 14 days. At steady state, serum DRSP levels in the group with mild renal insufficiency (N=10) were comparable to those with normal renal function (N=11). The serum DRSP levels were on average 37% higher in the group with moderate renal insufficiency (N=7) compared to those with normal renal function. No clinically significant hyperkalemia was seen in this small group, although one woman with moderate renal insufficiency had borderline hyperkalemia (5.5 mmol/l).

The applicant submitted a liver impairment study six months into the review cycle, and a detailed review of this study is in the appendix, below. In brief, women with moderate liver impairment had over twice the exposure to DRSP, measured by AUC, compared with women with normal liver function. One woman in the liver impairment study developed serious hyperkalemia.

A single dose, food effect study, using EE (0.03 mg) + DRSP 3 mg showed slower mean absorption and reduced mean Cmax for both DRSP and EE in the presence of food. The mean AUC of DRSP did not change, while the mean AUC of EE was 16% lower in the fed state.[8]

Effects of weight and race on pharmacokinetics were not studied.

3.2 Pharmacodynamics

DRSP 2 mg is the minimum inhibitory dose to suppress ovulation.[9] DRSP caused secretory transformation of the endometrium in seven of ten castrated women treated with either 4 mg or 6 mg each day for 10 days of a 28-day cycle during which they received daily ethinyl estradiol (EE) 0.05 mg.[10] (This dose of EE is similar to a daily dose of E_2 equal to 10 mg.[11])

DRSP is an aldosterone antagonist that is about seven times more potent than spironolactone, so DRSP 3 mg has antimineralocorticoid activity comparable to spironolactone 25 mg.[12]

Two studies explored the risk of hyperkalemia in the presence of drugs that increase the risk of hyperkalemia. The first study looked at serum potassium levels in women taking the ACE inhibitor, enalapril.[13] The FDA reviewer, Dr. Scott Monroe, reviewed the potassium findings for the Yasmin NDA and concluded there was no effect of DRSP/ E_2 treatment on serum potassium concentrations as measured by the protocol-defined analysis of AUC and Cmax. However, his *post hoc* analysis showed a slightly greater mean change in potassium from baseline in the DRSP/ E_2 group, 0.28 mEq/L, compared to placebo, 0.06 mEq/L.

The second study looked at serum potassium levels in women taking E_2 1 mg + DRSP 3 mg and indomethacin.[14] Because FDA requested this study to explore the risk of hyperkalemia and it was not reviewed for the Yasmin NDA, it is reviewed separately in the appendix, below. The applicant concluded there was no difference in AUC_{24} and Cmax in women taking indomethacin alone compared with women taking indomethacin plus E_2/DRSP. Furthermore, the study did not detect an interaction between indomethacin and E_2/DRSP causing hyperkalemia. However, since the sample size was small, investigators selected only healthy postmenopausal women with normal screening labs, fed them a predetermined diet, and removed the only woman who developed a low creatinine clearance during treatment with indomethacin, the likelihood of detecting hyperkalemia was low.

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[8] Report No. A733, Study No. 93053
[9] Report No. 7215, Study No. 83146; Report No. 7214, Study No. 83,146; Report No. A892, Study No. 91013
[10] Report No. 6961, Study No. 83146
[11] Speroff L, Glass RH, Kase NG. 1999 Clinical Gynecologic Endocrinology and Infertility, Sixth Edition., p. 729.
[12] Report No. 4417
[13] Report No. B990, Study No. 98106
[14] Report No. A00824, Study No. 304181

4. Description of Clinical Data and Sources

4.1 Sources of Clinical Data

The data used in the review came from the applicant's clinical trial program.

4.2 Overview of Clinical Trials

In the Integrated Summary of Safety for Angeliq, the applicant includes data from trials involving DRSP plus E_2. This includes four Phase 3 trials and five Phase 1 trials. Additionally, study reports from three small trials (total N=17) are included in the NDA, but not in the ISS because an electronic database was not created for the studies. There were no safety concerns in these three small studies.

Table 3 summarizes the clinical trials used to support the safety and efficacy of Angeliq.

Table 3. Clinical Trials Used to Support Safety and Efficacy of Angeliq

Report Number	Indication	Dosage-number exposed	Comments
A02827	Endometrial protection	0.5mg DRSP+ 1 mg E_2-227 1 mg DRSP + 1 mg E_2 - 231 2 mg DRSP + 1 mg E_2 - 227 3 mg DRSP + 1 mg E_2 -231	Pivotal clinical study for Angeliq NDA. U.S. sites
AR98	Vasomotor symptoms	1 mg DRSP + 1 mg E_2 - 55 2 mg DRSP + 1 mg E_2 - 52 3 mg DRSP + 1 mg E_2 - 57	No final report yet, safety data only for Angeliq NDA. European sites
AU18	Vasomotor symptoms	3 mg DRSP + 1 mg E_2 - 252 2 mg DRSP + 1 mg E_2 - 252	No final report yet, safety data only for Angeliq NDA. European sites
AR99	Osteoporosis	3 mg DRSP + 1 mg E_2 -57 2 mg DRSP + 1 mg E_2 - 60 1 mg DRSP + 1 mg E_2 - 58	No final report yet, safety data only for Angeliq NDA. Denmark
A00824	Indomethacin-K^+ safety	3 mg DRSP + 1 mg E_2 -32 Indomethacin 150 mg	Phase 1 Germany
AP01	Multiple dose PK and interaction of E_2 and DRSP	1 mg DRSP + 1 mg E_2 - 18 4 mg DRSP + 1 mg E_2 - 18 1 mg DRSP + 2 mg E_2 - 18 4 mg DRSP + 2 mg E_2 - 18	Phase 1, open-label. Germany
AX19	Bioavailability study	2x 1 mg DRSP + 1 mg E_2 - 18 2x 3 mg DRSP + 1 mg E_2 -18 6 mg DRSP + 2 mg E_2 - 18	Phase 1, open label, crossover, single dose. Germany
B274	Bioequivalence to Estrace trial	4 mg DRSP + 2 mg E_2 - 36 2 mg E_2 - 37	Phase 1, open label, randomized, crossover. 77% Hispanic. U.S. site.
B990	ACE inhibitor - K^+ safety	3 mg DRSP + 1 mg E_2 - 12 Placebo - 12	Phase 1, double blind, randomized. U. S.
Submitted six months into review cycle so not included in ISS, but reviewed in Appendix:			
A03161	Hepatic Impairment	3 mg DRSP + 1 mg E_2 - 20	Phase 1. U.S. sites
Estradiol-only trial, used to support bioequivalence claim:			
307-11	Bioequivalence	Berlex 2 mg E_2 - 36 Estrace 2 mg E_2 - 36	Phase 1, single dose, open label, randomized. U.S. site

4.3 Postmarketing Experience

Angeliq is not approved or marketed in any country.

4.4 Literature Review

The applicant included 29 published articles related to DRSP, most of which were reviews or news releases that mentioned DRSP. Ten studies present results of contraception trials and PK/PD trials. Although the articles generally did not list a source of funding, the data appear to come from drug development studies presented in the NDA.

My search of PubMed using drospirenone as the search term turned up 32 articles, with a large overlap with the applicant's list. I found no new issues.

5. Clinical Review Methods

5.1 Review Methods

Three trials were chosen for detailed review. Section 6 reviews the trial designed to show that DRSP protects the endometrium from E_2-induced hyperplasia. The appendix contains detailed reviews of two Phase I trials chosen because they study potassium safety in women at increased risk for hyperkalemia. The remaining trials were not reviewed separately, but were included in the integrated safety analysis.

5.2 Overview of Materials Consulted in Review

Materials included the electronic NDA submission, labels for related products such as spironolactone and E/P products, reviews for other E/P products, IND 53,842 reviews, reviews for Yasmin, and the literature on DRSP and E/P therapy during menopause.

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

The Office of Compliance inspected four sites, two from the endometrial safety trial (A02827) and two from the bioequivalence trial (B274). All four inspections were satisfactory. Although the bioequivalence trial was small, two sites were inspected because this trial was pivotal for efficacy claims.

The endometrial safety trial had 53 sites, with the number of randomized patients at each site ranging from 3-65. The names of the principal investigators were checked against the FDA list of restricted and disqualified clinical investigators[15]. None of the clinical investigators in the pivotal efficacy trial were named on the list.

Table 4 shows the sites from the endometrial safety trial that were chosen for audit. Both sites were chosen because they each had a large number of patients and neither had been audited recently.

[15] www.fda.gov/ora/compliance_ref/debar/

Table 4. Two Clinical Sites Chosen for Audit

Site # Investigator Address	Number of randomized patients
7 Corn, Lydia MD Clinical Studies, Sarasota 5969 Cattleridge Road, Suite 100 Sarasota, FL 34232 941-342-8288	45
36 Wehle, Susan MD ICSL, Clinical Studies 3105 W. Waters Avenue, Suite 109 Tampa, FL 33614 813-936-9764	50

5.4 Evaluation of Ethical Standards of Clinical Trial

According to the applicant, trials were conducted in accordance with the informed consent and IRB regulations set forth in the 21 Code of Federal Regulations and the ethical principles of the Declaration of Helsinki.

5.5 Evaluation of Financial Disclosure

Jeanine Best, Senior Regulatory Associate, evaluated the financial disclosure information, and concluded there were no financial interests disclosed that could bias the outcome of the trials.

The applicant did not submit enough financial disclosure information to meet regulatory requirements with the original NDA submission. The FDA asked for more information, including information from the two bioequivalence studies used to support efficacy, Study 307-11 and Study B274. The information submitted on January 21, 2002 was acceptable.

6. Integrated Review of Efficacy

6.1 Brief Statement of Conclusions

The clinical trial reviewed in section 6.3 showed efficacy for endometrial protection at DRSP doses of 1 mg, 2 mg, and 3 mg, when combined with E_2 1 mg. The one-year hyperplasia rates for these doses were less than 2%, with the upper bound of the one-sided 95% confidence intervals less than 4%. The lowest dose tested, DRSP 0.5 mg, did not meet these criteria.

However, there was evidence of bias and quality issues in the pathology readings. One pathologist appeared to have undue influence in cases of disagreement among pathologists. The same pathologist had wide discrepancies in his own readings of the biopsy slides, for example, reading three slides as "hyperplasia" (including one atypical hyperplasia) for the purpose of patient care, and re-reading them as "inactive, atrophic" for the purpose of calculating hyperplasia rates.

[redacted] Angeliq formulation containing DRSP 3 mg. DRSP 3 mg showed no benefit over DRSP 1 mg in endometrial protection, bleeding profile, or any of the other secondary endpoints in the trial.

The applicant showed efficacy for treatment of vasomotor symptoms and vulvar vaginal atrophy with two pharmacokinetic studies showing bioequivalence to Estrace. The FDA biopharmaceutical reviewer, Dr. Venkat Jarugula, reviewed these two studies. A summary follows.

Berlex presented two studies to support bioequivalence. The first study, No. 307-11, was a single dose, open-label, randomized, two-period, crossover study in which 36 postmenopausal women received two Estrace 2 mg tablets or two Berlex estradiol 2 mg tablets. Estrone and estradiol were evaluated. The study showed bioequivalence between the Berlex E_2 2 mg and Estrace 2 mg by AUC and C max, for E_2 and free estrone.

The second study, No. B274, was a multiple-dose, randomized, open-label, two-period, crossover study. Postmenopausal women took one study drug for 13 days, followed by a washout period of 14 days, followed by the other study drug for 13 days. Thirty-seven women started the study, and 36 women completed it, with one woman completing only the first treatment period. Women received either Estrace 2 mg each day (as two, 1 mg tablets), or E_2 2 mg + DRSP 4 mg each day (as two tablets, each containing 1 mg E_2 and 2 mg DRSP). The study demonstrated bioequivalence for E_2, free estrone, and estrone sulfate based on AUC and Cmax.

Dissolution data linked the Berlex product containing E_2 alone to the combination product.

6.2 General Approach to Clinical Review of the Efficacy of the Drug

The efficacy database consisted of one Phase 3 clinical trial, as well as a pharmacokinetic demonstration of bioequivalence between the E_2 in Angeliq and the approved product, Estrace. The next section reviews the Phase 3 clinical trial.

6.3 Detailed Review of Clinical Trial 96097A, Study Report A02827, Endometrial Protection Trial

6.3.1 Protocol

6.3.1.1. Objective

The primary objective was to evaluate efficacy of E_2-DRSP for the protection of the endometrium against E_2-induced hyperplasia in postmenopausal women.

Secondary objectives included

- Endometrial morphology and bleeding patterns
- Laboratory parameters
- Well-being as assessed by the Women's Health Questionnaire and the Medical Outcomes Study 36-Item Short-Form Health Survey
- The frequency and severity of hot flushes and relief of urogenital symptoms
- Drug levels

6.3.1.2 Overall Design

The study was a Phase 3, double blind, randomized, parallel arm study with five treatment arms, including an active control arm. The study population consisted of post-menopausal women, and treatment continued for one year. There were 53 study sites, all located in the U.S.

6.3.1.3. Population and Procedures

Women were randomly assigned to one of five daily oral treatments:

1. E_2 1 mg
2. E_2 1 mg/DRSP 0.5 mg
3. E_2 1 mg/DRSP 1 mg
4. E_2 1 mg/DRSP 2 mg
5. E_2 1 mg/DRSP 3 mg

Inclusion criteria were as follows:

- Age $\geq$ 45 and $\leq$75 years
- Intact uterus and negative endometrial biopsy or, if inadequate tissue, endometrial thickness < 5 mm on vaginal ultrasound
- Amenorrhea for $\geq$ 12 months or, if amenorrhea is < 12 months duration, but > 6 months, serum E_2 levels must be < 20 pg/mL and serum follicle stimulating hormone (FSH) level > 50 units/L
- Negative pregnancy test, within 1 year of amenorrhea
- Signed informed consent

Exclusion criteria were as follows:

- Baseline endometrial biopsy containing endometrial polyp alone or simple hyperplasia or worse
- Abnormal Pap smear suggestive of low grade squamous intraepithelial lesion (LGSIL) or worse

- Baseline ultrasound with abnormality that would preclude estrogen therapy
- Myocardial infarction within the last 6 months before Visit 1 or heart disease severe enough to need treatment with antiarrhythmic or antianginal drugs
- Idiopathic thrombophlebitis or thromboembolic disorders within the last 3 years unrelated to estrogen therapy or a history of these conditions at any time with previous estrogen therapy
- History of stroke or transient ischemic attacks
- Fasting baseline cholesterol ≥300 mg/dl, triglycerides ≥300 mg/dl, or glucose ≥140 mg/dl
- Hypertension: sitting systolic blood pressure ≥160 mm Hg or sitting diastolic blood pressure ≥95 mm Hg at rest
- Congestive heart failure
- Known or suspected malignant or premalignant disease, including malignant melanoma (excluding other successfully treated skin cancers)
- History of sex steroid-dependent malignancy
- Abnormal clinically significant findings during gynecological examination that may worsen under hormone treatment
- Insulin-dependent diabetes mellitus
- Uncontrolled thyroid disorders
- History of clinically significant depression
- History of alcohol or drug abuse within the last 2 years
- Treatment with anticoagulants (heparin or warfarin)
- Hormone therapy (oral, transdermal, intrauterine, implants or intravaginal administration) within 8 weeks prior to start of study, intramuscular administration within 6 months prior to start of study
- Participation in another clinical trial within 1 month or investigational drug use within the last 3 months prior to study
- Any disease or condition that compromises the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication
- Severe systemic disease that might interfere with the conduct of the study or the interpretation of the results
- Current significant liver dysfunction or disease
- Abnormal baseline laboratory values that are considered to be clinically significant
- For special metabolic subgroups only: use of medication for diabetes, hypertension, or hyperlipidemia

Comment: Limiting the study to generally healthy postmenopausal women with normal baseline labs made it less likely for the study to detect electrolyte disorders or thrombotic disorders.

The study was divided into four-week treatment periods termed cycles. Office visits occurred at the end of cycles. Table 5 shows the visit schedule and assessments done at each visit.

Table 5. Study Design and Schedule of Assessments

Study Evaluations	Visit 1 Screening	Visit 2 Baseline	Visit 3 1 cycle	Visit 4 3 cycles	Visit 5 7 cycles	Visit 6 10 cycles	Visit 7[a] 13 cycles
Medical and Medication History	X						
Physical Exam/Including Breast Exam	X				X		X
Blood Pressure and Heart Rate	X	X	X	X	X	X	X
Pap Smear	X						X
Mammography [b]	X						X
Endometrial Biopsy	X				X [c]		X
Transvaginal Ultrasonography	X				X [c]		X [d]
General Laboratory Tests	X				X		X
Special Laboratory Tests (at designated centers)	X			X	X		X
Serum FSH, TSH, and E_2 Levels [e]	X						
Patient Satisfaction Questionnaire							X
SF-36 and Women's Health Questionnaire		X		X	X		X
Concomitant Medications		X	X	X	X	X	X
Adverse Events			X	X	X	X	X
Medication Dispensed/Returned		X	X	X	X	X	X
Diary Cards Dispensed/Reviewed	X	X	X	X	X	X	X

E_2 = estradiol; FSH = follicle stimulating hormone; TSH = thyroid stimulating hormone

[a] If the subject was prematurely withdrawn from the study, all the evaluations described under Visit 7 were to be performed at the Final Visit.

[b] If a negative mammography was reported within 6 months prior to Visit 1 and report was available, a screening mammography was not required.

[c] Vaginal ultrasound was performed in all subjects, and endometrial biopsy was performed in only those with endometrial thickness $\geq$ 5 mm.

[d] Vaginal ultrasound was performed in those subjects whose biopsy contained tissue insufficient for diagnosis.

[e] E_2 and FSH levels were required if amenorrhea < 12 months.

6.3.1.4. Evaluations/Endpoints

The efficacy endpoint was endometrial hyperplasia, a recognized surrogate endpoint for endometrial cancer. Based on the natural history of endometrial hyperplasia, "Fewer than 2% of hyperplasias without cytological atypia progress to carcinoma, whereas 23% of hyperplasias with cytological atypia (atypical hyperplasias) progress to carcinoma.[16]"

[16] Blaustein's Pathology of the Female Genital Tract, fourth edition, p.412, 1994. J. Kurman, editor. Springer-Verlag, publisher.

The procedure for doing endometrial biopsies and for describing biopsy results conformed to recognized standards. The biopsy categories were:

A. Tissue insufficient for diagnosis
B. Strips of benign surface and glandular lining epithelium
C. Inactive/atrophic endometrium
D. Proliferative endometrium
E. progestational secretory endometrium
F. Menstrual type endometrium
G. Simple hyperplasia without cytological atypia
H. Complex hyperplasia without cytological atypia
I. Atypical hyperplasia
J. Cancer
K. Endometrial polyp

A central lab ([redacted] received all biopsy specimens.

A [redacted] pathologist read all biopsies for safety to aid clinical decisions at the study site. For example, a prestudy safety reading of hyperplasia excluded women from participation in the study. An in-study or end-of-study safety reading of hyperplasia prompted discontinuation of study drug and follow-up.

Two [redacted] pathologists read all biopsies for efficacy. A third pathologist acted as arbitrator in cases where the two readers did not agree. The majority opinion was then binding. If two out of three did not agree, the three efficacy readers met and reevaluated the slides under a multiheaded microscope to reach a consensus. The pathologists were blinded to treatment. In addition, the three efficacy readers met before reading any slides to agree on the criteria for hyperplasia.

Comments: Clearly the pathologists were not independent in this protocol and therefore there was potential for the opinions of one pathologist to dominate. In fact, there is evidence that Dr. [redacted] 's opinions dominated, as discussed below.

According to current FDA recommendations, the pathologists must be independent, and the analysis should use the most severe diagnosis when all three pathologists disagree. However, this study antedated current FDA recommendations. My analysis of efficacy will compare the applicant's method of analysis with the results obtained using current FDA recommendations. In addition, because of evidence of bias favoring the diagnoses of Dr. [redacted] I also analyzed the data using the safety readings only.

Blinding of the pathologists is imperfect in this type of study, because a progestin produces recognizable effects on endometrial tissue.

6.3.1.5. Statistical Plan

Statistical Procedures:

Investigators expected an endometrial hyperplasia incidence of 1% at one year in the E_2-DRSP groups, and group sizes were expected to give an upper limit of the 95% confidence interval no greater than 2% if no hyperplasia or cancer was observed. Efficacy analysis was done on the intention-to-treat (ITT) group.

The percent of hyperplasia or cancer was calculated for each group, and each group was compared to the E_2-only group.

6.3.2 Results

6.3.2.1. Subject Disposition

At least 1142 of 1147 randomized subjects received one or more doses of study drug. Whether the remaining five subjects took study medication is not known, because four subjects were lost to follow-up and one withdrew consent, without returning study medication packets. Table 6 shows randomization into treatment groups.

Table 6. Subject Disposition by Treatment Group

	1 mg E_2	1 mg E_2 + 0.5 mg DRSP	1 mg E_2 + 1 mg DRSP	1 mg E_2 + 2 mg DRSP	1 mg E_2 + 3 mg DRSP	Total
Randomized	227	228	231	228	233	1147
No information about whether they took study medication	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.8)	5 (0.4)
Intention to treat (ITT) Group	226	227	231	227	231	1142

Overall, 845 subjects completed the study medication. Table 7 shows withdrawals by reason and treatment group.

Comment: "Other" withdrawals for the DRSP 3 mg group included six women who were lost to follow-up, and two who moved. "Other" withdrawals for the DRSP 1 mg group included five women who were lost to follow-up, three who moved, and one whom the principal investigator wanted to discharge.

Table 7. Frequency of Withdrawals from Study Medication by Reason and Treatment Group (ITT)

Reason	E_2	E_2 + 0.5 mg DRSP	E_2 + 1 mg DRSP	E_2 + 2 mg DRSP	E_2 + 3 mg DRSP	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse Event	53 (23.5)	29 (12.8)	35 (15.2)	39 (17.2)	33 (14.3)	189 (16.6)
Lack of Efficacy	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Protocol Deviation	6 (2.7)	4 (1.8)	9 (3.9)	6 (2.6)	5 (2.2)	30 (2.6)
Withdrawal of Consent	10 (4.4)	11 (4.9)	9 (3.9)	3 (1.3)	11 (4.8)	44 (3.9)
Other	7 (3.1)	4 (1.8)	9 (3.9)	6 (2.6)	8 (3.0)	33 (2.9)
Total	77 (34.1)	48 (21.2)	62 (26.8)	54 (23.8)	56 (24.2)	297 (26.0)

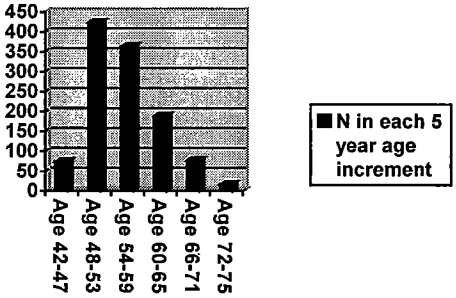
Table 8 lists the 30 women with protocol deviations leading to early discontinuation of study medication.

Table 8 Protocol Deviations Leading to Discontinuation of Study Medication

Protocol Deviation	Subject Number
Inclusion Criteria Not Satisfied	
E_2 & FSH not drawn at baseline and subject amenorrheic < 12 months	53026
No EBX and endometrial thickness ≥ 5 mm	39017
Exclusion Criteria	
Entered with possible polyp	01005
Entered another clinical trial	02016, 24002, 50021
Abnormal mammogram	13009
High LFTs at screening and at baseline	48015
Noncompliance	
Medication	02018, 02009, 06027, 06004, 15006, 25019, 33017, 36022, 47007, 48007, 51021, 52014
Due to center error	06019, 06028
Refused endometrial biopsy	36008, 43016
Drug Dispensing Error	
Dose for another subject given	14049, 25003
Endometrial thickness > 5 mm during study – no EBX	04009, 10002, 20018, 36029

Comment: Among the women in Table 8 with endometrial thickness > 5 mm and no biopsy, only one took DRSP + E_2. Her DRSP dose was 3 mg. This woman had an endometrial measurement that changed from 4 mm at baseline to 8 mm after ten months of therapy. She did not report vaginal bleeding as an adverse event, however, which makes it less likely that she had endometrial hyperplasia. No further information is available about her.

The mean age was 56 years (range 42 to 75 years). The following chart shows the age distribution.



The racial distribution was described as 92% Caucasian, 2.5% Black, 2.5% Hispanic, 1.3% Asian, and 0.9% listed as "Other".

Compliance, estimated from unused medication returned at each study visit, was similar across treatment groups and averaged 95% (range 93-96%).

The applicant summarized concomitant medication data for potassium-sparing medication. No one used digoxin or spironolactone. Only five women used potassium sparing diuretics, two women used indomethacin and 34 women used ACE inhibitors.

6.3.2.2. Efficacy Endpoint Outcomes

Endometrial hyperplasia

A safety reader evaluated all biopsies first. Pre-study safety readings determined eligibility for the study. Nonscheduled in-study readings determined if a woman should stop study medication and receive treatment. And finally, end-of-study safety readings identified women with hyperplasia so they could be treated.

By the applicant's analysis of the intention-to-treat (ITT) group based on the efficacy readings, DRSP 1 mg adequately protects the endometrium. There were 19 cases of endometrial hyperplasia (one atypical) in the E_2 group, one case of atypical endometrial hyperplasia in the E_2 plus DRSP 0.5 mg group, and no endometrial hyperplasia in the remaining groups.

Table 9 shows the applicant's analysis of the proportion of subjects with endometrial hyperplasia in each treatment group. Women whose biopsy results were "insufficient tissue for diagnosis" (n=129) were imputed to have "inactive/atrophic endometrium" if the vaginal sonogram showed an endometrial thickness <5 mm. This left 42 women with the diagnosis "insufficient tissue for diagnosis" but with endometrial thickness > 5 mm. Their diagnosis was not imputed.

Table 9. Proportion of Subjects with Endometrial Hyperplasia at Any Time[a] (ITT), Applicant Analysis

	E_2 1 mg N=226 n (%)	E_2 1 mg + 0.5 mg DRSP N=227 n (%)	E_2 1 mg + 1 mg DRSP N=231 n (%)	E_2 1 mg + 2 mg DRSP N=227 n (%)	E_2 1 mg + 3 mg DRSP N=231 n (%)
n[b]	155	171	157	161	162
Hyperplasia	19 (12.3)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

N = number of subjects in each treatment group with biopsy data

[a] Subjects without diagnosis of hyperplasia who did not complete 1 year of treatment were excluded.

[b] n = number of subjects in ITT minus number of subjects who withdrew without diagnosis of hyperplasia.

Comment:

The applicant does not justify imputing a diagnosis based on endometrial thickness for women with endometrial thickness < 5mm, and ignoring the women who have an endometrial thickness > 5 mm.

The applicant's method of obtaining consensus readings, putting all three pathologists together at a multi-headed microscope, may introduce bias. In particular, one pathologist might dominate the consensus reading. To explore this possibility, I looked at all consensus readings to see how many agreed with each reader's initial reading. Table 10 shows the results of this analysis.

Table 10. Proportion of Each Reader's Efficacy Readings that Agreed with Consensus Readings.

Reader Number (initials)	Number of initial readings that were the same as consensus readings	Percentage of readings that were the same as consensus readings
Reader 1 [redacted]	104	65%
Reader 2 ([redacted])	51	32%
Reader 3 ([redacted]	11	11%

The numbers add up to more than 100% because of the way polyps were handled. For example, if Reader 1 diagnosed "hyperplasia plus polyp", and Reader 2 diagnosed "hyperplasia", and Reader 3 diagnosed "proliferative", then a consensus read would be required. If the consensus read was hyperplasia, both reader 1 and reader 2 were considered to agree with the consensus read.

Comments: Reader 1 dominated the consensus reading, and therefore the applicant's method of calculating efficacy appears to be biased in favor of Reader 1. Reader 1 was [redacted]

This also raises the possibility that Dr. [redacted] *may have dominated the pre-reading meeting, where all three pathologists met to discuss the diagnostic criteria for hyperplasia, a potential source of bias that cannot be eliminated from these data. In addition, five* [redacted] *employees,*

including Dr. ——— did the safety readings, so the possibility that Dr. ——— exerted influence over the safety readings exists as well.

To eliminate the biased consensus read, the FDA statistical reviewer performed a "worst of three" analysis, using the worst diagnosis when all three readers disagreed. Eight more cases of hyperplasia were identified this way, including two in the DRSP treatment groups. Table 11 shows the analysis. In all DRSP groups, the upper bound of the one-sided confidence interval did not exceed 4% and was therefore acceptable.

Table 11. Incidence of Endometrial Hyperplasia Using Efficacy Readings- FDA Analysis

Treatment	N	Estimate of incidence of hyperplasia (n)	Upper bound of one-sided 95% confidence interval for incidence of hyperplasia or worse
E_2	186	0.134 (25)	0.183
E_2 + 0.5 mg DRSP	185	0.005 (1 atypical hyperplasia)	0.025
E_2 + 1 mg DRSP	187	0.005 (1 simple hyperplasia)	0.025
E_2 + 2 mg DRSP	188	0.000 (0)	0.016
E_2 + 3 mg DRSP	187	0.005 (1 simple hyperplasia)	0.025

The N in Table 11 comes from the ITT group, minus one woman who entered the study with hyperplasia, 5 women who received no drug, 136 women who had only a screening biopsy, 39 women who had no biopsies, and 28 women who had more than 3 months elapse between last drug intake and biopsy. None of the last group had hyperplasia, so removing them did not affect the numerator for hyperplasia incidence.

To assess whether there might be under-reading of hyperplasia, I looked at the percent of women in the E_2-only arm with hyperplasia (13.4%) and compared it to two historical controls, Activella (14.6%) and Ortho Prefest (29%). The Angeliq E_2 arm appears comparable to the Activella E_2-only group. Discrepancies may reflect differences in the population studied or differences in the pathologists reading the slides.

It is unclear why there were so many safety readings of hyperplasia (ten) in the DRSP groups, but so few efficacy readings of hyperplasia (one) in the same groups. By the applicant's analysis, there were ten safety readings of hyperplasia in women taking DRSP, and all but one resolved with the efficacy readings. In contrast, for women taking E_2 only, there were 22 safety reading and 20 efficacy readings of hyperplasia.

Table 12. Discrepancies between Safety and Efficacy Readings

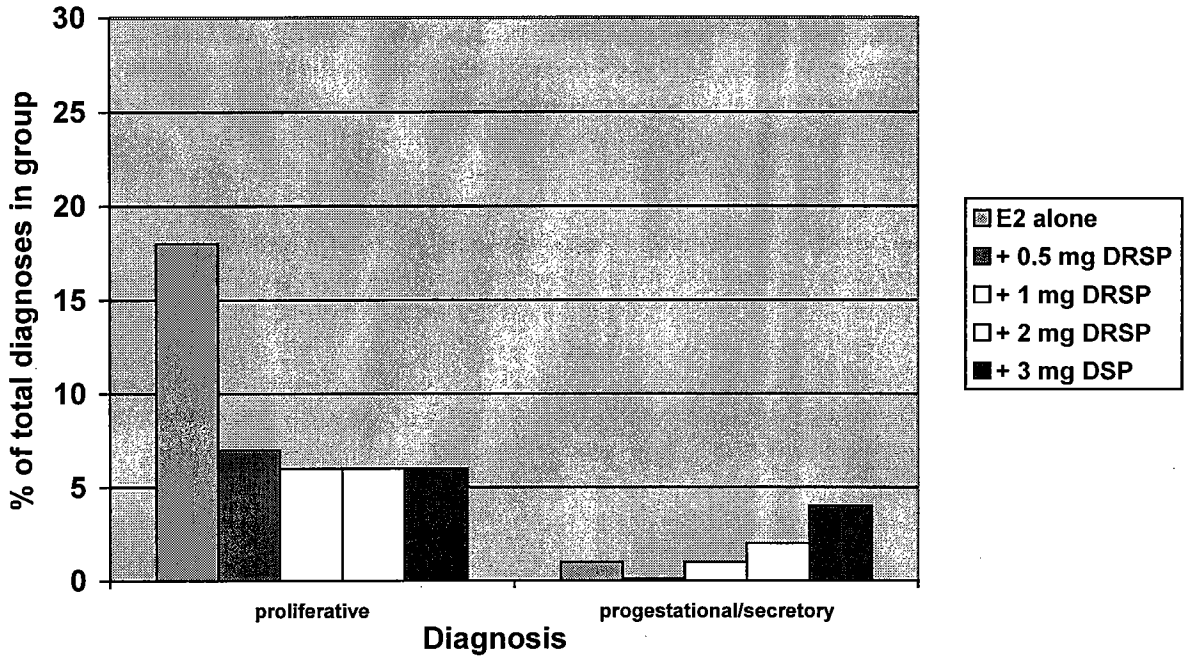
	DRSP + E_2	**E_2**
Safety reading	10	22
Efficacy reading	1	20

Comment: When asked to explain the discrepancy between the safety readings and the efficacy readings for the women on DRSP, the applicant responded that expert pathologists did the efficacy

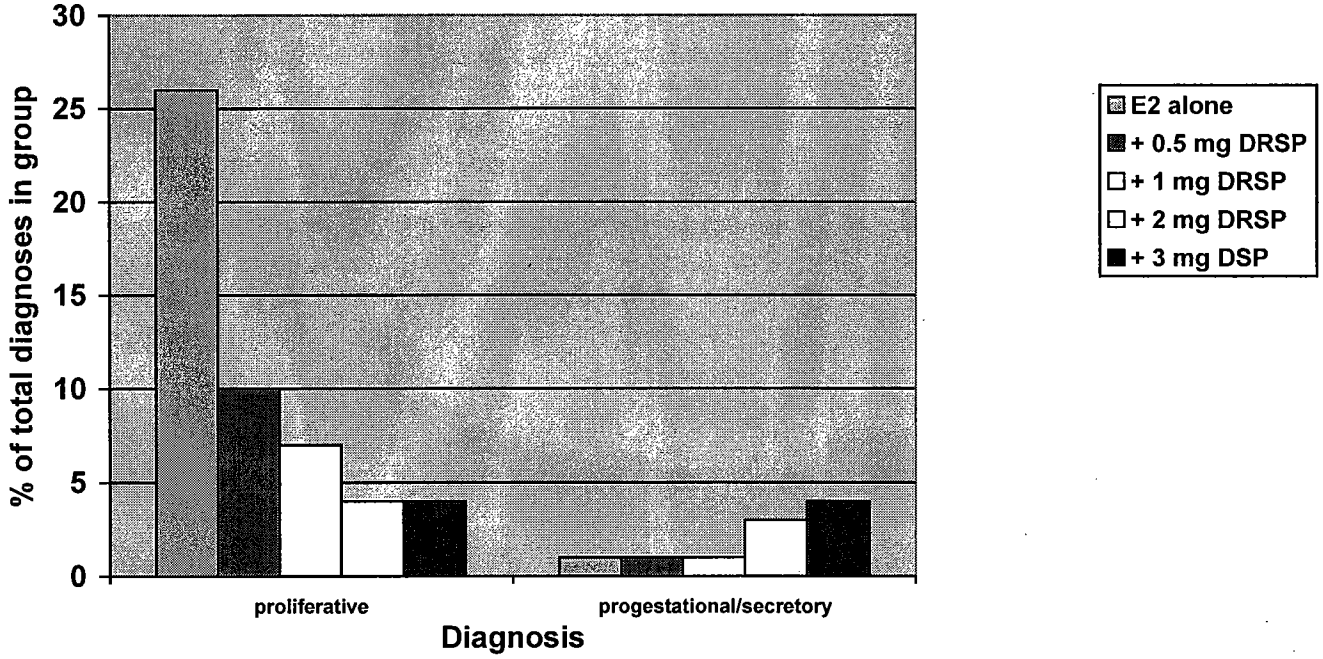
readings, while non-expert pathologists did the safety readings, and therefore the quality of the safety readings was less. However, we determined that the safety readers were all expert gynecologic pathologists. In fact, [redacted] one of the efficacy readers, was also the safety reader for one fourth of the slides.

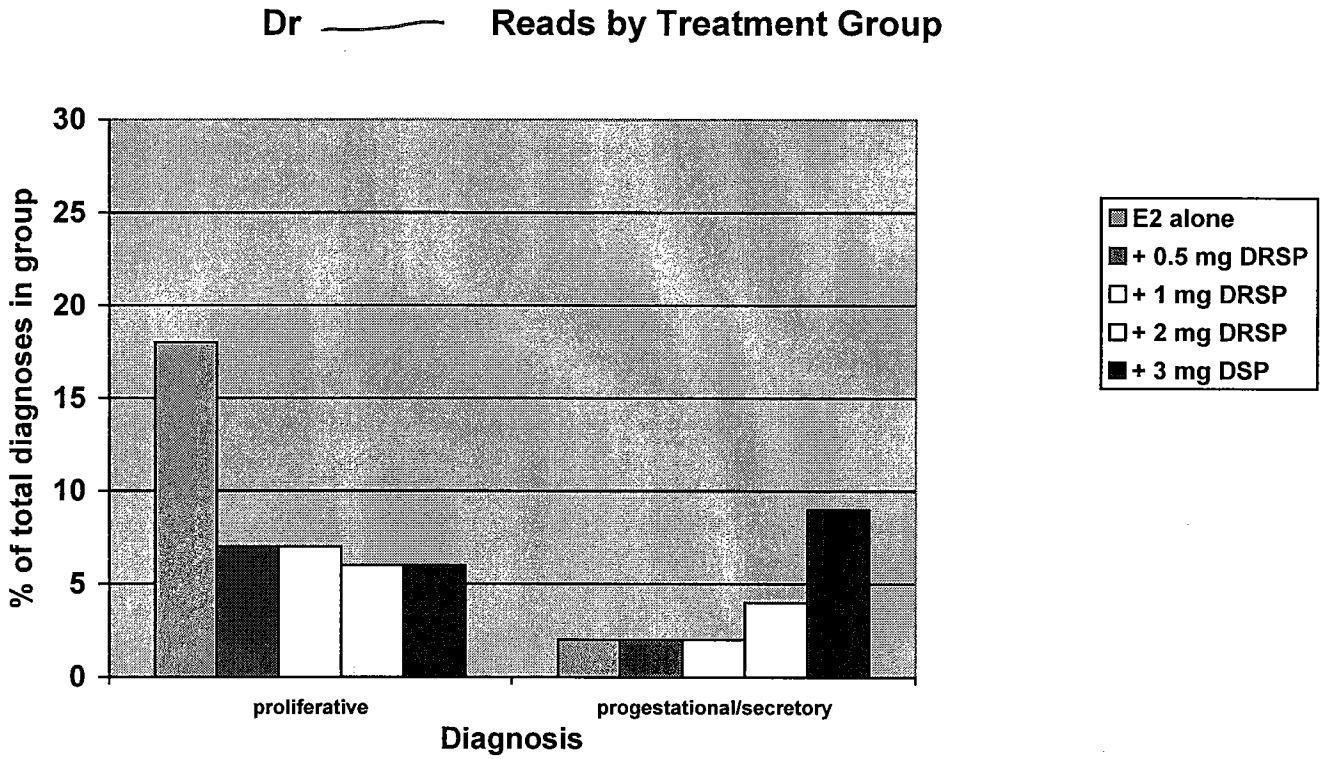
To further assess the applicant's claim that the quality of the safety readings is inferior to the quality of the efficacy reads, the diagnoses, "proliferative endometrium", and "progestational/secretory endometrium", were examined. Both of these diagnoses should show a dose-ranging effect in well-read biopsies, with the proportion of proliferative diagnoses decreasing with increasing progestin dose, and the proportion of progestational/secretory increasing with increasing progestin dose. The following charts show this analysis. The efficacy reads and the safety reads show similar dose-ranging effects. This analysis does not support the applicant's claim that the safety readings were inferior in quality to the efficacy readings.

Efficacy Reads by Treatment Group



Safety Reads by Treatment Group





Comments: Some of the difference between the safety and efficacy readings might be explained by problems with blinding of the pathologists to treatment group. Progestin effects in the DRSP exposed specimens may have made the blinding less than perfect.

The safety readings are likely to be conservative because they determine patient care. For example, a safety reader may have preferred to err on the side of overdiagnosis of hyperplasia in a case where the slide may have been difficult to read. An efficacy reader would not have to be concerned about a missed diagnosis of hyperplasia since his reading did not impact patient care.

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To see if the discrepancies between safety and efficacy readings were large or small, I compared the 10 safety readings and their matching efficacy readings. Table 13 shows this comparison.

Table 13. Safety Readings for Angeliq with Matching Efficacy Readings

Patient No.	Dosage DRSP (mg)	Safety Reading Biopsy Date Reader	Efficacy Readings by Reader	Exposure (months)
14022	*0.5*	*Simple hyperplasia 8/26/98*	*1. Inactive, atrophic* *2. Inactive, atrophic*	*13*
48006	0.5	Simple hyperplasia 8/26/98	1. Proliferative 2. Inactive, polyps 3. Proliferative	13
41001	*0.5*	*Atypical hyperplasia 2/1/99*	*1. Atypical hyperplasia* *2. Cancer* *3. Atypical hyperplasia*	*13*
52012	*0.5*	*Atypical hyperplasia 1/28/99*	*1. Inactive, atrophic* *2. Inactive, atrophic*	*13*
40037	1	Simple hyperplasia 9/29/99	1. Inactive 2. Inactive	7
01015	2	Atypical hyperplasia 9/30/99	1. Inactive 2. Inactive	13
20028	2	Atypical hyperplasia 4/26/00	1. Inactive, atrophic 2. Polyps 3. Strips of benign surface and glandular epithelium 4. Consensus= Inactive, atrophic	13
24003	*2*	*Atypical hyperplasia 8/18/98*	*1. Menstrual/polyps* *2. Menstrual/polyps*	*7*
12007	*3*	*Simple hyperplasia 1/28/99*	*1. inactive/polyps* *2. polyps* *3. polyps*	*7*
02002	3	Complex hyperplasia without atypia 9/4/98	1. Simple hyperplasia without atypia/polyps 2. Inactive/polyps 3. Polyps 4. Consensus = inactive/polyps	7

Comments: The discrepancies are large. In six cases listed in Table 13, the diagnosis makes a large jump from "hyperplasia" on the safety read to "inactive, atrophic" on the efficacy read.

Three of these large jumps are in cases read by Dr. ——— who acted as both a safety and efficacy reader.

All five safety readers are recognized experts in gynecologic pathology. One pathologist, Dr. ——— acted as both a safety and an efficacy reader, and there is no evidence that his readings were of higher quality than the readings of other safety readers. In fact, although Dr. ——— read about one quarter of the safety biopsies, he accounted for almost one half of the discrepancies between the safety and efficacy reads of hyperplasia in the DRSP groups.

The italicized rows in Table 13 point out cases where Dr. ——— was both safety and efficacy reader. Four of his five safety readings of hyperplasia resolve in his efficacy readings. Furthermore, Dr. ——— detected five cases of hyperplasia on his safety reads, when he read about 25% of the slides. However, he detected only three cases of hyperplasia on his efficacy reads, when he read 100% of the slides.

Because of the apparent bias in the efficacy readings, and because the safety readings seemed likely to err on the side of maximum patient safety, the safety readings provide a more conservative interpretation of hyperplasia incidence. Therefore, Table 14 shows the FDA analysis of hyperplasia incidence using the safety readings.

Using the safety readings, DRSP 1 mg, 2 mg, and 3 mg meet the FDA recommendations that the upper bound of the 95% confidence interval for the one-year incidence rates of hyperplasia not exceed 4%. However, three of the six safety readings of hyperplasia in these patients were atypical hyperplasia, which is a direct precursor of cancer.

There were 16 women who had either no biopsy or tissue insufficient for diagnosis by safety read, and endometrial thickness >5 mm, at their last data measurement. Of these sixteen patients, there was a normal resolution for three of them, an adequate plan for follow-up for seven of them, and no additional information for the remaining six. Three women were in the DRSP 1 mg group, and their sonographic endometrial measurements ranged from 6 to 9 mm. Two of them had had light bleeding.

Comment: Two women in the DRSP 1 mg group had bleeding, inadequate biopsies, and thickened endometrial measurements, and yet did not have records of adequate follow-up. This is outside of the standard of care. When asked for this information, the applicant responded that "Additional information has been requested from the investigator." However, if either one of these women in fact had hyperplasia, the incidence of hyperplasia would still be acceptable.

Table 14. Incidence of Endometrial Hyperplasia or Cancer in One Year Using Safety Readings - FDA Analysis

Treatment	N	Estimate of incidence of hyperplasia or worse (n)	Upper bound of one-sided 95% confidence interval for incidence of hyperplasia or worse
E_2	186	0.118 (22)	0.165
E_2 + 0.5 mg DRSP	185	0.022 (4)	0.049
E_2 + 1 mg DRSP	187	0.005 (1)	0.025
E_2 + 2 mg DRSP	188	0.016 (3)	0.041
E_2 + 3 mg DRSP	187	0.011 (2)	0.033

The average age of DRSP-exposed women who had hyperplasia by the safety readings was 58 years old, close to 56, the average age of all women in the study. This does not raise concern about age-related differences in endometrial safety. However, only 8% of the study population were over 65.

Bleeding Diary data:

Women reported bleeding/spotting data on diary cards. Table 15 summarizes the results for selected cycles.

Table 15. Proportion (%) of Women with Bleeding or Spotting for Selected Cycles

	E_2 only	E_2 + 0.5 mg DRSP	E_2 + 1 mg DRSP	E_2+ 2 mg DRSP	E_2 + 3 mg DRSP
Cycle1					
Bleeding	3.1	21.7	20.6	22.4	15.7
Spotting	3.1	9.7	12.3	11.9	10.9
Cycle 6					
Bleeding	18.2	24.6	20.7	15.3	20.2
Spotting	6.6	8.9	12.8	6	8.9
Cycle 13					
Bleeding	19.9	17.3	12.4	11.8	14.3
Spotting	7.6	11.3	8.3	9.5	9.3

The data do not show an advantage of one dose of DRSP over another with regard to bleeding or spotting. There is no clear effect of DRSP dose on the bleeding and spotting profiles. There appears to be less bleeding and spotting by cycle 13, which may indicate that the problem improves with time, or that women prone to the problem drop out of the study by cycle 13. By cycle 13, 20.7% of women in the DRSP 1 mg arm have bleeding/spotting, implying that 79.3% are amenorrheic.

Comments: It is interesting to compare the incidence of amenorrhea with historical data for related products. With Ortho-Prefest, 56 % of women were amenorrheic in month 12 in the endometrial protection trial, according to the clinical review of that NDA. With Activella, 86.2 % were amenorrheic starting in cycle 4, according to the clinical review of the Activella NDA. Angeliq, with 79% amenorrhea by cycle 13, is comparable.

In the absence of clinically serious bleeding/spotting, this is a nuisance side effect for women, who must deal with unpredictable needs for sanitary protection, as well as doctors, who must rule out pathological reasons for bleeding.

Hot flushes:

The mean number of weekly moderate to severe hot flashes decreased from baseline at all measured time points and for all treatment groups, as shown in Table 16. There was no statistically significant difference among treatment groups.

Table 16. Mean Weekly Number of Moderate to Severe Hot flushes by Treatment and Week (ITT)

Treatment	1 mg E_2	1 mg E_2 + 0.5 mg DRSP	1 mg E_2 + 1 mg DRSP	1 mg E_2 + 2 mg DRSP	1 mg E_2 +3 mg DRSP
Baseline	25	15	32	16	17
Week 4	5	2	3	3	3
Week 8	2	1	2	2	3
Week 12	1	1	1	1	2

The vasomotor data provide some clinical support to the bioequivalence studies. However, without a placebo group, it is not possible to measure how much of the decline in hot flashes is drug-related, and how much is either placebo effect or related to a natural decline in hot flash frequency with time. A large improvement in vasomotor symptoms is usually seen in the placebo group in placebo-controlled trials.[17] Nonetheless, historically, E_2 1 mg ameliorates hot flashes. Hot flash frequency declines similarly in all treatment groups in this study.

The number of vasomotor flushes at baseline was less than the entry criteria for a vasomotor trial (50-60 moderate-to-severe hot flushes each day), making it difficult to compare these data to historical data from vasomotor trials.

Vulvar and vaginal atrophy:

Subjects recorded urogenital symptoms, including vaginal dryness, dyspareunia, polyuria, dysuria, nocturia, and incontinence, on diary cards. The number of subjects contributing baseline

[17] For example, in the vasomotor trial submitted for approval of Ortho Prefest , there was a 50% decline in mean number of hot flushes by week 12 in the placebo group, and a 94% decline in the E2 1 mg group. In the vasomotor trial submitted for approval of Activella, there was a 58% decline in mean number of hot flushes per week by week 12 in the placebo group, and an 87% decline in the E2 1 mg group.

data was small (range=13 to 35 per treatment group). Table 17 shows summary data for subjects who were taking E_2 1 mg + DRSP 1 mg.

Table 17. Proportion of Subjects Who Experience Symptom for Group Taking E_2 1 mg + DRSP 1 mg (ITT)

	Dryness %	Dyspareunia %	Polyuria %	Dysuria %	Nocturia %	Incontinence %
Baseline	32	20	30	4	75	21
Cycle 6	13	9	24	2	59	28
Cycle 13	19	13	27	1	64	29

Comments: Little can be made of these data for several reasons. The number of women contributing baseline data was small. As with the vasomotor data, the data on vulvar and vaginal atrophy suffer from lack of a placebo control group. In addition maturation index was not assessed.

6.3.3 Conclusions about Efficacy Data

DRSP 1 mg adequately protects the E_2-primed endometrium against hyperplasia. Tripling the DRSP dose to 3 mg does not provide any added benefit in this study. The endometrial protection trial provided clinical support for the vasomotor symptom indication.

The applicant's method of determining endometrial hyperplasia incidence was flawed. There was evidence of bias in the efficacy readings, and, in particular, evidence that Dr. ——— exerted undue influence in these readings.

6.3.4 Brief Safety Analysis

This section provides a brief summary of safety findings for the endometrial safety study.

No deaths occurred during the study.

Overall, 189 subjects stopped study medication because of adverse events, as shown in Table 18. Of these, urogenital problems (n=104) accounted for most of the terminations. Vaginal/uterine hemorrhage (n=57) was the most common reason listed for termination, followed by breast pain (n=26). More discontinuations occurred in the E_2 arm than in any other arm of the study, because of more vaginal hemorrhage and endometrial hyperplasia in this arm.

Table 18. Gynecologic Adverse Events Leading to Termination of Study

Adverse Event	E_2 only N=226	+ 0.5 mg DRSP N=227	+ 1 mg DRSP N = 231	+ 2 mg DRSP N = 227	+3 mg DRSP N = 231
Total	53	29	35	39	33
Vaginal/uterine hemorrhage	16	4	16	14	7
Hyperplasia	11	2	1	1	1
Endometrial neoplasm	3	3	2	2	5
Endometrial disorder	6	0	0	0	0
Breast pain	4	4	5	6	7

Comment: To explore the clinical significance of vaginal /uterine hemorrhage, the patient data listings and the narratives of serious adverse events were searched for the terms "hysterectomy", "transfusion", "blood transfusion", "D and C", and "curettage". One hysterectomy was detected. The hysterectomy occurred at the end of the study, and was termed a voluntary hysterectomy in a subject who had completed a full year of E_2 + DRSP 2 mg. Although the indication for the hysterectomy was not given, this subject had not had bleeding listed as an adverse event in any of her study visits, and the investigator listed the event as not related to study drug . It would therefore appear that genital hemorrhage, though leading to discontinuation of study medication for some women, did not result in detectable serious morbidity.

The applicant evaluated the data for hyperkalemia in two ways. First, the serum potassium values were assessed. Next, clinical complaints that might be associated with hyperkalemia were evaluated. These data were sent to the FDA as part of a complete response to an approvable letter for the Yasmin NDA. The data has been evaluated previously by Dr. Monroe of the FDA (April 13, 2000), and Dr. Monroe's evaluation will be summarized here.

Eighteen subjects who started the study with normal baseline potassium levels had postbaseline hyperkalemia, diagnosed by the serum potassium $\geq$5.5 mEq/L. Three were in the E_2 group and 15 were in the DRSP groups. No DRSP dose effect was seen. The highest potassium value observed was 6.1 mEq/L.

Dr Monroe requested an analysis of the data showing the mean changes from baseline in only those subjects who were still on study drug or within 24 hours of the last dose of study drug. When evaluated this way, there appeared to be a small, dose-related increase in mean change from baseline, shown in Table 19. However, the difference between groups was not statistically significant.

Table 19. Mean Change from Baseline for Serum Potassium, by Treatment Group

	E_2 only N=190 mEq/L	+ 0.5 mg DRSP N=190 mEq/L	+ 1 mg DRSP N = 186 mEq/L	+ 2 mg DRSP N = 187 mEq/L	+3 mg DRSP N = 196 mEq/L
Average post-baseline value (mean $\pm$ SD)	-0.08 $\pm$ 0.42	-0.04 $\pm$ 0.40	-0.02 $\pm$ 0.40	-0.01 $\pm$0.40	0.00 $\pm$ 0.43
Maximum post-baseline value (mean $\pm$ SD)	-0.02 $\pm$ 0.42	0.06 $\pm$ 0.42	0.07 $\pm$ 0.43	0.10 $\pm$ 0.42	0.09 $\pm$ 0.44

There was no clear association between the incidence of subjects experiencing cardiovascular events and the dose of DRSP. The cardiovascular events evaluated included arrhythmia, bradycardia, dizziness, palpitations, syncope, and tachycardia. My search of the adverse event database did not uncover any instances of torsades de pointes.

Dr. Monroe asked Berlex if exclusion of samples because of hemolysis might also exclude samples with true hyperkalemia. Berlex' response:

"Berlex cannot ensure that instances of true clinical hyperkalemia were not overlooked due to the procedures that [redacted] followed. However, in accordance with their SOP, [redacted] does not release results from hemolyzed or prolonged cell contact and therefore Berlex provided serum potassium values for all samples provided to them by [redacted]

Comments: In this generally healthy postmenopausal group of women, no clinically significant hyperkalemia was detected. The ability of the study to detect hyperkalemia was limited, however. Nonetheless, no SAEs related to hyperkalemia were detected. The effects seen in the average and maximum post-baseline change in serum potassium, though too small to reach statistical significance, were consistent with the expected antimineralocorticoid activity of DRSP.

7. Integrated Review of Safety

7.1 Summary of Findings

The safety database raised two safety concerns beyond those expected for a hormone replacement therapy product. The first concern was the possibility of hyperkalemia, raised by the antimineralocorticoid properties of DRSP. The second concern was the possibility that DRSP is a "thrombogenic" progestin, raised by postmarketing reports of thrombotic events for Yasmin.

The pivotal clinical trials for Angeliq, and the related oral contraceptive product, Yasmin, did not detect symptomatic electrolyte abnormalities. However, most of the trials were not designed to detect hyperkalemia. Among four small trials designed to look at potassium levels under conditions of electrolyte stress, there were small increases in mean potassium from baseline. One woman with moderate liver disease and other risk factors developed serious hyperkalemia among 65 at-risk women in these four trials.

The clinical trials for Angeliq, and the related oral contraceptive product, Yasmin, did not detect an unusual incidence of thrombotic events compared to similar marketed products. The concern for thrombotic events came from postmarketing reports, particularly from Europe, where three thromboembolic deaths in Yasmin users were reported postmarketing.

7.2 Materials Used in the Review

The safety review used data from the NDA submission, postmarketing information from Yasmin, and previous reviews of Yasmin. Dr. Scott Monroe's review of the complete response to the approvable letter for Yasmin, dated April 13, 2001, was especially useful. In his review, Dr.

Monroe analyzed the potassium data from two Phase I and two Phase III studies, including the endometrial safety study discussed in section 6 above.

7.3 Description of Patient Exposure

1893 women took DRSP + E_2. Some of the studies included control groups of E_2 alone (N=392) or placebo (N=130).

Table 20 shows the exposure by dose. The total number (1947) is greater than 1893 because some subjects received more than one dose because of participation in a crossover study.

Table 20. Number of Women Exposed by Dose

Dose	0.5 mg DRSP + 1 mg E_2	1 mg DRSP + 1 mg E_2	1 mg DRSP + 2 mg E_2	2 mg DRSP + 1 mg E_2	2 mg DRSP + 2 mg E_2	3 mg DRSP + 1 mg E_2	4 mg DRSP + 1 mg E_2	4 mg DRSP + 2 mg E_2	6 mg DRSP + 2 mg E_2
N	227	362	18	591	18	641	18	54	18

Most women (N=1066) completed 52 weeks. Table 21 shows duration of exposure.

Table 21. Number of Women Exposed by Weeks of Exposure.

Weeks	<1 wk	1≤ wk<13	13≤ wk<26	26 ≤ wk<52	52≤ wk <105	>105 wk
N	47	274	201	257	1066	48

Most women were between 45 and 65 years old. Table 22 shows the number of women in each age group. The mean age was 55 years old.

Table 22. Number of Women Exposed by Age

Age Group (yr.)	≤44	45<age≤54	55<age≤65	>65
N	3	875	921	94

Most women were Caucasian (93.8%), with 3.3 % Hispanic, 1.7% Black, 0.6% Asian and 0.4 % other. The average weight was 71 kg, average height 163.5 cm and 21% were smokers.

7.4 Safety Findings from Clinical Studies

Deaths

One woman who had taken DRSP 1 mg + E_2 1 mg for 9 months died in an automobile accident. Details of the accident are unknown, but she had no medical history that would increase her risk for electrolyte disturbances. Her only concomitant medication was calcium 500 mg each day. She had normal electrolytes two months before the accident.

Other Serious Adverse Events

A total of 93 women (4.9%) who received DRSP + E_2 experienced SAEs and 7 women (2.7%) who received E_2 experienced SAEs.

Table 23 is a list of SAEs that might be related to hormone exposure or that involve the reproductive system. Since there are about seven times as many women in the DRSP + E_2 group as the E_2 group, we expect more SAEs in the DRSP + E_2 group by chance alone.

Table 23. Selected SAEs by Treatment Group

SAE	DRSP + E_2, N=1893 No. (%)	E_2, N=263 No. (%)
Breast neoplasm	1 (0.1)	0
Breast Cancer	8 (0.4)	0
Urogenital System	11 (0.6)	1 (0.4)
Vaginal Hemorrhage	0	1 (0.4)
Ovarian Carcinoma	1 (0.1)	0
Metrorrhagia	1 (0.1)	0
Endometrial Neoplasm	1 (0.1)	0
Cervical Cancer	1 (0.1)	0
Thrombotic events (total)	7 (0.4)	0
• Deep thrombophlebitis	3 (0.1)	0
• Cerebral embolism	1 (0.1)	0
• Myocardial infarct	1 (0.1)	0
• Pulmonary embolus	1 (0.1)	0
• Pulmonary artery thrombosis	1 (0.1)	0
Cholecystectomy/cholelithiasis	4 (0.2)	1 (0.4)

The breast neoplasm was a fibroadenoma, leaving eight cases of breast cancer in women exposed to DRSP + E_2 and none in women exposed to E_2. The eight breast cancers involved eight subjects. The breast cancers appeared in the higher doses of DRSP, but there was no clear dose response. DRSP doses were 2 mg (N=5) and 3 mg (N=3), combined with 1 mg of E_2. Breast cancer was diagnosed after a mean of 15 months of therapy.

Comments: It is not surprising that most of the women were diagnosed late in therapy, and, although it is consistent with the slower onset of cancer as an adverse effect, it can also be explained by women being prescreened with mammograms and therefore no women with detectable breast cancer entered the study. The apparent cluster of cases at the higher doses is interesting in light of some concern about progestin therapy and breast cancer. However, there was no clear dose effect, because there were more breast cancers at the 2 mg dose than the 3 mg dose.

For comparison, the U.S. incidence rates for breast cancer in the year 1998 for women between 55 and 64 was 360 per 100,000 women.[18] *Using this number, the expected number of breast cancers for a group of women between 55 and 64 years old would be seven, which is not much different from the eight seen in this database. However, using this historical control is problematic because women had to have a negative mammogram and no history of breast cancer to enter the Angeliq trials, whereas the U.S. incidence rates are estimates for all women.*

The SAE listed as "endometrial neoplasm" was an endometrial polyp that required operative removal in a woman who had been treated with DRSP 2 mg + E_2 1 mg for 1 year.

The seven serious thrombotic events involved only six subjects because one subject had both a deep vein thrombosis and a pulmonary artery thrombosis. There was a case of superficial thrombophlebitis in the adverse event data as well. DRSP doses were 1 mg (two cases), 2 mg (one case) and 3 mg (four cases), all combined with 1 mg of E_2. The median duration of therapy before thrombotic events was 3 months, with a range of 1 to 24 months (1, 1, 2, 3, 4, 8, 24 months). In contrast, the mean duration of exposure for all subjects in the safety database was 12 months (53.8 weeks).

Comment: The cluster of thrombotic events in the early months suggests a drug effect, consistent with the known thrombotic risks of estrogen.

Postmarketing reports of thrombotic events in Yasmin users has raised concern that DRSP may be a thrombogenic progestin. To explore this possibility in the Angeliq data, I looked for evidence of dose-response between DRSP and thrombotic events, and compared Angeliq to non-DRSP combination products.

Although four of seven women who had thrombotic events took the "high" 3 mg dose of DRSP, there was no clear dose-response between DRSP dose and thrombotic events. The 3 mg group was also the largest group (see Table 20).

Considering thrombotic events per woman exposed to both estrogen and progestin, Angeliq appears similar to related products. Table 24 displays the data obtained from the medical NDA reviews of Activella, Ortho Prefest, and Femhrt. Both Activella and Ortho Prefest contain E_2, and Femhrt contains EE.

[18] The National Cancer Institute, at http://seer.cancer.gov/

Total dropouts for adverse events, and five most frequent adverse events causing dropout, by dosage of DRSP.

Table 24. Thrombotic Events, Comparing Angelic to other E/P Therapies for Menopause

Product	Thrombotic Events	N in safety database for women who received E + P	% of women with thrombotic events
Angeliq	DVT DVT DVT + pulmonary artery thrombosis Cerebral embolism Myocardial infarct Pulmonary embolus and superficial phlebitis Superficial phlebitis	1893	0.4%
Activella	DVT DVT Cerebrovascular accident Pulmonary embolus	909	0.4%
Ortho Prefest	Superficial phlebitis Superficial phlebitis Superficial phlebitis	942	0.3%
Femhrt	DVT DVT CVA Superficial phlebitis Superficial phlebitis Superficial phlebitis	757	0.8%

Comment: A dose-response evaluation and comparison to related products did not support the notion that DRSP increases the thrombotic risks of E_2.

The age and race distribution of serious thrombotic events did not suggest age or race-related propensities. The average age of women with serious thrombotic events was 58 years old. Six women were described as Caucasian and one was described as Black.

Discontinuations for Adverse Events

One subject was lost to follow-up. A total of 247 women discontinued secondary to adverse events. Table 25 shows discontinuation secondary to adverse events by dosage of DRSP.

Table 25. Discontinuations for Adverse Events by Dose of DRSP

Dosage of DRSP (mg)	All doses	0.5	1	2	3	4
Vaginal hemorrhage	68	4 (1.8%)	14 (3.9%)	25 (4.2%)	25 (3.9%)	0
Breast pain	39	4 (1.8%)	9 (2.5%)	13 (2.2%)	13 (2.0%)	0
Headache and migraine	25	4 (1.7%)	6 (1.7%)	6 (1.0%)	9 (1.4%)	
Depression	15	2 (0.9%)	2 (0.6%)	7 (1.2%)	4 (0.6%)	0
Abdominal pain	14	7 (3.1%)	2 (0.6%)	5 (0.8%)	0	0
Total dropouts for adverse events N (%)	247	29 (12.8%)	53 (14.6%)	81 (13.7%)	84 (13.1%)	0

Comment: The data did not show an increase in adverse events causing discontinuation with increasing dosage of DRSP.

Other Significant Adverse Events

Table 26 shows adverse events that occurred in more than 5 % of subjects in the DRSP groups compared to the E_2-only group.

Table 26. Adverse Events in More than 5% of Subjects

Adverse Event	All DRSP groups n (%)	E_2 1 mg n (%)
Breast pain	369 (19.5)	35 (13.3)
Vaginal hemorrhage	205 (10.8)	44 (16.7)
Headache	181 (9.6)	29 (11.0)
URI	153 (8.1)	40 (15.2)
Abdominal pain	147 (7.8)	31 (11.8)
Flu syndrome	138 (7.3)	15 (5.7)
Back pain	121 (6.4)	15 (5.7)
Infection	115 (6.1)	3 (1.1)
Pain in extremity	98 (5.2)	16 (6.1)

Comment: There were no clinically significant differences identified between the DRSP group and the E_2 group for adverse events occurring in more than 5% of subjects. There are fewer "upper respiratory infections" and more "infections" in DRSP group, which may reflect chance differences in coding.

Hematology

There were no clinically significant hematology findings in women exposed to DRSP, compared with women exposed to estradiol or placebo. The applicant presented the hematology data as transitions from baseline. Lymphocyte transitions from normal to low occurred more frequently in the women exposed to DRSP than in women exposed to E_2 or placebo, but the studies detected no clinical effects of these transitions.

Potassium

FDA concerns about potential risk of hyperkalemia prompted the applicant to look for hyperkalemia in several ways. First the overall database was evaluated for women who had postbaseline potassium values >5.5 mEq/L. Next, the mean deviation from baseline was evaluated. Finally, the adverse events database was evaluated for cardiac events that might indicate hyperkalemia.

The potassium database included 1369 women who received DRSP, and 358 women who received E_2 or placebo. To be included the women had to have a postbaseline serum potassium. Women from the European Phase 2 and Phase 3 studies were excluded because the European potassium data was found to be unreliable during the Yasmin review. Table 27 does not show more hyperkalemia in the DRSP group compared to the E_2 or placebo groups.

Table 27. Postbaseline Hyperkalemia in DRSP-treated Women and Controls

Treatment Group	N	K+ ≥ 5.5 mEq/L
DRSP	1369	20 (1.5%)
E_2 or placebo	358	8 (2.2%)

Only one woman had a serum potassium > 6.0 mEq/ L (6.1 mEq/L), and this potassium normalized without symptoms or treatment, despite continued therapy with DRSP.

The applicant evaluated a subset consisting of women on NSAIDs or ACE inhibitors because NSAIDs or ACE inhibitor use is a risk factor for hyperkalemia. Again, there was no more hyperkalemia in the DRSP group compared to the E_2 or placebo groups (see Table 28).

Table 28. Postbaseline Hyperkalemia in the Women Using NSAIDs or ACE Inhibitors

Treatment Group	N	K ≥ 5.5 mEq/L
DRSP	605	8 (1%)
E_2 or placebo	186	4 (2%)

Comment: Looked at as the number of women with hyperkalemia, there was no indication the DRSP treated women were at greater risk for having hyperkalemia than the control group.

However, there are problems with the potassium data. Most of the studies were not designed to detect potassium abnormalities. For example, it is likely that the first few days of drug exposure would be the most likely time to detect potassium abnormalities, before compensatory mechanisms have responded. However, most studies checked potassium at routine visits that were remote from the first dose of drug. For example, in the endometrial protection trial reviewed above, potassium was checked only after cycles 7 and 13. Furthermore, most of the data comes from healthy postmenopausal women, and therefore may not apply to a sicker population.

Another problem with the data is the method of analysis of slightly hemolyzed specimens and specimens with potassium values between 6 and 7.3 mEq/L may have biased the results against detecting hyperkalemia. Study reports describe the protocol for detecting hyperkalemia as follows: " The presence of hemolysis was determined visually...Slightly hemolyzed specimens were analyzed, and the results were reviewed by the technologist. Changes of greater than approximately 20% from the previous results were indicative of hemolysis interference. If no previous result was available, rejection due to hemolysis was at the discretion of the reviewing technologist. Severely hemolyzed specimens were not analyzed. In addition, potassium values between 6.0 and 7.3 mEq/L were suspicious for extended cellular contact, except when these values correlated with previous results. Microscopic demonstration of>10 red blood cells per high-power field was indicative of prolonged cellular contact. In this case, the values for potassium, LDG, glucose and phosphorous were rejected."

Of interest, 9% of the control safety database and 28% of the DRSP database does not have potassium data, suggesting that the DRSP data may have been preferentially discarded. However, the Yasmin reviewer requested information about rejected samples for the endometrial protection study reviewed in section 6 above. For this study, [redacted], rejected 4.4% of samples from women exposed to E_2, and 5.1% of samples from women exposed to DRSP. The proportion of DRSP samples rejected showed no relationship to the dose of DRSP.

Four small studies looked at potassium in women at risk for hyperkalemia, and in all four studies serum potassium levels were evaluated often and early during therapy. Table 29 shows the mean change from baseline for three of these studies. In these three studies, five of six groups of women with risk factors for hyperkalemia had an average change from baseline that was positive, consistent with a small antimineralocorticoid effect. However the change was neither clinically nor statistically significant. The fourth study, which was submitted late in the review cycle, showed serious hyperkalemia related to DRSP exposure, and is reviewed in detail in the appendix.

To explore the potential effect of trial exclusions on the incidence of hyperkalemia, I asked the applicant to supply the number of women excluded from the endometrial hyperplasia, renal impairment, liver impairment, ACE inhibitor, and indomethacin trials because of baseline abnormalities in potassium, liver function, or renal function. Of 1825 women screened for these five trials, 55 were excluded based on abnormal baseline labs (7 for hyperkalemia, 47 for abnormal liver function, and 1 for abnormal renal function). Therefore, almost 3% of trial volunteers were excluded on the basis of abnormal baseline lab values.

Comment: Excluding women with risk factors for hyperkalemia decreased the ability of these trials to measure hyperkalemia risk in the general population. Since it is not the standard of care to screen women for liver, kidney, and electrolyte abnormalities before starting E/P for menopause symptoms, women in the general population with these problems receive E/P. The 47 women excluded with abnormal liver function tests are especially worrisome, since only 10 women with abnormal liver function tests were exposed to Angeliq, and one of these ten had severe hyperkalemia.

Table 29. Mean Change from Baseline of Potassium in Three Potassium Safety Studies

Report Number/Protocol Number	Group	Rx	Change from Baseline (mEq/L) Maximum Mean + SD	Change from Baseline (mEq/L) Average Mean + SD
B990/98106		3 mg DRSP + 1 mg E_2	0.64 ± 0.38	0.28 ± 0.28
(ACE inhibitor)		Placebo	0.40 ± 0.32	0.07 ± 0.29
B682/303063	No impairment	3 mg DRSP	0.42 ± 0.21	0.03 ± 0.12
(Renal impairment)	Mild impairment		0.41 ± 0.21	0.02 ± 0.26
	Moderate impairment		0.37 ± 0.21	-0.06 ± 0.36
A00824/304181 (Indomethacin)		3 mg DRSP + 1 mg E_2	0.80 ± 0.31	0.14 ± 0.17

Hyperkalemia is important because it is a surrogate for adverse cardiovascular events. Therefore, the database was evaluated for adverse cardiovascular events chosen by the applicant in consultation with two cardiologists. The cardiovascular events included arrhythmia, bradycardia, tachycardia, dizziness, palpitations and syncope. For this analysis the applicant looked at the entire DRSP database, including the Yasmin studies, as well as the safety database for Angeliq. Table 30 shows results for both databases. The results for the Angeliq database alone were similar. The analysis did not detect a trend toward increasing cardiovascular events in the DRSP-exposed subjects.

Table 30. Number of Subjects with Selected Cardiovascular Events by Treatment Group

Treatment	N	Arrhythmia n (%)	Bradycardia n (%)	Dizziness n (%)	Palpitation n (%)	Syncope n (%)	Tachycardia n (%)
Placebo	142	0	0	1 (0.7)	1 (0.7)	0	0
E_2 1 or 2 mg	263	0	0	7 (2.7)	3 (1.1)	1 (0.4)	0
DRSP (All Doses)	5204	7 (0.1)	1 (0.0)	162 (3.1)	29 (0.6)	10 (0.2)	23 (0.4)
DRSP (0.5 mg)	238	0	0	4 (1.7)	2 (0.8)	1 (0.4)	1 (0.4)
DRSP (1 mg)	386	2 (0.5)	0	15 (3.9)	1 (0.3)	0	3 (0.8)
DRSP (2 mg)	690	3 (0.4)	1 (0.1)	15 (2.2)	9 (1.3)	3 (0.4)	3 (0.4)
DRSP (2.5 mg)	6	0	0	0	0	0	0
DRSP (3 mg)	3749	2 (0.1)	0	121 (3.2)	14 (0.4)	6 (0.2)	15 (0.4)
DRSP (4 mg)	75	0	0	2 (2.7)	3 (4.0)	0	0
DRSP (6 mg)	78	0	0	4 (5.1)	0	0	1 (1.3)
DRSP (10 mg)	56	0	0	2 (3.6)	0	0	0
DRSP (25 mg)	6	0	0	0	0	0	0
DRSP (50 mg)	6	0	0	0	0	0	0
DRSP (100 mg)	6	0	0	0	0	0	0

Sodium

Because of the antimineralocorticoid properties of DRSP, the data were explored for low sodium. Eighteen women (1%) receiving DRSP went from normal sodium at baseline to low sodium at any other time. DRSP dose did not affect the incidence of low sodium. None of the women receiving estradiol group went from normal baseline to low sodium. Hyponatremia was not detected as an adverse event.

Glucose

The applicant presented glucose data as percent of subjects with transition from baseline. There was a slight increase in the percent of women who went from normal at baseline to high for any measurement, among the women treated with DRSP (4.8%), compared to women treated with estradiol only (3.8%). When looked at by dose of DRSP, there was a dose-ranging effect (3.2% for women exposed to 0.5 mg of DRSP, increasing with each dose to 5.7% for women exposed to 3 mg of DRSP). This is consistent with the known effects of progestins on glucose tolerance.

In a small Phase II trial[19] comparing EE + DRSP (3 mg) to an oral contraceptive containing EE + levonorgestrel, fasting plasma glucose was unchanged from baseline but oral glucose tolerance decreased slightly for both preparations (a 10% increase in the $AUC_{0\text{-}3hr}$ for glucose at 6 months, compared to baseline). Again, this is consistent with the known effects of progestins on glucose tolerance.

[19] Study Report No. 9970

Lipids

The applicant presented the lipid data in three groups by duration of therapy. All groups showed the same trends. Table 31 shows the mean changes from baseline between three and twelve months of therapy (N=877).

Table 31. Mean Change from Baseline of Lipids between Three and Twelve Months

Parameter	All DRSP	0.5 mg DRSP + 1 mg E_2	1 mg DRSP + 1 mg E_2	2 mg DRSP + 1 mg E_2	3 mg DRSP + 1 mg E_2	E_2 1 mg
Total cholesterol (mg/dl)	-9.0	-5.4	-8.1	-11.6	-11.0	-1.4
HDL (mg/dl)	0.3	1.8	1.0	-0.2	-1.5	4.0
LDL (mg/dl)	-9.8	-7.4	-10.1	-11.1	-10.5	-8.2
HDL/LDL	0.0	0.1	0.1	0.1	0.0	0.1
Triglycerides (mg/dl)	4.0	1.4	7.1	0.3	7.2	15.4

Comment: The lipid changes from baseline were small. The changes in cholesterol were favorable, while the changes in triglycerides were unfavorable. The clinical significance of these small changes is unknown.

Liver Function Tests

There was no clinical signal detected in the data on liver function tests. Six (2.3%) of women in the E_2 group, and 5 (0.3%) of women in the DRSP groups, had abnormal liver function test listed as an adverse event. However, there were no hospitalizations for liver function abnormalities.

Vital Signs

There were no clinically significant changes in blood pressure from baseline, as shown in Table 32.

Table 32. Mean Changes from Baseline in Blood Pressure Based on Last Value Carried Forward

	Total	0.5 mg DRSP + 1 mg E_2	1 mg DRSP + 1 mg E_2	2 mg DRSP + 1 mg E_2	3 mg DRSP + 1 mg E_2	1 mg E_2
Systolic:						
N	1745	225	343	584	593	225
Mean (SD) in mm Hg	-0.6 (13.73)	-1.7 (12.78)	0.7 (14.00)	-0.1 (14.09)	-1.5 (13.50)	0.2 (13.84)
Diastolic:						
N	1745	225	343	584	593	225
Mean (SD) in mm Hg	-1.2 (9.03)	-1.7 (8.57)	-0.5 (8.97)	-1.4 (9.71)	-1.3 (8.52)	-0.5 (8.14)

Weight

There were no clinically significant changes in weight from baseline, as shown in Table 33.

Table 33. Changes from Baseline in Weight, on the Last Value Carried Forward

	Total	E_2 1 mg + DRSP .5 mg	E_2 1 mg + DRSP 1 mg	E_2 1 mg + DRSP 2 mg	E_2 1 mg + DRSP 3 mg	E_2 1 mg
N	1743	225	343	583	592	225
Mean kg	-0.4	-0.3	-0.2	-0.5	-0.4	0.5
Min kg	-19	-15	-15	-19	-16	-14
Max kg	23	10	23	16	15	25

7.5 Postmarketing Surveillance

Postmarketing reports for Yasmin, the oral contraceptive containing DRSP, have raised concern that DRSP may be a thrombogenic progestin. By April 8, 2002, Berlex had received three reports of death in Yasmin users, all from Europe and all following pulmonary emboli. The women's ages were 17, 37, and 40 years old, exposures to Yasmin were 6 months, 2 1/2 months, and 2 months, respectively. Table 34 shows postmarketing reports for one year.

Table 34. Serious Thromboembolic Events reported to Berlex from Nov 2000 to 6 Dec 2001

Event	Total Cases	US Cases	Non-US Cases
DVT or PE	39	3	34
Cerebral sinus thrombosis	2	0	2
Myocardial Infarct with possible PE	1	0	1
Cerebrovascular accident	6	2	4

The FDA's Office of Drug Safety (ODS) was asked to compare thrombotic events with Yasmin to thrombotic events with Cyclessa, a new pill approved in December 2000, and Triphasil, an old pill. Although there were no thrombotic events reported to AERS in 2001 for Cyclessa, according the annual report for Cyclessa, only [redacted] packs of Cyclessa were distributed in 2001, compared to [redacted] for Yasmin between November 2000 and October 31, 2001. The FDA Office of Drug Safety conclusions were:

- Postmarketing data cannot be used to calculate reliable incidence data, because the extent of underreporting and extent of exposure are unknown.
- Nonetheless, ODS attempted to calculate incidence and derived a domestic thromboembolic reporting rate of 0.2 per 100,000 users for Yasmin and 0.05 per 100,000 users for Triphasil.
- However, because of many factors that influence reporting, including enhanced reporting of newly marketed products, ODS cannot conclude that Yasmin carrier a higher risk of thromboembolic adverse events.

Overall, the domestic reporting rate for thrombotic complications was about four times higher for Yasmin compared with Triphasil, but as the ODS pointed out, the source of distribution data was different, and reporting frequency is usually less for an older product like Triphasil.

European concerns are mounting about the thrombotic risks of Yasmin. The proportion of thrombotic events per pill pack distributed has been higher in Europe than the U.S. The reasons for this are unclear. The applicant speculates that interest in thrombotic events in oral contraceptive users is high in Europe because in September 2001, the Committee for Proprietary Medicinal Products released a statement on the increased incidence of thrombotic events with third generation oral contraceptives (OCs). In addition, the British Medical Journal published a news article in April 2002 stating that the Dutch College of General Practitioners was advising its members not to prescribe Yasmin until studies show its safety. A 17-year-old Dutch woman was among the three women who have died of thrombotic events since Yasmin was approved.

In 2001, The European Active Study Surveillance group launched a large prospective cohort study, whose purpose is to evaluate the risk serious adverse events, particularly thrombotic events, in women using Yasmin compared with women using all other OCs. Investigators expect to enroll 30,000 women by 2003, and end the study in 2006. An Advisory Committee will evaluate interim results every six months. Although Schering, the parent company of the applicant, is funding the study, the study protocol describes Schering's grant as unconditional,

and the study is described as scientifically independent. The first interim report, which covered the period from study start to the end of August 2001, described baseline characteristics of the first 6061 enrollees. Two potentially confounding differences were seen in Yasmin users - a higher BMI in "starters" and "switchers", and more treated hypertension among the "switchers". These findings are not surprising, as marketing efforts by the company have focused on possible weight and blood pressure benefits.[20,21] The interim study reports are published online in *Life and Medical Sciences Online* (LAMSO).

Other postmarketing safety efforts include an Active Surveillance Program in the US as part of a Phase 4 commitment for Yasmin. However, the purpose of the Active Surveillance Program is to evaluate the risks of hyperkalemia. When the program started, thrombotic risks were not an issue.

Comment: Thrombotic issues surfaced postmarketing, and suffer from the usual flaws of data arising from spontaneous reports. There were no unusual thrombotic signals in the clinical trial data for Angeliq or Yasmin.

7.6 Safety Update

The applicant's first safety update added a case of serious hyperkalemia to the data; otherwise, the update raised no new safety issues. The single case of hyperkalemia occurred in a small PK study of women with impaired liver function. However, this case occurred in one of the few studies specifically designed to look for hyperkalemia in women who are not in good health, and is therefore noteworthy. Because of its importance, the case of hyperkalemia is reviewed in detail in the Appendix below. The reporting interval for the first safety update was June 1, 2001 to March 15, 2002. Five clinical studies were ongoing or completed in the reporting interval.

The applicant's second safety update added a myocardial infarction to the data. The myocardial infarction occurred in a 58 year old woman taking DRSP 3 mg plus E_2 1 mg for less than two months. The applicant is pursuing further information on this event. The reporting interval for the second safety update was March 16, 2002 through July 31, 2002. Four clinical studies were ongoing and one clinical study was completed in the reporting interval. At the time of the second safety update, marketing applications for Angeliq were pending in the U.S., Holland, and Australia.

[20] www.yasmin.com. (April 2002) The international site features an animated weight scale, BMI counter, and multiple questions related to weight, all in English. (sponsored by Schering). The US site contains a slide show for health professionals emphasizing the drospirenone-spironolactone connection, and also directs users to the international site for more information.

[21] August 2001 supplement to Contemporary OB/GYN, supported by Berlex Laboratories

7.7 Drug Withdrawal, Abuse and Overdose Experience

There is no potential for abuse or dependence. Overdose of products containing estrogen and progestin may cause nausea, vomiting and vaginal bleeding. Since DRSP has antimineralocorticoid effects, serum electrolytes should be monitored in the event of overdose.

7.8 Adequacy of Safety Testing

The extent of exposure, described in section 7.3 above, meets general ICH guidelines.[22] However, the safety expectations must be high for Angeliq, because the expected benefit of one more product that provides symptomatic relief for a normal stage of life is small.

8. Dosing, Regimen, and Administration Issues

The applicant did not show an advantage of the higher dose over the lower dose [redacted]

9. Use in Special Populations

9.1 Evaluation of Applicant's Analyses of Effects of Gender, Age, or Ethnicity

The applicant did not evaluate gender effects, which is acceptable because Angeliq is only indicated for women.

The applicant did not evaluate race effects, and most subjects were Caucasian (92% in the endometrial protection trial and 94% in the safety database).

9.2 Evaluation of Pediatric Program

The applicant did not perform any pediatric studies and requests a waiver from the requirement for pediatric studies, citing a FDA draft guidance entitled "Recommendations for Complying with the Pediatric Rule", which categorizes symptoms of menopause as a disease-specific waiver.

Comment: Granting the waiver is recommended.

9.3 Comments on Data Available in Other Populations

A lactation study concluded that the daily dose of DRSP received by a baby through breast milk was 1/1000 of the daily dose ingested by the lactating women. This estimate was based on the average concentration of DRSP in breast milk over 24 hours, and on the assumption that a baby

[22] ICH-E1A "The extent of population exposure to assess clinical safety: for drugs intended for long-term treatment of non-life-threatening conditions" http://www.fda.gov/cder/guidance/iche1a.pdf

drinks about 800 ml of breast milk daily. The study evaluated serum and breast milk concentrations of DRSP at multiple time points after administration of a single tablet of 30 ug ethinyl estradiol and 3 mg DRSP.

Comment: Angeliq is not intended for use during lactation.

10. Conclusions and Recommendations, and Labeling

10.1. Conclusions about Efficacy and Safety

Efficacy

Based on bioequivalence of the E_2 in Angeliq to the E_2 in Estrace, Angeliq is effective for the indications filed. Based on data from the endometrial protection trial, DRSP in dosing ranging from 1 mg to 3 mg protects the endometrium from E_2-induced hyperplasia. However, the endometrial protection trial was flawed. There were troublesome quality issues in the pathology readings. One pathologist appeared to have undue influence in cases of disagreement among pathologists. The same pathologist had wide discrepancies in his own readings of the biopsy slides.

, the applicant did not show any advantage of the 3 mg dose over the 1 mg dosage. In a *post hoc* analysis of one trial, the applicant noted a decrease in blood pressure in women who were mildly hypertensive and were taking the 3 mg dose; however, this "data-mining" needs confirmation in controlled clinical trials. Since electrolyte risks are likely to be greater with the higher dose, and since there is no proven advantage of the 3 mg dose for the studied indications,

Safety

Postmarketing case reports for Yasmin, the oral contraceptive containing DRSP, have raised the possibility that DRSP may be a thrombogenic progestin. Case reporting may be enhanced because there is indeed a thrombotic problem, or because of many other reasons, such as enhanced reporting for a new product, recent concerns about certain progestins, and a recent statements from Europe's Committee for Proprietary Medicinal Products. In addition, Yasmin may be preferentially prescribed to women who are heavier or who have high blood pressure, both risk factors for thrombotic events (see Section 0)

European prescribers appear to be favoring Yasmin for heavier women and women with hypertension. Promotion may be contributing to Yasmin being favored for higher risk women. Promotion directed to physicians has emphasized Yasmin's similarity to spironolactone, a drug that reduces mortality in certain patients with severe heart failure. Promotion directed to patients has stressed salutary effects on weight, effects not shown to the satisfaction of the FDA's Yasmin reviewers. There is no reason to think promotion for Angeliq would be less aggressive.

The clinical trials for Angeliq did not show a greater thrombotic risk than we have seen for other E/P products for menopause. Nonetheless, the ability of a clinical trial to detect an uncommon event is limited. Therefore the question of whether DRSP is a thrombogenic progestin may need to be answered by epidemiologic studies. An ongoing European study described in Section 0 hopes to address this issue.

The risk of hyperkalemia in generally healthy and carefully screened women appears to be small. However, in four small studies that exposed women with other risk factors for hyperkalemia to DRSP 3 mg, one instance of hyperkalemia needing treatment was detected out of 65 at-risk women. The risk factors in these four studies included indomethacin use, ACE inhibitor use, moderate liver impairment, and mild or moderate renal impairment. The single instance of significant hyperkalemia occurred in a woman with moderate liver impairment, and was related to DRSP exposure. A second woman in the indomethacin study was removed from the study on day 1, after a drop in creatinine clearance following exposure to indomethacin, and before any exposure to DRSP. What might have happened had she not been in a clinical trial and getting daily labs will never be known.

It is of course reasonable to expect the 1 mg dose of DRSP would be less likely to cause electrolyte abnormalities than the 3 mg dose. One could also argue that liver impairment is a contraindication for Angeliq, and therefore women with liver impairment will not take Angeliq. However, prescription errors do occur. Any risk must be measured against expected public health benefit of yet another product to treat normal symptoms of menopause.

In contrast to Angeliq, none of the E/P products marketed for menopause symptoms have any known or suspected risk of electrolyte abnormalities. At this time, the applicant has shown no advantage for Angeliq over marketed products.

10.2 Recommendations on Approvability

Angeliq is not approvable because of unresolved safety questions related to thrombotic events in Yasmin users, and the possibility of hyperkalemia in high-risk women. In addition, the formulation of Angeliq containing DRSP is not approvable, because DRSP is times more than needed for endometrial protection.

To achieve approval, we should have convincing data about the safety of Yasmin with respect to thrombosis. Epidemiologic results, such as the final study report on the European Active Surveillance Study on Oral Contraceptive Prescribing Practice, Benefits and Safety (EURAS), may be enough to show that DRSP has no greater thrombotic risk than other progestins. The applicant may propose other ways to show thrombotic safety.

In addition, because the risk of hyperkalemia is not shared with other E/P regimens, the applicant should perform a clinical trial showing an important benefit compared to other E/P products that treat menopause symptoms. The ongoing hypertension trial may satisfy this requirement.

The safety bar must be high for a product that treats symptoms of a normal stage of life. We should not approve Angeliq until we believe it is as safe as other E/P products or it has an advantage that justifies added risk.

Appendix

1. Review of Study Report A00824, Protocol 304181, Potassium PK in Women taking Indomethacin

This study was chosen for detailed review because it is a response to a FDA request for further potassium safety data in women who have risk factors for hyperkalemia. In this case the risk factor was indomethacin therapy. The data for this study were not available for the Yasmin NDA.

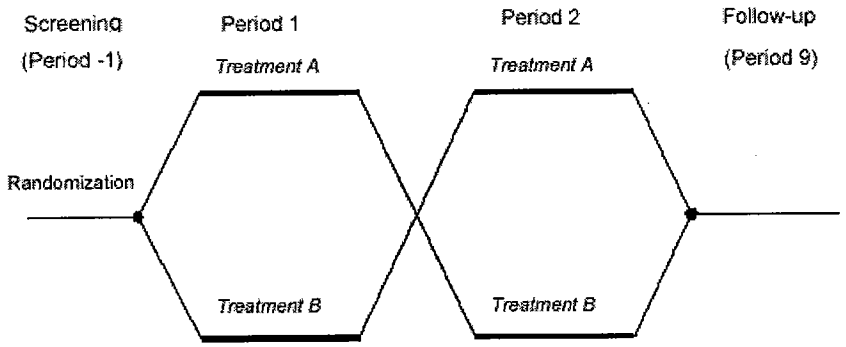
Title: Open-label, randomized, crossover study to evaluate the potential of E_2 1 mg plus DRSP 3 mg to cause hyperkalemia after repeated oral administration for 17 days when coadministered with indomethacin 150 mg.

Objectives: The primary objective was to assess the risk of hyperkalemia when E_2/DRSP was given with indomethacin. The secondary objective was to evaluate the effect of E_2 1 mg plus DRSP 3 mg on calcium excretion.

Background: Hyperkalemia is a recognized risk of indomethacin therapy, and a potential risk of E_2/DRSP therapy. This study explores the possibility of increased risk of hyperkalemia when the two drugs are used together.

Design: The study was an open-label, randomized, crossover study with two periods, two treatments and two sequences. Treatment A consisted of indomethacin 50 mg capsule taken three times daily for five days. Treatment B consisted of a daily tablet containing E_2 1 mg plus DRSP 3 mg, taken for 17 days, plus a 50 mg indomethacin capsule, taken three times daily on days 13-17. There was a minimum 8-day washout when Treatment B followed Treatment A and a minimum 14-day washout when Treatment A followed Treatment B.

Overview:



Treatment A: 1 capsule containing 50 mg indomethacin, 3 times daily oral administration on Treatment Days 1 – 5.[1]
Total treatment phase length (including other measures): 8 days

Treatment B: 1 tablet SH T 641 DA containing 1 mg E2 and 3 mg DRSP, daily oral administration (Days 1 – 17); and
1 capsule containing 50 mg indomethacin, 3 times daily oral administration on Treatment Days 13 - 17 [1]
Total treatment phase length (including other measures): 19 days

Serial potassium levels were drawn on Days 1 and 5 during Treatment A, and Days 13 and 17 of treatment B. Women also had standard meals at the study site on the days when they had potassium measured. Urine was collected for 24 hours for calcium analysis at baseline and on day 12 of DRSP/ E_2 administration. Potassium was also measured daily for days 1 to 5 of each treatment, on day 12 of E_2/DRSP treatment, and 48 hours after indomethacin treatment. Women who had potassium levels > 5.5 mmol/l were removed from the study unless the high potassium was the result of technical problems. Adverse events were elicited by open questioning.

There was a minimum 8-day washout for the AB sequence, and a minimum 14-day washout for the BA sequence. The study took place at a single study site in Germany. The protocol-defined endpoints were the AUC_{24} of plasma potassium and the Cmax of plasma potassium on day 5 of Treatment A and day 17 of Treatment B.

Comments: Although removing women from the study if their potassium levels exceeded 5.5 mmol/l was a safety precaution, it might also have removed women who were at risk for the antimineralocorticoid effects of DRSP. However, only one woman had a potassium level exceeding 5.5 mmol/l. Her sample was clearly hemolyzed and she continued in the study.

Controlling dietary intake made it less likely that a hyperkalemia event would be detected, and make the study less applicable to a real-life situation.

Population: Thirty-three, healthy postmenopausal women were randomly assigned to one of the two treatment sequences.

Inclusion/Exclusion Criteria:

Inclusion Criteria

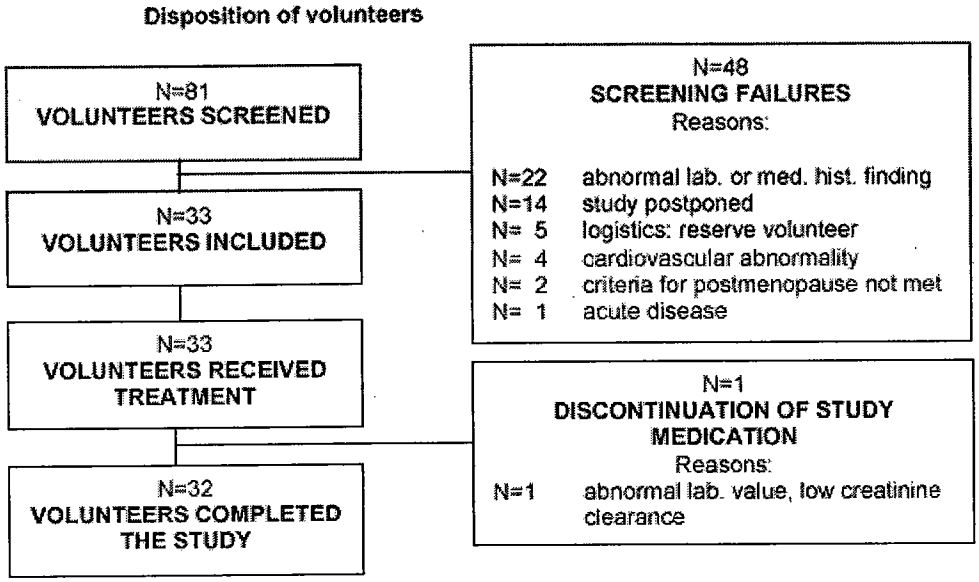
- Postmenopausal women between 45-75 years old
- 20 kg/m2 $\leq$ BMI < 30 Kg/m2
- Good health

Exclusion Criteria

- Significant disease, regular intake of medication
- Cancer
- Thromboembolic diseases
- Migraine
- Allergy to treatment
- History of recurrent GI lesion
- Use of drugs known to inhibit or induce metabolic enzymes
- Smoking
- Special diets
- Normal laboratory findings and physical exam findings.

Comment: These criteria selected only healthy postmenopausal women with normal labs and physical findings.

Results:



One volunteer had a low creatinine clearance in period 1 on Day 1 (44ml/min), and was therefore withdrawn from the study. She received only five doses of indomethacin, and did not develop hyperkalemia on Day 1. She did not have potassium measured beyond Day 1. There were 12 minor protocol violations and no major protocol violations.

Comments: Although removing the woman who developed decreased creatinine clearance abnormalities from the study was wise for safety reasons, it may have also prevented the detection of hyperkalemia. Renal damage is one reason for hyperkalemia during indomethacin use. This close follow-up and rapid discontinuation of a drug would not likely occur in clinical practice.

Of 81 women who were screened, 48 were not eligible, including 22 who had abnormal labs or history at baseline. Such careful screening is not the standard of care outside of clinical trials and affects the applicability of the study to the usual woman seeking care for menopausal symptoms.

Demographics

The mean age was 60 years old, mean weight was 68.4 kg and the mean BMI was 25.1 kg/m2.

Per-protocol endpoints

The study showed bioequivalence, as defined by the protocol, for AUC_{24} and Cmax of plasma potassium on day 5 of Treatment A and on Day 17 of Treatment B by showing the 90% confidence interval was well within the predetermined equivalence margin of 80-125%.

In addition mean urinary excretion of calcium in 24 hours was lower after a 12-day treatment with E_2/DRSP (5.9 mmol/d) than before treatment (4.7 mmol/d), and was within the normal range in both groups.

Comment: The decrease in 24-hour excretion of calcium in women treated with E_2/DRSP is not surprising because estrogen has a calcium-sparing effect.

Other Potassium Analyses

More women had high (N=27) than low (N=10) potassium levels. More women had high potassium levels while taking indomethacin plus EE/DRSP (N = 27) than while taking indomethacin alone (N=15). Only one woman had serum potassium greater than 5.5 mEq/L (5.82 mEq/L) but her sample was clearly hemolyzed.

The point estimates for Cmax and AUC_{24} for women taking both drugs were the same or higher than the estimates for women taking indomethacin alone, as shown in Table 35. However, the difference was not statistically significant.

Table 35. Descriptive Statistics for Potassium, Cmax and AUC_{24}

Treatment	1st day Indomethacin	5th day Indomethacin
	Mean Cmax (mmol/l) ± SD	Mean Cmax (mmol/l) ± SD
A - Indomethacin alone	4.31 ± 0.29	4.33 ± 0.25
B - Indomethacin and DRSP + E_2	4.43 ± 0.24	4.44 ± 0.33
	Mean AUC_{24} ± SD	Mean AUC_{24} + SD
A - Indomethacin alone	95.09 ± 3.80	96.07 ± 4.36
B - Indomethacin and DRSP + E_2	95.93 ± 3.57	96.07 + 5.03

The reviewer for Yasmin, Dr. Monroe, found small mean increases from baseline in serum potassium in studies he analyzed before Yasmin approval, and therefore I looked at mean changes from baseline in this study as well, using data from pages 119 and 120 of the Study Report. Table 36 shows mean changes from baseline for both treatments and for both treatment periods.[23]

[23] Derived from tables on page 119 and 120 of applicant's study report A0082

Table 36. Mean change of Potassium from Baseline by Treatment Group and Study Period

Treatment	Period 1 Mean change from baseline (mEq/L)	Period 2 Mean change from baseline (mEq/L)
Indomethacin	0.14	0.11
Indomethacin plus E_2/DRSP	0.0	0.10
E_2/DRSP	0.14	0.15

Comments: These numbers for mean change of potassium are positive or zero, consistent with a small increase in serum potassium with either treatment. However, since there was no placebo group, other explanations, such as diet effects, are possible as well.

I explored the data to see if there was any relationship of potassium levels to time in women exposed to DRSP. The following chart shows the mean potassium by day, with day 0 as the first day of DRSP ingestion.

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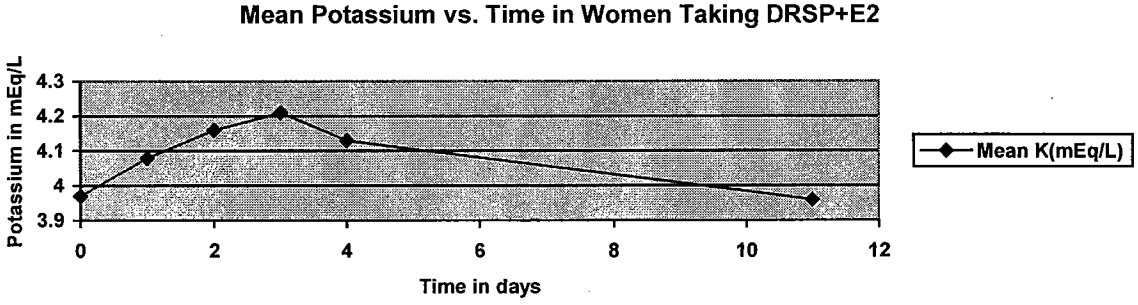

Comment: There was a slight rise in potassium, starting on day 1 and persisting through at least day 4. However, the standard deviations of the means overlap, and therefore nothing can be concluded definitively. Nonetheless, the same small increase starting about 24 hours after DRSP exposure was seen in the liver-impairment trial reviewed in the next section, which suggests that the effect of DRSP on serum potassium may take 24 hours or more to develop.

Cardiovascular events

ECGs

There was no evidence of a QT prolongation of 10 msec or greater or torsade de pointes, as shown in Table 37.

Table 37. QT-intervals, corrected by the Bazett Formula

Treatment sequence	Treatment	Mean (msec)	S.DR SP.	Min. (msec)	Median (msec)	Max. (msec)
N/A.	None (Screening)	420	15	393	416	451
BA	Indomethacin + E/P	423	13	404	421	445
BA	Indomethacin	423	17	399	418	454
AB	Indomethacin	427	14	410	428	447
AB	Indomethacin + E/P	422	16	405	420	463

Adverse Events

There were no deaths or serious adverse events.

76% of women had AEs during treatment with indomethacin alone and 81% of women had AEs during treatment with indomethacin plus DRSP+ E_2. Table 38 lists the most frequently occurring AEs.

Table 38. Most Frequent AEs by treatment

Reaction HARTS Code	Indomethacin	E_2/DRSP + Indomethacin
dizziness	19 (16.8%)	13 (11.5%)
headache	10 (8.8%)	8 (7.1%)
diarrhea	3 (2.7%)	4 (3.5%)
injection site inflammation	6 (5.3%)	1 (0.9%)
nausea	4 (3.5%)	2 (1.8%)
gastrointestinal disorder	1 (0.9%)	3 (2.7%)
breast pain	--	4 (3.5%)
hot flashes	--	3 (2.7%)

Reviewer Conclusions: The usual woman taking E/P and indomethacin does not benefit from comprehensive screening labs, diet control during therapy, and daily in-treatment labs with immediate discontinuation of therapy for renal deterioration. Therefore this study cannot be used to claim that concomitant use of Angeliq and indomethacin is safe in the "real world".
This small study did not detect an interaction between indomethacin and EE/DRSP causing hyperkalemia. The study also did not detect any clinically significant hyperkalemia in healthy postmenopausal women exposed to indomethacin alone or indomethacin plus E_2/DRSP. However, the likelihood of detecting hyperkalemia was low because of the small sample size (N=33) and the study procedures described above.

2. Review of Study Report No. A03161, Protocol 304666, DRSP and Potassium PK in Women with Liver Impairment

This study was chosen for detailed review because the study contributes important potassium safety data in women who have risk factors for hyperkalemia. In this case the risk factor was liver impairment. These data were not available for the Yasmin NDA.

Title: A study to evaluate the pharmacokinetics and safety of DRSP after single oral administration in female volunteers with moderately impaired or normal liver function

Objectives: The objectives were to study the pharmacokinetics and safety of DRSP in women with normal liver function or moderate liver impairment following a single tablet containing DRSP 3 mg and E_2 1 mg. The applicant changed the protocol at the FDA's request to collect more potassium safety data.

Design: The study was an open label, unblinded study, with two parallel arms. Group 1 contained ten women with normal liver function and Group 2 contained ten women with moderate liver impairment.

Overview: Table 39 shows the study assessments.

Table 39. Study Assessments

Assessment	Screening[a]	Pretreatment Day –2	Baseline [b]	Treatment Day [c]	24 h post	Follow-up/ Discharge [d]
Written informed consent obtained	x					
Gynecological examination	x					
Demographics and medical, surgical, gynecological, smoking, and medication histories	x					
Clinical variables for Child-Pugh classification (encephalopathy grade and ascites)	x					
Urine alcohol/drug screen	x		x			
Check in/exclusion criteria	x		x			
Urine pregnancy test	x		x			
Blood sample collection for analysis of DRSP				within 10 minutes prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 16 h postdose	x	at 34, 48, 72, 96, 120, 144, and 168 h postdose
Laboratory tests	x		x		x	x
Blood sample collection for analysis of serum potassium		x	x	within 10 minutes prior to dosing and at 2, 4, 6, 8, 12, and 16 h postdose		at 48, 72, 96, 120, 144, and 168 h postdose
Adverse events				x	x	x
Physical examination	x		x			x
Vital signs	x		x	x(2 h postdose)	x	x
12-lead ECG	x		x	x(2 h postdose)	x	x
Concomitant medication			x	x	x	x

Inclusion/Exclusion Criteria:

Inclusion

- Female between 18 to 75 years old
- Body weight greater than 100 lb. and within 30% of ideal body weight
- For fertile volunteers:
  Cycle 24 to 35 days
  Willingness to use nonhormonal methods of contraception or abstinence
  At least 6 months since childbirth, abortion, or lactation
  Negative pregnancy test at screening and at baseline
- For postmenopausal volunteers:

Volunteers must have undergone natural menopause at least 1 year before study participation, or have had a bilateral oophorectomy at least 3 months before study participation. Volunteers who have not had a bilateral oophorectomy and who have menstruated during the 12 to 24 month period before the study must have had a negative pregnancy test. Serum E_2 levels must be $\leq$20 pg/mL and serum follicle stimulating hormone (FSH) levels $\geq$40 mIU/mL within 3 weeks before drug administration. Volunteers must have been in good state of health except for moderate hepatic impairment and associated conditions in Group 2.

- A negative urine substance abuse and alcohol screen at screening and at the time of check-in at the facility
- Volunteers were assigned to Group 2 (moderate hepatic impairment) at screening if they scored between 7 and 9 according to the Child-Pugh classification.

Exclusion

- Preexisting or current disease (other than moderate hepatic impairment in Group 2) that could counteract the study objectives
- Thromboembolic diseases
- Severe metabolic disturbances (e.g. insulin dependent diabetes)
- Migraine accompanied by disturbances in sensory perception and/or locomotion
- Known allergic reactions to the study drugs
- Severe disease or any condition within 4 weeks prior to study drug administration that may have affected serum potassium such as dialysis, hematological disorders, or traumatic tissue damage
- Encephalopathy greater than grade 2
- Psychiatric diseases, personality disorders, or epilepsy
- Cerebrovascular ischemia
- Cardiovascular or renal disease
- Any malignancy including breast cancer
- Use of systemic or topical medications or substances that opposed the study objectives or might have influenced them (e.g., an investigational compound, or any other drug known to induce or inhibit liver enzymes within 8 weeks of study
- Use of sex hormone including contraceptives (oral, transdermal, transvaginal) within 6 weeks of study drug administration, or use of any long-acting injectable or implanted preparations within 6 months of study drug administration
- Donation of blood within 1 month of study drug administration
- Special diets (e.g., strict vegetarian or low calorie diet) or unbalanced eating habits
- Ingestion of food or beverages containing grapefruit within 2 days of study drug
- Exclusion periods from other studies, simultaneous participation in another clinical study, or participation in another clinical study within 1 month of study drug administration
- After resting for at least 10 minutes in the sitting position, systolic blood pressure < 100 or >160 mm Hg, diastolic blood pressure < 50 or >95 mm Hg, pulse rate <50 beats/min or >100 beats/min

- Clinically relevant ECG findings
- Clinically relevant findings (e.g., pronounced varicosities, thrombophlebitis, evidence of peripheral circulatory disturbances) or findings which were not related to hepatic impairment
- Clinically relevant findings during pelvic and breast examinations
- Cervical cytologic diagnosis of Papanicolaou smear > II
- Undiagnosed vaginal bleeding
- Human immune deficiency virus antibodies (anti-HIV-AB)
- Positive urine drug screening
- Clinical laboratory tests beyond the normal limits of the laboratory with the exception of minor deviations considered by the investigator to be clinically insignificant.

Demographics

The women were similar in baseline demographic characteristics, as shown in Table 40.

Table 40. Demographics and Baseline Characteristics

		Group 1 Normal Hepatic Function N = 10	**Group 2 Moderate Hepatic Impairment N = 10**
Age (years)	Mean ± S.D.	53 ± 13	55 ± 12
Height (cm)	Mean ± S.D.	161 ± 6	163 ± 8
Weight (kg)	Mean + S.D.	73 ± 13	72 ± 18
Ethnic group	Caucasian	1	4
	Black	3	3
	Hispanic	6	3
Current smoker	No	6	6
	Yes	4	4

Investigators screened 22 women and enrolled 20. All 20 completed the study. After hyperkalemia was detected in one woman, she was excluded from the applicant's "valid case" analysis.

There were six minor protocol deviations and one major deviation, according to the applicant. The major deviation was a woman who continued with her regular dose of K-Dur, a potassium supplement, during the study. This woman was removed from the applicant's analysis, on the basis of "excluded concomitant treatment."

Comment: The woman who developed serious hyperkalemia should not have been removed from the analysis. She entered the study with stable serum potassium concentrations and was told by study personnel to discontinue her potassium at baseline. If she had discontinued her regular intake of potassium, the study might have been biased. However, continuing on a stable dose should not have been a problem. Furthermore, the use of K-Dur was not an excluded concomitant treatment in the protocol, and should not have affected the primary endpoint of

DRSP kinetics. She was excluded from the analysis after she had hyperkalemia. The protocol did not specify any plan to exclude women with unusual intakes (high or low) of potassium.

Efficacy Results

The applicant did a "valid case" analysis, excluding the woman who developed hyperkalemia and was found to be taking her K-Dur. I performed an ITT analysis, adding back the woman who developed hyperkalemia, because the justification for removing her was inadequate. The results for the primary target variables were similar for both the "valid case" analysis and the ITT analysis.

The primary target variables for DRSP were AUC, Cmax, unbound AUC and unbound Cmax. In addition, the mean change in potassium and the mean change in potassium from baseline were evaluated.

DRSP Kinetics:

Table 41 compares the applicant's analysis for the primary target values with an ITT analysis.

Table 41. DRSP Kinetics by Group

	Applicant's valid case analysis		**ITT analysis**	
	Group 1	Group 2	Group 1	Group 2
Geometric Mean Cmax ng/mL	33	31	33	33
Geometric Mean $AUC_{(0\text{-tlast})}$ ng/mL	495	925	495	1035
Geometric Mean Cmax unbound ng/ML	1.1	1.2	1.1	1.3
Geometric Mean AUC $unbound_{(0\text{-tlast})}$ ng/mL	16	37	16	42

Comments: Cmax was no different between Group 1 and Group 2, using the applicant's analysis or the ITT analysis, suggesting no difference in absorption/distribution between groups. However, AUC was over twice as great in the liver-impaired group, suggesting slower metabolism/elimination in women with liver disease. The applicant's valid case analysis and the ITT analysis produced similar results.

Women with moderate liver impairment have greater total exposure to DRSP than women with normal liver function, when treated with a single dose of DRSP 3 mg and EE 1 mg.

Five women had detectable "DRSP" levels at baseline. All five, and only these five, were taking spironolactone during the study, and all five were in the liver-impaired group. This suggests that spironolactone may have cross-reacted with the DRSP assay. However, the mean baseline concentration of DRSP at baseline was low enough to have little impact on the PK results for DRSP.

Potassium Kinetics:

The summary statistics, mean and mean change from baseline for potassium, did not show a difference between the normal group and the liver-impaired group.

Table 42. Mean Potassium at Each Time Point by Group (ITT)

Time (hours)	Group 1 Mean Potassium (mEq/L)	Group 2 Mean Potassium (mEq/L)
-48	4.25	4.18
-24	4.15	4.06
0	4.27	4.36
2	4.26	4.25
4	4.21	4.1
6	4.06	3.96
8	4.1	4.11
12	4.03	4.23
16	4.15	4.06
24	4.54	4.42
48	4.37	4.55
72	4.53	4.37
96	4.42	4.26
120	4.47	4.46
144	4.4	4.55
168	4.42	4.53

A graphic display of the same data follows.

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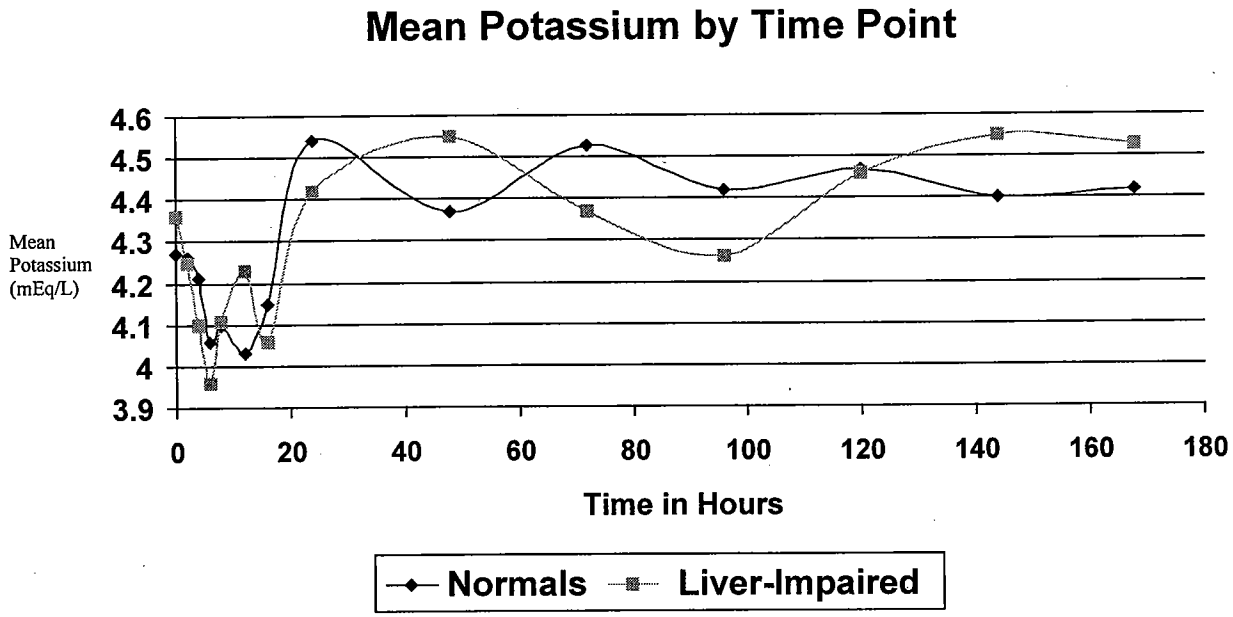

Both groups had a decrease in potassium from baseline in the first 24 hours, followed by an increase from baseline. There is no obvious difference between the groups. However, the number of subjects is small and the standard deviations of the means overlap.

Table 43 shows the mean change from baseline in serum potassium, by time point. Again, there is no obvious difference between the groups. There is no evidence from the means of a greater trend to hyperkalemia in the liver-impaired group.

Table 43. Mean Change from Baseline in Serum Potassium, by Time and Treatment Group

Time (hours)	Group 1 Mean Change from Baseline (mEq/L)	Group 2 Mean Change from Baseline (mEq/L)
0	0	0
2	-.01	-.11
4	-.06	-.26
6	-.21	-.40
8	-.17	-.25
12	-.24	-.13
16	-.12	-.30
24	.27	.08
48	.10	.19
72	.26	.01
96	.15	-.10
120	.20	.10
144	.13	.19
168	.15	.17

A graphic display of the same data follows.

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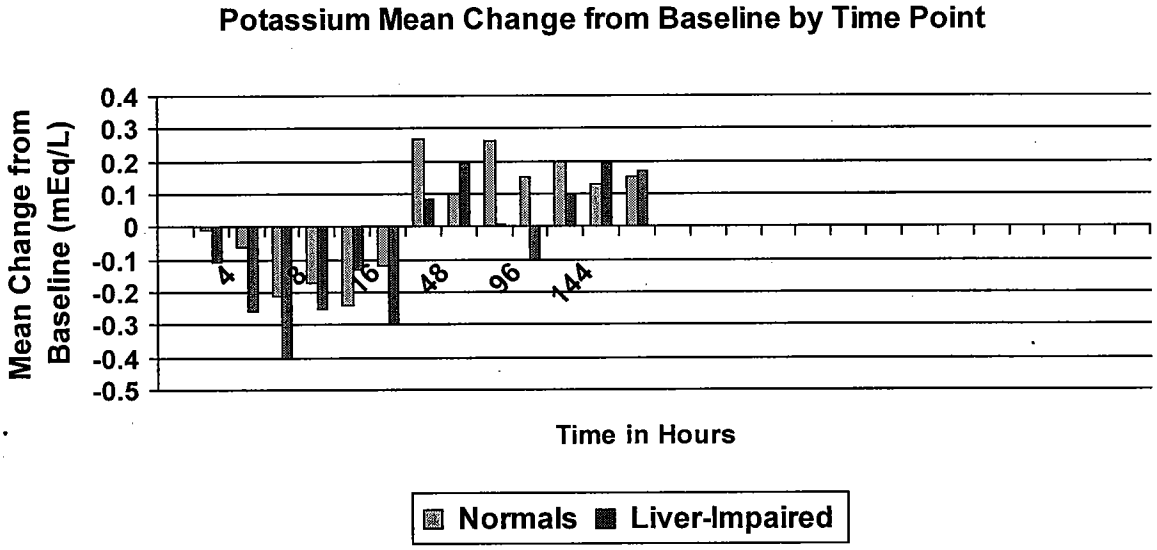


Safety Results

There were no deaths. The single serious adverse event was an episode of severe hyperkalemia, which occurred in a 46-year-old, African-American woman (subject 20203) with moderate liver impairment. She had type II diabetes and hypertension. Her baseline medications included furosemide 40 mg, spironolactone 100 mg, K-Dur 40 mEq, doxycycline for acne, and insulin. She had had an above-the-knee amputation in ———. Her creatinine clearance at baseline was 49 mL/min. Study personnel told her to continue all medication except her K-Dur, even though her baseline and screening potassium were normal. She was to continue her furosemide

and spironolactone. She inadvertently continued all her medications, including K-Dur. She developed hyperkalemia, which started at 72 hours and persisted for eight days, and was treated by stopping spironolactone and K-Dur, and administration of Kayexalate. There were no untoward clinical effects and her ECGs remained normal throughout.

Comments: This woman had at least three exclusion criteria, and therefore shows that treatment errors can occur, even in a clinical trial. Among her exclusion criteria were insulin dependent diabetes, evidence of renal compromise at baseline, and possible vascular disease as shown by the amputated extremity, although the case report form does not give a reason for the amputation.

Despite a pre-treatment workup that included three serum electrolyte measurements, liver function tests, creatinine clearance, an EKG, as well as an assessment of exclusion criteria, she received Angeliq. Since few women in actual practice have the benefit of such a workup before starting E/P, it is easy to imagine prescribing to an older woman with undetected medical problems.

Table 44 shows lab results for this subject.

Table 44. Lab Data from Subject who Developed Serious Hyperkalemia

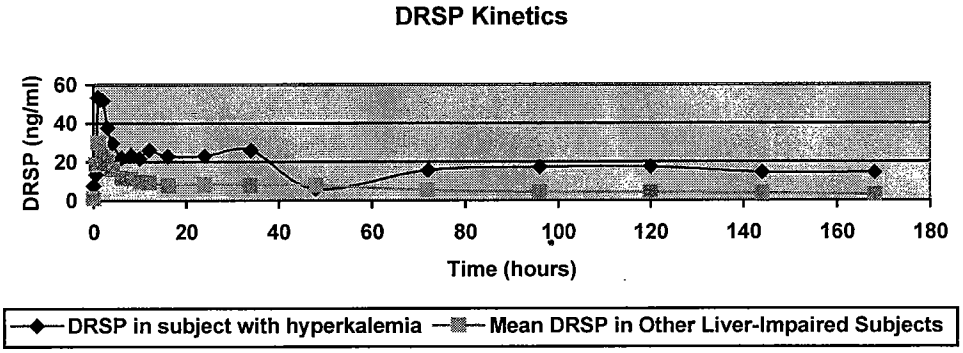
Time	Date	Time	K [a] (mEq/L)	Cr (mg/dL)	Na (mEq/L)	Glucose (mg/dl)
Screen		10:42	4.6	1.2	133	205
Day - 2		12:30	4.5	...	...	...
Day - 1		14:23	4.9	1.3	137	76
Predose		08:30	4.9	...	...	...
Received single dose of DRSP/E_2 on 17 May 2001 at 08:40 hours						
2 h post		10:40	5.3	...	...	...
4 h post		12:40	4.4	...	...	...
6 h post		14:40	4.7	...	...	...
8 h post		16:40	4.3	...	...	...
12 h post		20:40	4.8	...	...	...
16 h post		00:40	4.5	...	...	...
24 h post		08:40	5.3	1.3	134	152
48 h post		08:40	4.7	...	...	...
72 h post		08:40	5.9	...	...	...
96 h post		08:40	5.3	...	...	...
120 h post		08:40	6.5	...	...	...
Unscheduled		06:35	5.9	...	...	...
144 h post		08:40	6.1	...	...	...
Unscheduled		07:10	6.2	...	...	...
Unscheduled[b]		08:00	**6.7**	1.3	**131**	69
168 h post		08:40	6.3	1.6	133	117
Unscheduled		11:46	...	...	...	...
Unscheduled		20:45	5.7	...	...	...
Unscheduled		08:00	4.6	...	...	...
Unscheduled		08:30	4.7	1.7 [d]	136	97
Unscheduled		15:35	4.3	0.9	137	127

After this woman became hyperkalemic, she was excluded from the pharmacokinetic analyses because she had continued to take her K-Dur throughout the study.

However, a causal relationship between DRSP exposure is suggested by several findings. First, low sodium accompanied this woman's peak potassium, which is consistent with a DRSP effect (Table 44). Next, she had the highest overall exposure to DRSP (see bolded line, Table 45). And finally, with the exception of the 48-hour level, her DRSP levels remained above average throughout the period in which she experienced hyperkalemia, as illustrated in the chart below labeled "DRSP Kinetics".

Table 45. DRSP PK Parameters in Liver-Impaired Subjects

Subject Number	AUC(0-168h) (mEq*h/L)	Cmax (mEq/L)
10201	757	4.9
10202	783	5.2
10203	792	5.1
10204	687	4.4
10205	659	4.1
10206	623	4.4
20201	724	4.9
20202	699	5.6
20203	**937**	**6.5**
20204	741	5.2



Comment: Although spironolactone may have contributed to this woman's hyperkalemia, she was not the only woman taking spironolactone, nor was she taking the highest dose of spironolactone. There were five women on spironolactone, all in the liver-impaired group, taking doses ranging from 50-200 mg daily.

There were two other women who developed hyperkalemia during the study, one from each group (see Table 46). Both of these women had mild hyperkalemia at a single time point.

Table 46. Subjects with Mild Hyperkalemia

Subject	Group	Time Postdose	Potassium (mEq/L)	Comments
20102	Normal	120 h	5.5	No sequelae
20202	Liver impairment	48 h	5.6	No sequelae

There were no other significant adverse events.

Reviewer Conclusions:

DRSP exposure, measured by AUC, is higher in women with moderate liver impairment compared to women with normal liver function.

DRSP likely contributed to serious hyperkalemia in one woman. This woman from the liver-impaired group developed hyperkalemia following a single dose of DRSP 3 mg + E_2 1 mg. Her hyperkalemia did not cause death, but early detection, treatment, and exposure to only a single dose of DRSP may have played a role in the successful outcome. She had the greatest overall exposure to DRSP of all women in the study, as measured by AUC (0-168), supporting a cause-effect relationship between DRSP and hyperkalemia. In addition her sodium levels were lowest at the time her potassium was highest, consistent with an antimineralocorticoid effect. And finally, her case shows that drug errors can and do occur, even in a clinical trial setting, where subjects have the benefit of a methodical and stringent exclusion checklist.

3. Glossary

Acronym	Name
AE	adverse event
AERS	adverse event reporting system
ANDA	abbreviated new drug application
AUC	area under the curve
BMI	body mass index
Cmax	maximum concentration
DRSP	drospirenone
DVT	deep venous thrombosis
E_2	estradiol
EE	ethinyl estradiol
ECG	electrocardiogram
E/P	Estrogen plus progestin
EURAS	European Active Study Surveillance Group
FDA	Food and Drug Administration
IND	investigational new drug
IRB	institutional review board
ITT	intention to treat
LFTs	liver function tests
NDA	new drug application
NSAID	nonsteroidal anti-inflammatory drug
OCs	oral contraceptives
ODS	Office of Drug Safety
PK	pharmacokinetic
SAE	serious adverse event
SHBG	sex hormone binding globulin

4. List of Tables

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Leslie Ann Furlong
10/18/02 09:40:19 AM
MEDICAL OFFICER

Shelley Slaughter
10/18/02 03:40:52 PM
MEDICAL OFFICER
I concur that application should not be approved. See also Team Leader Review.

MEMORANDUM

TO: S. Slaughter MD, PhD
Medical Team Leader, DRUDP

FROM: S. Monroe MD
Acting Medical Team Leader, DRUDP

COPY: D. Shames MD
Director, DRUDP

L. Furlong MD
Medical Officer, DRUDP

DATE: 16 October 2002

SUBJECT: Serious Thrombotic and Thromboembolic Adverse Events in Yasmin Users

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The Division of Reproductive and Urologic Drug Products (DRUDP) and the Office of Drug Safety (ODS) are continuing to monitor closely postmarketing spontaneous adverse event reports for the occurrence of serious thromboembolic and thrombotic events in women who are using Yasmin. Yasmin is a combination oral contraceptive that contains 0.03 mg of ethinyl estradiol and 3 mg of drospirenone. It was approved for marketing in the U.S. in May 2001. Clinical trial data submitted by the Sponsor in support of NDA 21-098 for Yasmin did not suggest that there was an increased incidence of serious thromboembolic or thrombotic events in women using Yasmin for prevention of pregnancy. However, after the launch of Yasmin, it appeared that a greater number of postmarketing safety reports for serious thromboembolic and thrombotic adverse events were received by the FDA for Yasmin users than had been received for other combination oral contraceptives in a similar time frame after launch. In December 2001, the Office of Drug Safety (ODS) was asked to compare the incidence of these events in women using Yasmin to that in women using Triphasil (a second generation oral contraceptive containing levonorgestrel) or Cyclessa (a recently approved third generation oral contraceptive containing desogestrel).

The complete Consultation from ODS is included as an Attachment to this memorandum. Excerpts from the Executive Summary of the ODS Consultation are provided below. (I have added bolding to facilitate your review). It should be noted that the data for Yasmin included both cases entered into the AERS database and labeled foreign cases submitted by the Sponsor at the request of DRUDP that had not been entered in the AERS database. Data for Triphasil and Cyclessa included only those in the AERS database.

> "A search was conducted on February 19, 2002 using the Adverse Event Reporting System (AERS) for Triphasil and Cyclessa (including established names). AERS was searched using the MedDRA High Level Group Term "Embolism and Thrombosis." The search revealed 69 unduplicated cases of thromboembolic events reported with Triphasil and 8 unduplicated cases reported with Tri-Levlen (same product, different brand). No cases were identified for Cyclessa. When comparing the Berlex data to the AERS data, we noted that the Yasmin population was older and had more risk factors than the Triphasil/Tri-Levlen population. Sixty-five percent of the Yasmin cases involved patients with at least one documented risk factor. Only four domestic Yasmin cases were identified and these cases involved patients who were older than 35 years of age (49, 46, 44, and 38) and the oldest patient was also a nicotine user.
>
> ODS cannot use AERS data to calculate incidence rates because reporting of adverse events is a voluntary process, underreporting exists, and we only have access to projected drug usage (i.e., not

exact figures). Additionally, incidence rates cannot be compared to reporting rates. **Using Berlex's distribution data we calculated a domestic thromboembolic reporting rate of 0.2 per 100,000 users and an all-inclusive (domestic and foreign) reporting rate of 0.62 per 100,000 users. Using IMS and AERS data, the reporting rate for Triphasil/Tri-Levlen is 0.05 per 100,000 domestic users.** As noted, reporting rates of thromboembolic events in oral contraceptive users can be calculated using AERS spontaneous reporting data. **However, because of the multiple factors that influence reporting, comparisons of drug safety cannot be made from these data. Although the thromboembolic reporting rates for Yasmin are higher than those calculated for Triphasil, ODS cannot determine that, when compared to Triphasil, Yasmin carries a higher potential risk of developing thromboembolic adverse events."**

Because of continuing reports of serious thrombotic and thromboembolic adverse events and deaths in women using Yasmin, the ODS has been asked to review again the safety of Yasmin in comparison to other combination oral contraceptives. This review is presently ongoing. However, a summary of reported deaths in women using Yasmin and other contraceptives, based on an AERS DataMart search for "OUTCOME=DEATH" on October 16, 2002 conducted by Lesley Furlong MD, DRUDP, is presented in the table below. Most of the deaths are thromboembolic.

Pill Name	Total Adult Deaths (excludes fetal deaths from miscarriages, congenital anomalies, etc)	Approval Date	Deaths per Year [1]
Alesse	1	March 97	0.2
Mircette	1	April 98	0.3
Ortho Tri-Cyclen	9	July 92	0.9
Yasmin	6 [2]	May 00	3
Triphasil	22	Nov 84	1.2

1. "Deaths per Year", is calculated from the number in Column 2 divided by the number of years since approval.
2. One addition postmarketing death (not entered into the AERS Database) occurred prior to the U.S. approval of Yasmin.

Although these data have not been adjusted for patient exposure, patient risk factors, and potential differences in reporting rates, Alesse, Mircette and Ortho Tri-Cyclen are popular oral contraceptives in the U.S. Ortho Tri-Cyclen has the highest sales of any oral contraceptive in the U.S. Therefore, it seems unlikely that the apparently higher death rate associated with Yasmin use is related to greater patient exposure.

Attachment 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**OFFICE OF DRUG SAFETY POSTMARKETING SAFETY REVIEW**	
TO: Daniel Shames, M.D., Acting Director Division of Reproductive and Urologic Drug Products HFD-580	**FROM:** Denise Toyer, Pharm.D., Safety Evaluator, Division of Drug Risk Evaluation II HFD440	**OPDRA PID #** D010616 March 6, 2002
DATE REQUESTED: January 20, 2002 **DATE RECEIVED:** December 19, 2001	**REQUESTOR/Phone #:** Scott Monroe, M.D. 7-3203 Jennifer Mercier, 7-4260	
DRUG (Est): Drospirenone and Ethinyl Estradiol	**NDA/IND #** 21-098	**SPONSOR:** Berlex Laboratories, Inc.
DRUG NAME (Trade): Yasmin		
EVENT: Thromboembolic Events		

Executive Summary:

The Division of Reproductive and Urologic Drug Products received a number of reports of thromboembolic adverse events reported with Yasmin. Included in these reports were three foreign fatal cases. DRUDP requested further information from Berlex on all cases (foreign and domestic/labeled and unlabeled) of thromboembolic adverse events reported with Yasmin. These data were submitted January 10, 2002. DRUDP requested a review of the Berlex data by ODS. DRUDP wanted (1) to know if the incidence of serious thromboembolic adverse events in women using Yasmin is greater than that in women using other oral hormonal contraceptives and (2) a comparison of the incidence of thromboembolic events in women using Yasmin, Triphasil, and Cyclessa. The labeling for Yasmin contains the oral contraceptive class labeling Warnings pertaining to "thromboembolic disorders and other vascular problems..."

A search was conducted on February 19, 2002 using the Adverse Event Reporting System (AERS) for Triphasil and Cyclessa (including established names). AERS was searched using the MedDRA High Level Group Term "Embolism and Thrombosis." The search revealed 69 unduplicated cases of thromboembolic events reported with Triphasil and 8 unduplicated cases reported with Tri-Levlen (same product, different brand). No cases were identified for Cyclessa. When comparing the Berlex data to the AERS data, we noted that the Yasmin population was older and had more risk factors than the Triphasil/Tri-Levlen population. Sixty-five percent of the Yasmin cases involved patients with at least one documented risk factor. Only four domestic Yasmin cases were identified and these cases involved patients who were older than 35 years of age (49, 46, 44, and 38) and the oldest patient was also a nicotine user.

ODS cannot use AERS data to calculate incidence rates because reporting of adverse events is a voluntary process, underreporting exists, and we only have access to projected drug usage (i.e., not exact figures). Additionally, incidence rates cannot be compared to reporting rates. Using Berlex's distribution data we calculated a domestic thromboembolic reporting rate of 0.2 per 100,000 users and an all-inclusive (domestic and foreign) reporting rate of 0.62 per 100,000 users. Using IMS and AERS data, the reporting rate for Triphasil/Tri-Levlen is 0.05 per 100,000 domestic users. As noted, reporting rates of thromboembolic events in oral contraceptive users can be calculated using AERS spontaneous reporting data. However, because of the multiple factors that influence reporting, comparisons of drug safety cannot be made from these data. Although the thromboembolic reporting rates for Yasmin are higher than those calculated for Triphasil, ODS cannot determine that, when compared to Triphasil, Yasmin carries a higher potential risk of developing thromboembolic adverse events. Additionally, any comparable comparisons among oral contraceptives using AERS data would lead to similar conclusions.

Reason for Request/Review:
The Division of Reproductive and Urologic Drug Products received a number of reports of thromboembolic adverse events reported with Yasmin. Included in these reports were three foreign fatal cases. DRUDP requested further information from Berlex on all cases (foreign and domestic/labeled and unlabeled) of thromboembolic adverse events reported with Yasmin. These data were submitted January 10, 2002. DRUDP requested that ODS evaluate the following:

1. Based on the information in the January 10, 2002 (i.e., final document, December 14, 2001 document was preliminary) communication from Berlex and other information available to ODS, does it appear that the incidence of serious thrombotic and thromboembolic adverse events in women using Yasmin is greater than that in women using other oral hormonal contraceptives?
2. DRUDP requests a comparison of the incidence of these events in women using Yasmin versus Triphasil (a second generation oral contraceptive containing levonorgestrel) and Cyclessa (a recently approved third generation oral contraceptive containing desogestrel) as well as comparisons to any other oral contraceptives that you believe would be appropriate.

Relevant Product Labeling:
The labeling for Yasmin contains the class labeling Warnings pertaining to "thromboembolic disorders and other vascular problems (myocardial infarction, thromboembolism, cerebrovascular diseases, dose-related risk of vascular disease from oral contraceptives and the persistence of risk of vascular disease)."

Usage Information:
Berlex Laboratories' December 14, 2001 submission notes that [redacted] total number of cycle packs were distributed in the United States between June 2001 and October 31, 2001. As a comparison Berlex has distributed [redacted] cycle packs in Germany during the timeframe of November 2000 to October 31, 2001. The total number or cycle packs distributed, between November 2000 (earliest approval date) and October 31, 2001 is [redacted].

Search Date: February 19, 2002 | **Search Type(s):** ☒ AERS ☐ Literature ☐ Other _____

Search Criteria: Drug Names: Triphasil, Tri-Levlen, and Cyclessa
MEDDRA Terms: High Level Group Term (HLGT) -- Embolism and Thrombosis

Search Results: *The Adverse Event Reporting System (AERS) search did not reveal any cases of thromboembolic events reported with Cyclessa.*

The Adverse Event Reporting System (AERS) search revealed 69 unduplicated cases of thromboembolic events reported with Triphasil and 8 unduplicated cases of thromboembolic events reported with Tri-Levlen. The combined demographics associated with these cases are listed below and the category will be referred to as Triphasil..

Domestic 67 **Foreign** 9 **Unknown** 1

Mean Age: (n=71) 28 years
Median Age: 25 years
Range of Ages: 16 through 54 years

Year of Event:	**1984** 1	**1986** 2	**1987** 3	**1988** 4
	1989 4	**1990** 3	**1991** 3	**1992** 2
	1993 8	**1994** 2	**1995** 5	**1996** 7
	1997 7	**1998** 2	**1999** 6	**2000** 5
	Unknown 13			

Mean Time to Onset: (n=52) 9.9 months
Median Time to Onset: 3.0 months
Range of Time to Onset: 0.2 months to 60 months

Search Results Continued:

Adverse Event Reported (Cases may contain more than one term)

Pulmonary Embolism	23	Deep Vein Thrombosis	14	Stroke	12
Thrombosis (unspecified)	6	Thrombophlebitis	5	Cardiovascular Accident	5
Blood Clot (unspecified)	3	Retinal Occlusion	2	Retinal Thrombosis	1
Thromboembolic Occurrence	1	Portal Vein Thrombosis	1	Unknown	3
Cerebral Artery Thrombosis	1				

Risk Factors Identified (26 of the 77 patients had at least one documented risk factor)

Prior OC use-timeframe unspecified	2	Smoker	10	Prior History DVT/PE	3
Switched from another OC to Yasmin	4	History Cardiovascular Dx	1	Family History DVT/PE	4
Obesity (all degrees)	3	Post-partum	1	Family History Cardiovascular Dx	2

Review of Yasmin Data:

Yasmin demographic data were obtained from Berlex Laboratories' January 10, 2002 submission. The same demographic data points obtained for Triphasil and Tri-Levlen are listed below for Yasmin.

Domestic 4 **Foreign** 44

Mean Age: (n=44)* 33.7 years
Median Age: 34.5 years
Range of Ages: 17 through 49 years*
* One additional case was omitted from the above calculations because the case listed an age of 63 but stated "Pt has been taking Yasmin for three months for contraception (age of pt is probably incorrect)."

Year of Event: **2000** 1 **2001** 45 **Unknown** 2

Mean Time to Onset: (n=47) 3 months
Median Time to Onset: 3 months
Range of Time to Onset: 0.07 months to 10 months

Adverse Event Reported

Deep Vein Thrombosis	16	Pulmonary Embolism	11	Thrombosis	7
Lower Leg Venous Thrombosis	2	Transient Ischemic Attack/Stroke	2		

One each for: Blood Clot, Cardiovascular Accident, Cerebral Bleed, Cerebral Infarct, Cerebral Venous Thrombosis, Paresthesia, Cavernous Sinus Thrombosis, Pelvic Venous Thrombosis, Popliteal Venous Thrombosis and Thrombophlebitis

Risk Factors Identified (31 of the 48 patients had at least one documented risk factor)

Prior OC use timeframe unspecified	11	Smoker	7	Orthopedic Trauma/Surgery	3
Switched from another OC to Yasmin	10	Coagulation Risk Factor	5	Family History DVT/PE	2
Obesity (all degrees)	10	Immobilization	3	Family History Cardiovascular Dx	2

Discussion:

- The Yasmin population was older and had more documented risk factors than the Triphasil population. It should be noted that 65% of the Yasmin cases involved patients with at least one risk factor. Whereas only 34% of the Triphasil cases had at least one risk factor. Deep vein thrombosis and pulmonary emboli were the two adverse events reported the most in both groups.
- A small number of the Yasmin cases were domestic (8%). Yasmin was approved in May 2001 in the United States and was first marketed in November 2000 in Germany. Foreign distribution started approximately 6 months prior to marketing in the United States. The majority of the Triphasil cases were domestic (87%).

Discussion Continued:

- An interesting finding is that the four domestic Yasmin cases involved patients who were older than 35 years of age (49, 46, 44, and 38) and the oldest patient was also a nicotine user. These factors placed the four patients at increased mortality from circulatory disease.[1]
- Contraception was the indication for eighty-seven percent of the Yasmin cases. This includes two of the domestic cases. Sixty-eight percent of the Triphasil cases were used for the contraceptive indication. Four of the Yasmin and ten of the Triphasil cases did not list an indication. The remaining cases had various indications (e.g., irregular menses, dysmenorrhea, and menorrhagia).
- Both Yasmin and Triphasil had a 3-month median time to onset of the adverse event. However, the mean time for Triphasil was approximately 7 months longer than the mean time for Yasmin.
- Using Berlex's distribution data we calculated a domestic thromboembolic reporting rate of 0.2 per 100,000 users and an all-inclusive (domestic and foreign) reporting rate of 0.62 per 100,000 users. Using IMS and AERS data the reporting rate for Triphasil is 0.05 per 100,000 domestic users. The Yasmin reporting rate is higher than the Triphasil reporting rate. However, several factors should be considered before comparing these rates. First, the Yasmin reporting rates are calculated on definitive distribution data from Berlex whereas the Triphasil data were based on projected IMS use data. Secondly, Yasmin has only been on the market for a limited time while Triphasil has an extensive marketing history. The use of Triphasil reached its peak in 1997 and the use has continuously decreased since that point. Finally, the number of spontaneously reported adverse events usually decreases as the product becomes older. All of these factors make comparison of the raw reporting rates for these two products unreliable.
- As a point of reference, it should be noted that a 25-year Population-Based Study entitled "Trends in the Incidence of Deep Vein Thrombosis and Pulmonary Embolism" found that the age and sex-adjusted annual incidence of deep vein thrombosis and pulmonary embolism was 48 per 100,000 and 69 per 100,000 respectively. These rates increased with increasing age and were higher in males than in females.[2] However, the results of this study cannot be applied to the general population because the number of minorities included in the study were limited. The introduction of this study noted that reported annual incidences of deep vein thrombosis and pulmonary embolism varied widely from 43.7 to 145 per 100,000 and 20.8 to 65.8 per 100,000 respectively.

Conclusion: ODS cannot use AERS data to calculate incidence rates because reporting of adverse events is a voluntary process, underreporting exists, and we only have access to projected drug usage (i.e., not exact figures). Additionally, incidence rates cannot be compared with reporting rates. As noted above, reporting rates of thromboembolic events in oral contraceptive users can be calculated using AERS spontaneous reporting data. However, because of the multiple factors that influence reporting, comparisons of drug safety cannot be made from these data. Some of these factors include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions.

Although the thromboembolic reporting rates for Yasmin are higher than those calculated for Triphasil, ODS cannot determine that, when compared to Triphasil, Yasmin carries a higher potential risk of developing thromboembolic adverse events. Additionally, any similar comparisons among other oral contraceptives using AERS data would lead to similar conclusions.

References:

1. Yasmin 28 (drospirenone and ethinyl estradiol) Physician Package Insert. #6073300. May 2001
2. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study/ Archives of Internal Medicine. 1998; 158:585-593.

Denise P. Toyer, Pharm.D. 3/6/02 **Reviewer's Signature / Date:**	Debra E. Boxwell, Pharm.D. 3/6/02 **Team Leader's Signature / Date:**

Division Director Signature / Date: Julie Beitz, M.D. 3/6/02

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/s/

Scott Monroe
10/18/02 12:04:25 PM
MEDICAL OFFICER