end of Cycle 9, rated as moderate intensity and non-serious. The episode lasted 5 hours. The study medication was not discontinued, and the subject was treated with Dilantin.

Thyroid function

One patient developed hyperthyroidism during the study. She was a 27 year old nulligravid woman who switched from Lo-Estrin. She weighed 127 pounds at Baseline. She started Yasmin™ on 2/25/97. On 6/27/97, she was diagnosed with Graves Disease after presenting with nausea, weight loss, and tachycardia. Her thyroid tests were normal at baseline. Her past medical history was unremarkable. She was discontinued from the study and treated with PTU and radioactive iodine.

Another was a 34 year old subject who weighed 178 pounds at baseline and had a negative medical history. Thyroid tests at baseline included T4 of 13.10 (normal range 4.5 to 12.5), T-uptake 42 (normal range 25-38), and Free thyroxine index (FTI) 5.5 (normal range 1.1-4.6). She developed hyperthyroidism prior to her Cycle 1 Visit. She was treated with tapazole and continued the study medication.

A third subject also had elevated T4 of 16.6 and FTI of 5.9 at baseline. Repeat 2 weeks later revealed T4 17.6 and FTI 5.9. This subject reported no related adverse events, and there is no mention of thyroid abnormalities in her medical history.

Reviewer's comment:
Thyroid function tests were performed at baseline only and not routinely monitored during the study. Therefore, no conclusions can be drawn as to any effect of Yasmin™ on thyroid function.

Hematology

Hematology tests were performed at Baseline, Cycle 6, and Cycle 13 or the Final Visit.

- The mean change in hemoglobin from baseline to the final visit was a decrease of 0.27 g/dL (range of –2.3 to +2.2 g/dL). Hemoglobin values changed from normal at baseline to low at Final Visit for 3 (1%) subjects and from low to normal in 2 (<1%). The lowest reported hemoglobin value was 10.4 g/dL.
- The mean change in hematocrit to final visit was a decrease of 1.82% (range of –12% to +9%). Hematocrit values changed from normal at baseline to low at Final Visit for 5 (2%) subjects and from high at baseline to normal at Final Visit for 6 (3%) subjects. No subjects had hematocrit values that changed from low to normal or normal to high. The lowest reported hematocrit was 33.0%.
- The mean change in WBC count was a decrease of 0.65 $x10^3/\mu L$ (range of –8.7 to +5.6 $x10^3/\mu L$). WBC changed from normal to low in 12 (5%) and low to normal in 1 (<1%). WBC also changed from normal to high in 2 (<1%) and high to normal in 8 (3%). The lowest reported WBC count at the Final Visit was 2.2 $x10^3/\mu L$ and the highest was 12.7 $x10^3/\mu L$.

  Reviewer's comment

  Three subjects had final WBC counts below 3.0 $x10^3/\mu L$.
  - **One had a baseline of 6.38 $x10^3/\mu L$ and a final value of 2.23 $x10^3/\mu L$. She reported no adverse events throughout the study.**
  - **Another had a baseline value of 3.92 $x10^3/\mu L$ and a final value of 2.87 $x10^3/\mu L$. Her only adverse event was flu syndrome at the final visit.**
  - **A third Yasmin™ subject had a baseline WBC of 4.5 $x10^3/\mu L$ and a final value of 2.27 $x10^3/\mu L$. Her adverse events included blepharadenitis in cycles 1 and 3, abdominal bloating, cervical polyp, and breast tenderness at cycle 6, and headaches in cycle 9.**
- The mean change in platelet count was a decrease of 1.08 $x10^3/\mu L$ (range of -131 $x10^3/\mu L$ to +216 $x10^3/\mu L$.) The lowest reported platelet count at the Final Visit was 144 $x10^3/\mu L$ and the highest was 603 $x10^3/\mu L$). Platelet counts changed from low to normal, normal to high, and high to normal in 2 subjects (<1%) each.

  Reviewer's comment
  - **Only one subject had a platelet count over 500 $x10^3/\mu L$. She had a baseline platelet count of 387 $x10^3/\mu L$ and a Final Visit value of 603 $x10^3/\mu L$. Her only adverse event was dysmenorrhea in all cycles.**

- **No subject had a platelet count below 120.**

Two of 248 subjects had abnormal hematology values at Cycle 6 and two at Cycle 13/Final Visit (low hemoglobin, and increased lymphocytes) that were considered clinically significant. No clinically significant abnormal hematology value was attributed to the study drug.

Urinalysis
Two subjects had clinically significant urinalysis evaluations at Cycle 13/Final Visit. Neither of these was attributed to the study drug. One subject had 51 WBC/hpf, suggesting a urinary tract infection. Another had 2+ albuminuria.

Clinical chemistry
Chemistry tests were performed (following a 12-hour fast) at Baseline, Cycle 6, and Cycle 13 or the Final Visit. There were no subjects who had clinically significant abnormal serum chemistry, lipid, or electrolyte measurements.

The mean change in serum potassium values from baseline to the final visit was 0.0 mEq/dL (range Potassium values changed from normal at Baseline to low at Final visit in 3 (1%) subjects and normal to high in none. The lowest recorded serum potassium value at the Final Visit was and the highest (normal range 3.4-5.4 mEq/dL)

The mean change in serum sodium values from baseline to the Final Visit was an increase of 1.72 mEq/dL (range of Sodium values changed from normal to low in 1 subject and normal to high in 1 subject. The lowest recorded serum sodium value at the Final Visit was highest (normal range 132-147 mEq/dL).

The mean change in alkaline phosphatase levels from baseline to Final Visit was an increase of 0.52 U/L (range of). Alkaline phosphatase values changed from low at baseline to normal at the final visit for 6 (2%) subjects and normal to low for 6 (2%). Alkaline phosphatase values also changed from normal to high and high to normal in 1 subject each. The highest recorded value at baseline U/L and at the final visit (normal range 31-110 U/L).

The mean change in ALT/SGPT values from baseline to the Final Visit was an increase of 1.15 U/L (range of). ALT changed from normal at Baseline to high at Final Visit for 8 (3%) subjects, high to normal for 10 (4%) and normal to low for 2 (<1%). The highest recorded ALT value at baseline was and at the Final Visit U/L (normal range 6-34 U/L).

The mean change in AST/SGOT values from baseline to the final visit was an increase of 0.79 U/L (range of). AST changed from normal at baseline to high at final visit for 8(3%) subjects and high to normal for 4 (2%), and low to normal for 1 subject. The highest AST value at baseline was and at the final visit (normal range 9-34 U/L).

Reviewer's Comment
One subject, a 23 year old, had a baseline AST of Cycle 6 value of L and a final (Cycle) value of L. Her bilirubin values were normal (0.5mg/dL) at all 3 times, and the only other abnormality was a borderline elevation of ALT to 36 U/L. She reported no adverse events. No further clinical information is available.

The mean change in total bilirubin values from baseline to final visit was a decrease of 0.04 mg/dL (range of). No subject changed from a normal value at baseline to low or high at the final visit. Of 5 subjects with high values at baseline, 4 were normal at the final visit. The highest value at baseline was mg/dL and at the final visit was g/dL (normal range 0.2 to 1.2 mg/dL).

Reviewer's comment
One subject had a bilirubin level of 1.3 at baseline, 1.7 at Cycle 6 and 2.1 at the final visit (Cycle 13). All other chemistry values for this subject were normal, and she reported no adverse events throughout the study. All other bilirubin values were normal.

The mean change in glucose values from baseline to the final visit was an increase of 4.09 mg/dL (range of –40 to +74 mg/dL). Glucose values changed from low at baseline to normal at final visit for 10 (4%) subjects, normal to low in 7 (3%), normal to high in 8(3%), and high to normal in 2 (<1%). The lowest recorded value for glucose at baseline was 55 mg/dL and at the final visit 49 mg/dL. The highest value at baseline was 155 mg/dL and at the final visit 156 mg/dL (normal range 70-115 mg/dL). There were no adverse events suggestive of diabetes.

There were no significant findings relative to BUN, Creatinine, Calcium, chloride, phosphorus, serum albumin, total protein, or uric acid.

Lipids
Total cholesterol, triglycerides, and HDL had statistically significant increases at Cycles 6 and 13, while the LDL decreased at Cycle 6 and was stable at Cycle 13. The HDL/LDL ratio increased statistically significantly from baseline for both Cycle 6 and 13. No subjects had clinically significant abnormal lipid measurements.

- The mean change in total cholesterol from Baseline to the Final Visit was an increase of 15.68 mg/dL, with a range of -
- The mean change in triglycerides from Baseline to the Final Visit was an increase of 21.27 mg/dL, with a range of
- The mean change in HDL cholesterol from Baseline to the Final Visit was an increase of 9.54 mg/dL, with a range of
- The mean change in LDL cholesterol from Baseline to the Final Visit was an increase of 2.28 mg/dL, with a range of
- The mean change in HDL/LDL ratio from Baseline to the Final Visit was an increase of 0.11, with a range of

Reviewer's comment
There were wide variations in lipid changes between subjects. Although the mean changes are statistically significant, they are of doubtful clinical significance.

Cervical cytology
4 (1.3%) of 300 subjects had a change from normal cervical cytology findings at baseline to abnormal posttreatment. 5 subjects (1.6%) had a change from normal at baseline to benign cellular changes posttreatment. One (0.3%) had a change from benign cellular changes at baseline to abnormal posttreatment. All abnormal Pap smear results were read as atypical squamous cells of undetermined significance. The changes from baseline were considered to be clinically non-significant.

Gonorrhea and chlamydia
No subject had an abnormal gonorrhea culture. Six (2%) subjects had an abnormal chlamydia culture at baseline and normal posttreatment.

Weight change.
Although the mean weight did not change appreciably during the study, individual change in weight from baseline to the final visit varied from 45 pounds lost to 53 pounds gained. The following table shows the distribution of weight change from baseline to the final visit:

Weight change	Number of subjects (%)
Lost > 20 pounds	3 (1%)
lost >15 to 20 pounds	7 (2%)
lost >10 to 15 pounds	13 (4%)
lost >5 to 10 pounds	27 (9%)
gained or lost ≤ 5 pounds	201 (65%)
gained >5 to 10 pounds	30 (10%)
gained >10 to 15 pounds	16 (5%)
gained >15 to 20 pounds	6 (2%)
gained > 20 pounds	5 (2%)

One subject discontinued the study because of weight gain

Reviewer's Comments

- **Body weight was self-recorded by the subjects.**
- **Results may be confounded by the use of weight control medications. 3 subjects were taking medications for weight control at entry into the study, and for 9 others they were noted as concomitant medications started during the study.**

Blood pressure

There were no clinically significant changes in mean systolic or diastolic blood pressure during the study. Changes in systolic blood pressure of more than 10 mm Hg were seen in 0.4% to 3.7% of subjects during the study. Diastolic blood pressure changes of more than 10 mm Hg occurred in 8.5% to 10.9%. Diastolic blood pressures ≥ 95 mm Hg were recorded for 2 subjects at least once during the study. One had a blood pressure of 130/80 at baseline, a maximum of 121/96 at Cycle 6 and a Final reading of 120/92 at Cycle 13. Another had a blood pressure of 124/78 at Baseline, a single elevation to 140/100 at Cycle 1, and a Final reading of 118/74 at Cycle 13.

5.0 CLINICAL STUDY 93044 (Report No. AJ06): Supporting Phase 3 Efficacy and Safety Study

5.1 Title

Study of cycle control and tolerance of SH T 470 FA in comparison with Marvelon® in up to 2100 healthy women over 13 cycles of contraceptive use

5.2 Study objective

The study was conducted to obtain data on contraceptive reliability, cycle control, and tolerance of SH T 470 FA (Yasmin™) including blood pressure, heart rate and body weight, using the commercial preparation Marvelon®, which contains the same estrogen (30 µg EE) with a different progestin (150 µg desogestrel) as the reference preparation.

5.3 Study design

Open-label, randomized, multicenter study, with two treatment groups conducted at 80 study centers in 8 European countries. 2100 subjects were to be randomized to receive either Yasmin™ or Marvelon® in a 4:1 ratio. Both preparations were to be given one tablet daily for 21 days, starting on the first day of menstrual bleeding, and followed by a 7-day tablet-free interval for 13 cycles of use and a follow-up phase of 3 months after the last study medication. By protocol amendment, the follow-up phase was shortened to 6 weeks.

5.4 Study population

Subjects were recruited from healthy menstruating women seeking oral contraception who had no contraindications. A total of 2098 subjects were randomized, 1680 to the Yasmin™ group and 418 to the Marvelon® group. There were 2069 subjects valid for ITT (1657 under Yasmin™ and 412 under Marvelon®). 1209 were valid for efficacy (948 under Yasmin™ and 261 under Marvelon®). 29 subjects were listed only (23 Yasmin™ and 6 Marvelon®).

All except 3 Yasmin™ subjects and 1 Marvelon® subject were between 18 and 35 years old.

98.9% of Yasmin™ users and 99.7% of Marvelon® users were Caucasian. There were 6 Blacks, 2 Asians and 7 "others" in the Yasmin™ group and 1 Black in the Marvelon® group.

27% of Yasmin™ subjects and 24% of Marvelon® subjects were current smokers.

65% of Yasmin™ subjects and 60% of Marvelon® subjects were switchers from other oral contraceptives.

5.5 Inclusion and exclusion criteria

Inclusion Criteria

- Age between 18 and 35
- In the case of smokers, the maximum age was 30
- Both new users and women switching from other oral contraceptives; if the latter had used preparations containing drospirenone or desogestrel, they had to observe one washout cycle before treatment.
- Willingness not to use other sex hormone preparations during treatment
- Willingness not to use other contraceptive methods during treatment, other than condoms for AIDS prophylaxis
- Following delivery, abortion, or lactation, subjects were admitted to the study only after the first normal cycle (28±days)
- Pregnancy was ruled out with a β-HCG test prior to tablet taking
- Only women who were prepared to take the study mediation over the planned duration of the study and were willing to undergo regular medical controls and self-checks (cycle, weight) were admitted into the study.
- Ethnicity was of no consequence

Reviewer's comment
There was no requirement that subjects in this trial be at risk for pregnancy.

Exclusion Criteria

- Pregnancy or lactation
- Liver disease
- Vascular and metabolic diseases: past, present, or family history of thromboembolic processes, disturbed coagulation with a tendency to clotting, certain cardiac disorders, hypertension (constantly ≥ 140/90 mm Hg or requiring treatment), diabetes mellitus, sickle cell anemia, disturbances of lipometabolism
- Tumors: all malignant tumors and benign tumors of the liver and pituitary
- Other diseases: Obesity, epilepsy, migraine accompagnee, herpes gestationis, otosclerosis with worsening in previous pregnancy, acute sensory disorders, endometriosis, genital bleeding of unknown origin
- Use of sex hormones: drospirenone or desogestrel in the cycle preceding treatment
- Pap smear classification > CII
- Genital infection (e.g., chlamydia trachomatis, gonorrhea)
- Parenteral depot contraceptives in the last half year
- Smokers over 30 years of age

- Alcohol, drug and medicine abuse
- Use of preparations which experience had shown could affect the activity of hepatic enzymes or absorption
- Use of diuretics or preparations for the treatment of PMS

5.6 Screening period

The study was explained and informed consent obtained. A medical and surgical history was obtained, including demographic data, history of medication use, smoking, menstruation history, premenstrual syndrome, acne and seborrhea, and gynecological history. A thorough general and gynecological examination was performed, including breast examination and a cervical smear for cytology (Pap) if results of a Pap smear performed within the previous 3 months was not available.

Special attention was paid to the presence of acne and seborrhea. If acne was present, its status was graded according to the Cunliffe grading scale and locations (face, chest, back) were recorded. Seborrhea was classified with regard to the leading symptom (oily skin, oily hair, dandruff, not definite).

Blood pressure and heart rate were recorded. Blood pressure was measured in the sitting position after 10 minutes rest and was repeated twice at 3 minute intervals.

Non-fasting blood specimens were obtained for general clinical chemistry parameters. Urine glucose was evaluated by dipstick.

At three centers, liver ultrasound examinations were performed at the recruitment visit.

Visit 2 was planned for within 1 month after the recruitment visit. Blood pressure and heart rate were recorded. Examination and laboratory results were reviewed. Subjects who satisfied inclusion and exclusion criteria and maintained informed consent were randomized to treatment and given the first 3 packs of their study medication. Menstrual and weight charts were distributed and instructions given for completing them.

5.7 Treatment period

Treatment began with the first day of menstrual bleeding (Cycle day 1) and ended 7 days after the last tablet had been taken in the 13th treatment cycle. Pregnancy was to be ruled out by a β-HCG test before the first tablet was taken. Tablets were taken in the normal manner for oral contraceptives, 21 days of tablet-taking followed by a 7-day tablet-free interval.

Subjects were instructed to start their menstrual charts on Cycle day 1, and they were to present them to the investigator at each scheduled visit. They were required to weigh themselves once weekly, without clothes and before breakfast, and to record the weight in their weight charts and present them to the investigator at each scheduled visit.

Visits were to be scheduled between days 14 and 21 in treatment cycles 2 or 3 (visit 3), 6 (visit 4), 9 (visit 5), and 13 (visit 6). At each visit, blood pressure, heart rate, acne, and seborrhea were assessed. Adverse events and concomitant medications were recorded. Possible premenstrual syndrome (PMS) complaints were recorded as such if the investigator determined that the temporal relationship of the complaint to the menstrual cycle indicated a relation to PMS. These were not recorded as adverse events.

Blood sampling for general clinical chemistry parameters and urine dipstick for urine glucose were done at visits 3 and 6. A gynecological examination was performed at visits 4 and 6, including breast examination and Pap smear. A protocol amendment waived the Pap requirement at visit 4 in The Netherlands. At visits 4 and 6 liver ultrasound examinations were performed on subjects at 3 study centers in Germany.

During treatment, if withdrawal bleeding failed to occur during the tablet-free interval, pregnancy was ruled out with a β-HCG test before the next tablet was taken.

Subjects were to continue their menstrual charts and weight charts during the 6-week follow-up period. 6 weeks after the completion of treatment, subjects returned for blood pressure and heart rate measurements. Menstrual and weight charts were evaluated. Acne or seborrhea were assessed.

5.8 Statistical Procedures

A distribution ratio of 1:4 was chosen in order to collect more information on Yasmin™. The type I error rate was set to α=5% and the power to be 1-β=90%.

Contraceptive reliability of Yasmin™ is the first objective of the study. However, the primary target variable for statistical analysis was the occurrence of intermenstrual bleeding during the 2nd through 13th treatment cycles. Intermenstrual bleeding during the 2nd to 6th cycles was analyzed as secondary target variable.

All target variables were described according to their type using descriptive statistics. The number of subjects with intermenstrual bleeding at least once during cycles 2 to 13 was compared between the treatments using the two-sided χ^2 test with α of 5%.

The Pearl Index and corrected Pearl Index were calculated for pregnancy rates. Pearl Index = 1300 x number of pregnancies / number of cycles.

5.9 Evaluation Criteria

Efficacy: Cycle control, contraceptive effectiveness, Pearl Index, Pregnancy Ratio

Safety: General physical and gynecological examination; cervical smear for cytology, general clinico-chemical and hematological parameters, blood pressure and heart rate, body weight, adverse events, premenstrual symptoms (PMS), acne and seborrhea.

5.10 Withdrawals and Compliance

Subjects had the right to withdraw from the study at any time. In addition, the following were grounds for immediate termination from the study:

- Pregnancy
- First signs of venous inflammation or blood clots, 6 weeks in advance of scheduled operations, and prolonged immobility (e.g., after accidents)
- Headache occurring for the first time in the form of migraine or more frequently with unusual severity
- Sudden sensory disturbances
- Motor disturbances, particularly paralysis, speech disorders of short duration (transient ischemic attacks)
- Increases in blood pressure (> 140/90 mm Hg by repeated measurements)
- Occurrence of liver inflammation, jaundice, itching over the entire body, disturbances of bile drainage (cholestasis), and unusual liver function values
- Fresh occurrence of epileptic seizures while on the medication
- Repeated, excessive persistent intracyclic bleeding

Disposition of Subjects			
		Yasmin™	Marvelon®
Total subjects screened	2236		
Total randomized	2098	1680	418
Listed only	29	23	6
Intent to treat	2069	1657	412
Valid cases analyzed	1209	948	261

Completed study and follow-up 1615		1288	327
Completed study medication But not follow-up		381	88
Missing data	14		
Premature discontinuation of study medication		361	81

Criteria for VCA were the same as previously cited for study 92052 (Report #A151)

Premature discontinuations				
Reason for Discontinuation	Yasmin™ (n = 1680)		Marvelon® (n = 418)	
	n	% of randomized subjects	n	% of randomized subjects
Adverse events	148	8.8%	29	6.9%
Pregnancy	14	0.8%	2	0.5%
Protocol deviation	14	0.8%	3	0.7%
Withdrawal of consent	37	2.2%	7	1.7%
missing	15	0.9%	4	1.0%
other	133	7.9%	36	8.6%
Desire for pregnancy	30	1.8%	9	2.1%
Lost to follow-up	60	3.6%	14	3.3%
Total	361	21.5%	81	19.4%

5.11 Efficacy analysis

Pregnancies

10 pregnancies were reported in Yasmin™ users and 1 in Marvelon® users. For all but 1 pregnancy in the Yasmin™ group, interactions were documented that have the potential to impair the contraceptive reliability of the method. The Pearl Index for Yasmin™ is 0.70 (corrected Pearl Index 0.71) and for Marvelon® is 0.28 (corrected Pearl Index 0.28).

The ratio of pregnancies divided by the number of subjects taking at least 19 tablets in each cycle for cycle 1 to 13 is 0.80 for Yasmin™ and 0.31 for Marvelon®. The corresponding ratios corrected for condom use are 0.84 for Yasmin™ and 0.32 for Marvelon®. At each visit, 1.1- 2.7% of Yasmin™ subjects and 0.3-2.0% of Marvelon® subjects reported use of condoms for protection against AIDS.

A total of 19 subjects became pregnant during the entire study course, including the time period before and after medication phase, 16 using Yasmin™ and 3 using Marvelon®. 11 subjects became pregnant while taking study medication, 10 with Yasmin™ and 1 with Marvelon®.

The following subjects became pregnant during the treatment phase:

1. A 25 year old Yasmin™ subject with prior IUD use and no previous pregnancy completed 7 cycles of study drug with intracyclic bleeding in cycles 2 and 5 and absence of withdrawal bleeding in cycles 4 and 7. In cycle 8, she had intracyclic bleeding days 2-5 (February 27 to March 3, 1995), then amenorrhea. Her calculated date of conception was March 10, 1995, on day 12 of cycle 8. Pregnancy was diagnosed in the 2nd week. She had a normal pregnancy and delivered a boy on December 8, 1995, with esophageal atresia.
2. A 21 year old Yasmin™ subject who switched from another oral contraceptive and had one previous birth completed 11 cycles of use with a 9-day tablet free interval in cycle 2. She omitted tablets on days 14 and 15 of the conception cycle, October 18-19, 1994. Her calculated date of conception was October 19, day 15 of cycle 12. Pregnancy was diagnosed in the 6th week. She had a normal pregnancy and delivered a normal girl June 30, 1995.
3. A 25 year old Yasmin™ subject who switched from another oral contraceptive and had one previous birth and one abortion completed 4 cycles with 19 days irregular bleeding in cycle 1, absence of withdrawal bleeding in cycle 1, and early withdrawal bleeding in cycles 3 and 4. In cycle 5 she had

diarrhea on days 6 and 7 (February 15-16, 1994) and midcycle irregular bleeding days 7 to 11(February 16-20). Calculated date of conception was March 1, 1994, on day 20 of cycle 5. Pregnancy was diagnosed in the 5th week. She had a normal pregnancy and delivered a healthy girl on November 26.

4. A 29 year old Yasmin™ subject switched from a previous oral contraceptive after one month. She had 3 previous births and a history of amenorrhea. In the first cycle one tablet was delayed and the tablet-free interval was 11 days. In cycle 2, the tablet-free interval was 9 days. Tablet use in cycle 3 was October 28 to November 17, 1994. Her calculated date of conception was November 6, 1994, day 10 of cycle 3. Pregnancy was diagnosed in the 5th week. She delivered a healthy girl at term on July 30, 1995.
5. A 20 year old Yasmin™ subject switched from another OC after 6 months. She had one previous abortion. She completed 6 cycles with no adverse events and no concomitant medication. She had amenorrhea in the conception cycle 7. Her calculated date of conception was October 10, 1994, day 9 of cycle 7. Pregnancy was diagnosed in the 7th week. She had a normal pregnancy and delivered a healthy girl on July 10, 1995.
6. A 26 year old Yasmin™ subject with 6 years of OC use and no previous pregnancy completed 4 cycles with midcyclic irregular bleeding in cycle 4 for 4 days. She had enteritis and diarrhea in the pre-conception cycle 4. Her calculated date of conception was May 12, 1994, day 12 of cycle 5. Pregnancy was diagnosed in the 5th week. She had a normal pregnancy and delivered a healthy girl on January 25, 1995 by cesarean section.
7. An 18 year old OC switcher with a history of amenorrhea and atopic rhinitis and asthma completed 6 cycles. For cycles 7 to 9 diary charts were filled out in advance. In cycle 4, she reported 13 tablet-taking days (July 13-25, 1994) and an 8 day tablet-free interval with no withdrawal bleeding. Cycles 5 and 6 were regular. Cycles 7 to 9, starting with August 28, 1994, were documented in advance. The medication for those cycles was dispensed on November 18, 1994. Her calculated date of conception was December 30, 1994, diagnosed in the 6th week on January 27, 1995 (in cycle 10). She had an abortion on February 14, 1995.
8. A 25 year old Yasmin™ subject with 8 years history of prior OC use and no previous pregnancy completed 7 cycles. She did not start tablet intake on the first bleeding day of the first cycle and omitted 2 tablets in cycle 3. She omitted tablets on days 3, 4, 17-21 (June 25 – July 6, 1994), giving a 12-day tablet-free interval preceding the conception cycle 9. The first day of cycle 9 was July 7, 1994. Conception was calculated to have occurred July 11, 1994, on day 5 of cycle 9. Pregnancy was diagnosed in the 5th week. She had a normal pregnancy with normal outcome but no details available.
9. A 29 year old Yasmin™ subject, OC switcher after 6 months of use and one previous pregnancy, completed 11 cycles with 6-day tablet-free intervals in cycles 1, 3, 5, 6, 7, 11. In cycle 8, she took 16 consecutive tablets. She had amenorrhea in the conception cycle. Her last tablet-taking interval was April 4 to 26, 1995. From March 20, 1995 she experienced insomnia and from April 6, vomiting and diarrhea. She had intracyclic bleeding for the first time on days 4-8 of cycle 12 (April 4-11). Her calculated date of conception was April 25, 1995, day 22 of cycle 12. Pregnancy was diagnosed in the 6th week. She had a normal pregnancy and delivered a boy with suspicion of a coarctation of the aorta but no further information available.
10. A 25 year old Yasmin™ subject, OC switcher with no previous pregnancies and a history of intracyclic bleeding and PMS completed 10 cycles with a 6-day tablet-free interval in cycles 3, 9, 10. She missed one tablet in cycle 4. The conception cycle 11 began on February 22, 1995. The last tablet was taken on March 14. One tablet was omitted. She had gastrointestinal problems and diarrhea from February 5 to 14. Conception occurred between February 22 and 28, the first week of cycle 11. Pregnancy was diagnosed in the 6th week on March 22, 1995. She had a normal pregnancy and delivered a healthy girl.
11. A 19 year old Marvelon® subject, OC switcher after 6 months of use, with 2 previous abortions and a history of intracyclic bleeding and history of salpingitis, appendectomy completed 4 cycles with intracyclic bleeding in 2 cycles, one tablet-free interval exceeded by one day, one shortened by one day, no withdrawal bleeding in cycle 4 and conception cycle 5. Her calculated date of conception was August 17, 1994, day 5 of cycle 5. Pregnancy was diagnosed in the 5th week. She experienced premature labor, and underwent a cerclage. She delivered a boy on April 26, 1996, weighing 2380 g.

The following subjects became pregnant before or after taking the study medication:

1. A 29 year old Yasmin™ subject with one previous birth and no previous contraception had one irregular cycle under study medication and discontinued after the diagnosis of pregnancy at week 4. Her calculated date of conception was day 14 of the cycle before medication. She had an abortion.
2. A 20 year old Yasmin™ subject with no previous pregnancy and no prior OC use did not follow the medication regimen, and waited in both medication cycles for withdrawal bleeding to start with a new pill cycle. In Cycle 1, the tablet-free interval was 20 days. The last tablet of cycle 2 was July 11, 1994. Her calculated date of conception was July 23, 1994, 12 days after her last tablet. Pregnancy was diagnosed at the 7th week. She had a normal pregnancy and delivered a healthy girl on April 15, 1995.
3. A 31 year old Yasmin™ user with two previous pregnancies and irregular cycles, who switched from 18 months of previous OC use completed one regular cycle of study medication March 13 to April 2, 1994. After a prolonged tablet-free interval, pregnancy was diagnosed at 10 weeks on April 22. Conception was believed to have occurred on day 10 of the precycle. She had an uneventful pregnancy and delivered a healthy boy.
4. A 33 year old Yasmin™ user with 3 previous births and 1 spontaneous abortion, previously used an IUD. Her last menstrual period was July 14, 1994. Pregnancy was diagnosed August 5, 1994. She never started medication. She had a spontaneous abortion September 9, 1994.
5. A 25 year old Yasmin™ user with 6 months of prior OC use and no previous pregnancies took only 7 tablets in the first cycle (November 15-22, 1993). She had foot surgery on November 25, and the study drug was discontinued. Conception was estimated to have occurred December 9, 1993. Pregnancy was diagnosed in the 6th week on January 6. She continued the pregnancy and delivered a healthy boy.
6. A 30 year old Yasmin™ user with one previous pregnancy completed one regular cycle but had no withdrawal bleeding. She stopped tablet intake and performed a β-HCG which was positive. Her calculated date of conception was February 12, 1994, day 20 of the cycle before start of medication. Her gestational age was 7 weeks at diagnosis.
7. A 29 year old Marvelon® subject with 2 previous births and no previous OC use had a positive β-HCG before the start of study medication and never started study medication. Conception occurred during the screening phase. Gestational age was 5 weeks at diagnosis.
8. A 27 year old Marvelon® subject with 8 years of prior OC use and no previous pregnancies threw away her menstrual charts for cycles 6-9 and stated that she stopped study medication after cycle 9 (January, 1995) because of a desire for pregnancy. Her gestational age at diagnosis was 8 weeks. The calculated date of conception was February 18, 1995. She had a spontaneous abortion May 9, 1995.

Reviewer's comment

1. Insufficient information is provided regarding gestational dating parameters to confirm that the above pregnancies were not conceived during treatment.

2. *There was no requirement that subjects be at risk for pregnancy.* The following Yasmin™ subjects may have been at no risk or reduced risk of pregnancy

- **4 subjects were noted to be virgins.**
- **1 subject had a previous hysterosalpingography for "subfertility"**

In this trial of 1288 subjects, even if these subjects were excluded from the efficacy analysis, the pregnancy rate would be acceptable.

Cycle control

Cycle control was similar between the two treatments. 59 (6.2%) of the Yasmin™ group and 20 (7.7%) of the Marvelon® group reported intracyclic bleeding during the last half year before the start of the study. 381 (40.5%) of the Yasmin™ group and 104 (40%) of the Marvelon® group reported at least one intracyclic bleeding during the treatment phase. Intracyclic bleeding occurred most often in the first treatment cycle and dropped continuously thereafter. After 6-7 cycles intracyclic bleeding rates were comparable to or lower than the rates reported at baseline. Most bleeding was scanty with both treatments, The frequency and intensity of bleeding was similar in both groups. Amenorrhea occurred in 0.8% of the cycles with both Yasmin™ and Marvelon®.

5.12 Safety analysis

Deaths

One unrelated death was reported in a 28 year old Yasmin™ subject who died suddenly at home May 19, 1994 after 5 months of tablet intake. Her medical history was unremarkable except for one birth September 1993 and one abortion in 1990. She did not smoke. Clinical findings at her initial visit were normal except for a minimally elevated alkaline phosphatase of 185 U/L (normal range 60-170 U/L) and GPT of 18 U/L (normal range 0-17 U/L). Her blood pressure at visit two was 110/70 and heart rate 60, and pregnancy test negative. At visit 3, GPT was 21 U/L and there was no indication of concomitant disease. The postmortem examination revealed a severe post-streptococcal myocarditis with extensive inflammatory infiltrates, which was assumed to be the cause for the cardiac arrest. This was judged to be unrelated to the study drug.

Adverse events

63.9% of Yasmin™ subjects and 64.9% of Marvelon® subjects reported adverse events during treatment. At the follow-up visit, 23.9% of Yasmin™ subjects and 25.2% of Marvelon® subjects reported adverse events. The most frequently reported AEs were the following:

Adverse event	Yasmin™	Marvelon®
PMS (coded menstrual disorder)	23.5%	18.2%
Headache	16.2%	14.1%
Breast pain	8%	5.8%
Nausea	7.4%	4.4%
Abdominal pain	6.9%	5.3%
Migraine	3.3%	4.1%
Depression	1.9%	2.2%
Back pain	2.1%	1.0%
Acne	1.4%	1%

One Yasmin™ subject had elevated blood pressure levels but refused a referral. She was 23 years old, Caucasian, with a history of smoking for 3 years, 15 cigarettes/day. She reported breast pain as an adverse event at visits 3 and 4, and a tooth disorder at visit 5. Her blood pressure was 150/85 at recruitment, 130/80 at visit 2, 140/85 and visit 3, 110/70 at visit 4, 160/100 at visit 5, 140/90 at the last medication visit, and 180/100 at the 6 week follow-up visit.

One Marvelon® subject reported thrombosis as a complication to surgery, treated with heparin and later with coumarin.

149 (9.0%) Yasmin™ subjects and 29 (7.0%) Marvelon® users discontinued the study drug due to adverse events. The most common adverse event leading to withdrawal was headache, reported by 23 (1.4%) Yasmin™ users and 2 (0.5%) Marvelon® users. All other events leading to discontinuation were reported in less than one percent of subjects.

Serious adverse events

Altogether, 35 subjects experienced serious adverse events, 4 of them possibly related to the study drug, including otosclerosis, uterine myoma, and toxidermia in Yasmin™ subjects; and progressive thrombocytopenia in a Marvelon® subject.

Clinical chemistry

Clinical chemistry parameters remained virtually unchanged, with no difference in risk profile between the study preparations. The following subjects had clinically significant liver function values:

1. A Yasmin™ subject had normal liver function values at baseline and ALAT/GPT elevated to more than 3 X ULN at 53 U/L (normal range 0-17 U/L) at visit 3. At the last medication visit, the value was 46 U/L. Gamma-GT was mildly elevated at 22 U/L (normal range 0-18 U/L) at visit 3 and 29 U/L at the

last medication visit. Bilirubin was normal throughout at 0.2 – 0.5 mg/dl. She reported no adverse events.

2. A Yasmin™ subject had an elevated ALAT/GPT of 57 U/L (> 3 x ULN) at baseline which returned to 18 (normal range 0-17 U/L) at visit 3. Her ASAT/GOT was also elevated at 33 U/L (normal range 0-18 U/L) at baseline and returned to normal at 13 U/L at visit 3. Her bilirubin was normal at 0.4 mg/dl at both visits. She reported adverse events of nausea, headaches, and PMS.
3. A Yasmin™ subject had ALAT/GPT of 88 U/L (> 3 x ULN, normal range 0-17 U/L)) at baseline. GGT at baseline was elevated at 29 U/L (normal range 0-18 U/L) and ASAT/GOT elevated at 30 U/L (normal range 0-18 U/L). All values had returned to normal at visit 3 and the last medication visit. Her bilirubin was normal (0.2 to 0.4 mg/dl) at all times.
4. A Yasmin™ subject had an elevated ALAT/GPT of 101 U/L (>3 x ULN) and ASAT/GOT of 55.0 U/L at visit 1. She had no further laboratory values. She reported no adverse events but discontinued the study after 3 months (withdrawal of consent).
5. 4 Yasmin™ subjects had bilirubin values elevated to 2.2 – 2.9 mg/dl at visit 1. All returned to normal at subsequent visits, and none were associated with other significant abnormal values.
6. Except for 2 subjects with bilirubin values of 1.9 mg/dl at visit 3 and 1.8 mg/dl at visit 3, the maximum bilirubin value after visit 1 in the Yasmin™ group was 1.5 mg/dl.

Reviewer's comment
Numerous LDH values were elevated, most of them with a notation that the serum samples were hemolyzed or incompletely separated. No meaningful conclusions can be made using those results.

Electrolytes
In the Yasmin™ group, the range of potassium values at baseline was 3.3 to 15.0 mmol/l and at the last medication visit 2.4 to 15.0 mmol/l. In the Marvelon® group, the range was 3.5 to 15.0 mmol/l at baseline and 3.2 to 13.1 mmol/l at the last medication visit.

Reviewer's comment
12 Yasmin™ subjects are identified with potassium values above 10 mmol/l, which are not likely to be compatible with life. Many specimens are noted to be hemolyzed or incompletely separated and raise concern about the adequacy of laboratory procedures. No valid conclusions regarding the effect of study medication on electrolytes can be made using the data presented.

Hematology
Four Yasmin™ subjects and 2 Marvelon® subjects had platelet counts below 100/nl, including 2 Yasmin™ subjects and 1 Marvelon® subject with values below 50/nl. In the Yasmin™ group, platelet counts ranged from 19 to 637/nl at baseline and from 56 to 570 /nl at the last medication visit. In the Marvelon® group, platelet counts ranged from 56 to 570/nl at baseline and 23 to 567/nl at the last medication visit.

1. A Yasmin™ subject had a normal platelet count of 156/nl at visit 1 and low value of 93/nl (normal range 150-450/nl) at last medication visit.
2. A Yasmin™ subject had a normal platelet count of 179/nl at visit 1, 170/nl at visit 3, and low value of 56/nl and 37/nl at last medication visit.
3. A Yasmin™ subject had a normal platelet count of 403/nl at visit 1, 463/nl at visit 3, and a high value of 557/nl at the last medication visit.
4. A Yasmin™ subject had a normal platelet count of 152/nl at visit 1, 125/nl at visit 3, and a low value of 93/nl at the last medication visit.
5. A Yasmin™ subject had a normal platelet count of 204/nl at visit 1 and a reported low value of 8/nl at visit 3. Her only reported adverse event was premenstrual syndrome. Her hemoglobin value was 11.7 g/dl, and hematocrit 41.0%. WBC was 6.7 $x10^3/\mu L$.
   Reviewer's comment
   This value should be considered an error in laboratory procedure or reporting, as it is extremely low, and would be expected to be associated with spontaneous life-threatening bleeding.
6. A Yasmin™ subject had a low platelet count of 97/nl at visit 1, 163 at visit 3, and a low value of 75/nl at the last medication visit.

Reviewer's comment
Although 3 Yasmin™ subjects in this trial changed from a normal platelet value at baseline to low during this trial, another one changed from normal to high. The other trials presented in this NDA did not show any significant trends in platelet counts.

Body weight
Mean body weight showed a decrease over the treatment phase under Yasmin™ (mean 0.455 kg loss) and a smaller decrease under Marvelon® (mean 0.192 kg loss). The difference between treatments was statistically significant. The range of weight change in Yasmin™ subjects was a loss of 15.6 kg at cycle 13 and 16.0 kg at follow-up to a gain of 8.9 kg at cycles 4 and 8 and 10.9 kg at follow-up. The range of weight change in Marvelon® subjects was a loss of 16.4 kg at cycles 8 and 9 to a gain of 10.1 kg at cycle 5 and 12.7 kg at follow-up.

Blood pressure
More Yasmin™ subjects than Marvelon® subjects had a decrease of up to 10 mm Hg in systolic blood pressure, and more Marvelon® subjects had an increase of more than 10 mm Hg in systolic blood pressure. Individual subjects in individual cycles had blood pressure $\geq$ 140/90 mm Hg. These did not lead to premature discontinuation of the study. No negative trend was seen. There was no demonstrable trend in heart rate change with either preparation.

Acne
Subjects' skin was assessed for acne lesions with the Cunliffe grades at each visit. Acne was observed less often under treatment compared to baseline in both treatment groups. The subjects with more severe acne improved most with both preparations. Seborrhea was also distinctly reduced throughout the study compared to baseline in both treatment groups.

Liver size
In 3 centers in Germany the liver size was measure by ultrasonography at recruitment, visit 4 and the last medication visit. There were two clinically significant changes from baseline noted in the Yasmin™ group and none in the Marvelon® group. One of these was felt to represent a measuring error. At the last medication visit no individual had clinically significant changes from baseline. The mean index of liver size was slightly higher at the end of treatment (n=42) than at recruitment (n=68) in the Yasmin™ and slightly lower in the Marvelon® group (n=13 at recruitment and n=10 at the end of treatment). A further analysis including only subjects who were examined fasting revealed a lower mean index of liver size at visit 4 and at the last medication visit than at the recruitment visit.

Reviewer's comment
The clinical significance of this finding is unknown.

6.0 CLINICAL STUDY 90031 (Report No. A187): Supporting Phase 2 Efficacy and Safety Study

6.1 Title

Study of the cycle control, contraceptive reliability and tolerance of SH T 470 F (Yasmin™), SH T 470 I and SH T 470 K in Comparison to Microgynon®

6.2 Study objective

The aim of the present study was to assess cycle control, contraceptive reliability, influence on body weight, blood pressure and the tolerance over 6 cycles of use in order to establish which DRSP preparation was more suitable for further development as a hormonal oral contraceptive. In addition, the minimum concentrations of DRSP in serum at steady state were determined in cycles 1, 3, and 6.

6.3 Study design

Double-blind, randomized, multicenter (5 centers) trial with 4 study groups:

1. SH T 470 F (DRSP 3 mg + EE 30 µg /Yasmin™)
2. SH T 470 I (DRSP 3 mg + EE 20 µg)
3. SH T 470 K (DRSP 3 mg + EE 15 µg)
4. Microgynon® (levonorgestrel 150 µg + EE 30 µg)

Subjects in each group were to take the study medication, beginning on the first day of menstrual bleeding or withdrawal bleeding, for 21 days followed by a 7-day tablet-free interval for 6 cycles of use.

6.4 Study population

200 female volunteers of ages 18 to 37 years, 50 per treatment group, were recruited. 198 volunteers were regarded as valid cases, and 1 subject each in the SH T 470 F group and the Microgynon® group were considered valid for ITT only.

6.5 Inclusion and exclusion criteria

Inclusion Criteria

Any healthy woman 18-35 years of age could be enrolled as long as she did not display any of the exclusion criteria after giving written informed consent to participate. For women who smoked more than 10 cigarettes per day, the upper age limit was 30. Preference was to be given to DRSP 3 mg/EE 0.030 mg novo users. Long-term users were to be switched from another oral contraceptive to one of the trial preparations without a wash-out phase.

Reviewer's comment
There was no requirement for subjects to be at risk for pregnancy.

Exclusion Criteria

- Pregnancy and lactation: Pregnancy was to be ruled out by a β-HCG test before the start of medication
- Liver diseases: acute and chronically progressive liver diseases, disturbances of bile secretion, disturbances of bile drainage (cholestasis, including a history thereof), past or present liver tumors, Dubin-Johnson syndrome, Rotor syndrome, idiopathic jaundice of pregnancy.
- Vascular and metabolic diseases: past or present thromboembolic processes (thrombosis, embolism) in veins or arteries (particularly stroke, cardiac infarction), also thrombophlebitis, hypertension requiring therapy, severe diabetes (mellitus) with changes of the vessel walls, sickle cell anemia, disturbances of lipometabolism.
- Tumors: all malignant tumors (e.g., mammary or endometrial carcinoma) and benign liver and pituitary tumors, including after treatment or a suspicion thereof.
- Other diseases:
  - marked obesity, 20% above normal weight (height in cm – 100, expressed in kg)
  - epilepsy
  - migraine accompagnee
  - eruption of vesicles during a previous pregnancy (gestational herpes)
  - severe pruritis and jaundice of pregnancy
  - all 3 forms of porphyria
  - middle ear deafness (otosclerosis) with deterioration in previous pregnancies
  - endometriosis
- Use of sex hormone preparations
- Smokers >30 years of age

6.6 Screening period

Gynecological and obstetric history and pretreatment and concomitant medications were ascertained. A thorough medical (including blood pressure after 5 minutes sitting down, special liver diagnostics only in cases with a relevant history) and gynecological examination (including the breasts) were conducted in

order to detect any diseases requiring treatment or risk factors and to rule out pregnancy. A pap smear was taken if no results were available from the last 3 months. Routine laboratory parameters (blood and urine) and progesterone levels were to be determined between the 22nd and 25th days of the tablet-free pretreatment cycle. Informed consent was obtained.

6.7 Treatment period

Starting on the first day of a menstrual period (cycle day 1), the assigned preparations were to be taken according to the normal scheme of use for oral contraceptives, 1 tablet daily at the same time each morning over 21 days, followed by a 7-day tablet-free interval. Each new pack was to be started on the same day of the week following the 7-day interval.

Subjects were instructed to keep a daily record of cycle control (bleeding days and intensity) and adverse events. They were also instructed to weigh themselves every second day and to record their weight on a weight chart.

Pregnancy was to be ruled out by means of a β-HCG test before every treatment cycle. Routine laboratory parameters (blood and urine) and progesterone were to be determined between the 18th and 21st days of tablet-taking. Blood pressure was to be taken 3 times at 2-3 minute intervals after 5 minutes of sitting down. Each subject was to be questioned in general terms regarding her cycle pattern and general well-being.

During cycles 1, 3, and 6, a subset of subjects had blood samples taken on days 11, 13, 1, 17, 19, and 21 for PK analysis.

At the end of the study, the gynecological examination, including breast examination and Pap smear, and routine laboratory parameters and progesterone were to be determined.

6.8 Statistical Procedures

A "probit regression line" was adapted to the dose groups of SH T 470 for the primary variable (rate of intermenstrual bleeding up to the third cycle).. Similar methods were employed for the secondary variables. The analytical results were to be presented as confidence intervals and other descriptive methods.

6.9 Evaluation Criteria

The primary variable was the rate of intermenstrual bleeding up to the third cycle. Secondary variables are tolerance and contraceptive reliability.

6.10 Withdrawals and compliance

Subjects were to be immediately discontinued from the study in the event of pregnancy, the first signs of venous inflammation or blood clots, before planned operations and on prolonged immobilization, with first-time occurrence of migraine headache or the more frequent occurrence of unusually severe headache, sudden disturbances of perception, motor disturbances, immoderate increase of blood pressure (above 140/90), repeated profuse break-through bleeding, occurrence of liver inflammation, jaundice, itching over the whole body, disturbances of bile drainage (cholestasis) and conspicuous liver function values, first-time occurrence of epileptic seizures, or unusual abdominal complaints which did not soon subside spontaneously, since in rare cases benign and in even rarer cases malignant changes of the liver which can occasionally lead to life-threatening hemorrhage in the abdominal cavity have been observed after the use of hormonal substances.

88% to 96% of subjects completed the study. One Yasmin™ subject, 3 SH T 470 I subjects, 2 SH T 470 K subjects, and 3 Microgynon® subjects discontinued due to adverse events.

6.11 Efficacy analysis

There were no pregnancies. 283 cycles were documented for Yasmin™, 283 cycles for SH T 470 K, 293 cycles for SH T 470 I, and 281 cycles for Microgynon®.

Because the start of tablet-taking was the first day of bleeding, the first cycle was shortened in all groups. From the 2nd cycle onwards, the cycle length in nearly all subjects ranged between 26 and 30 days.

Compared to previous cycles, the duration of withdrawal bleeding was shorter in all groups, although to a greater degree with SH T 470 K and Microgynon®. Compared to the pre-cycle, the intensity of flow became lighter with all treatments in up to half of the subjects.

Amenorrhea occurred most often with SH T 470 K and was otherwise comparable in all groups.

Intracyclic bleeding occurred most frequently at the start of treatment: 27%(n=13) of Yasmin™ users, 42% (n=21) of SH T 470 I users, 34% (n=17) of SH T 470 K users, and 35% (n=17) of Microgynon® users. With increasing duration of treatment, the bleeding rates dropped continuously. In cycle 6, only 7% (n=3) of Yasmin™ users, 18% (n=8) of SH T 470 I users, 19% (n=9) of SH T 470 K users, and 25% (n=11) Microgynon® users had intracyclic bleeding.

In all treatment groups, complaints of dysmenorrhea were less under treatment than in the precycle.

6.12 Safety analysis

2 subjects had CIII Pap smears at the pre-trial examination. At post-examination, the findings were CII. All other Pap smears were CII or lower. After treatment one ovarian cyst was diagnosed in the Microgynon® group.

Mean body weights fell slightly but not significantly with the DRSP preparations (most of all with SH T 470 K). The mean body weight in the Microgynon® group was virtually constant. In the DRSP groups, weight loss of more than 2 kg was recorded more often than weight gain of more than 2 kg. With Microgynon®, reports of weight gain of more than 2 kg were more frequent than weight loss of more than 2 kg.

There were no significant changes in mean systolic or diastolic blood pressure in any group, and no subject discontinued the study because of increased blood pressure.

Minor adverse events occurred at the onset of treatment but improved with continued treatment. The most frequently mentioned symptoms during treatment were nausea, headache, depressive mood, breast tension, and acne. The symptom acne was categorized by yes/no and not by number of lesions. It was reported most often with Microgynon® throughout the treatment period. With the DRSP preparations, acne was documented only at the beginning of the treatment. Acne occurred least often with Yasmin™.

Compared to baseline, mean plasma triglyceride levels increased slightly with all DRSP preparations and showed no change with Microgynon®. Mean cholesterol levels remained unchanged in all groups. Mean HDL-cholesterol levels increased with all DRSP preparations, but fell slightly with Microgynon®. Among DRSP preparations, the HDL levels increased with increasing EE dose. Mean LDL-cholesterol levels fell slightly with the DRSP preparations and remained unchanged with Microgynon® .

Progesterone concentrations were low in all 4 groups with no cyclical increase, consistent with suppression of ovulation.

General clinical chemistry parameters showed no significant changes and no differences between groups.

Mean trough levels of DRSP amounted to 10.9 ± 6.8 ng/ml in treatment cycle 1, 22.3 ± 5.8 in cycle 3, and 23.3 ± 7.4 in cycle 6. Steady state drug concentrations were achieved after the 10th tablet. Statistical analysis showed that the individual mean trough levels were not affected by the EE dose, but were affected by the cycles.

7.0 Clinical Study ME91013 (Report No. A892): Phase 2 Ovulation inhibition study

A multicenter, open-label randomized study of the dose-dependency of the ovulation-inhibitory effect under administration of dihydrospirorenone alone.

This phase 2 study was conducted with 48 subjects, 12 in each of four dosage groups, receiving 0.5, 1, 2, or 3 mg DRSP alone for 21 days (starting on the first day of menstrual bleeding) following a pretreatment cycle in which ovulation and peripheral parameters of cervical function were documented. One subject in the 0.5 mg group was discontinued because ovulation could not be proven in the pretreatment cycle, and one subject in the 3 mg group was discontinued because of discrepancies in pill taking and blood sampling.

Ovulation occurred once in each of the 0.5 mg, 1 mg, and 2 mg groups and in no subjects in the 3 mg group. Ovulation was diagnosed as 17β-estradiol > 50 pg/ml, LH peak, mid-FSH peak, increase in plasma progesterone, and follicular maturation (> 10 mm). The "rapid decrease of the maximum follicular diameter" following the "follicular maturation" was achieved for 2 cases, but could not be demonstrated for the case in the 2 mg group, since it was sonographically scanned only up to day 28, when the follicle still had a diameter of 28 mm.

Follicular maturation occurred in 6 (55%) of 11 subjects in the 0.5 mg group, 8 (67%) of 12 subjects in the 1 mg group, 5 (42%) of 12 subjects in the 2 mg group, and 1 (9%) of 11 subjects in the 3 mg group. No follicular activity was observed in 25% of the 0.5 mg group, 36% of the 1 mg group, 50% of the 2 mg group, and 91% of the 3 mg group.

Peripheral cycle parameters, including cervical score, spinnbarkeit, and crystallization (fern phenomenon) were diminished in all trial preparations, including all but one (from the 0.5 mg group) of the subjects that ovulated. The sponsor therefore suggests that DRSP acted not only by inhibition of ovulation but, possibly by establishing a cervical barrier, similar to the effects of a progestin-only pill.

SHBG remained virtually unchanged under all trial preparations.

Mean plasma renin activity (PRA) was higher under all preparations in comparison to the pre-cycle, except on day 20 with the 0.5 mg dose. In all groups, the PRA levels were decreased on day 25, four days after the last tablet intake, in comparison with the pre-cycle and with day 20 of active treatment.

Mean plasma aldosterone levels increased in a dose-dependent manner under the trial preparations. These levels also decreased after treatment and were slightly lower than on day 25 of the pretreatment cycle.

A dose-linear increase of the individual mean DRSP trough levels was demonstrated. On average, steady state concentrations of DRSP in serum were achieved on day 8 of the treatment cycle irrespective of the dose administered.

Conclusions

1. Adequate inhibition of ovulation was demonstrated only with the 2 mg and 3 mg doses of DRSP. This is consistent with earlier studies in which the threshold dose for ovulation inhibition was 2 mg. It also demonstrates that the 3 mg dose provides a safety margin and is the recommended dose for use as an oral contraceptive in combination with an estrogen
2. The aldosterone antagonistic effect of DRSP could be demonstrated for all dose ranges studied. Dose dependency was seen for the rise of plasma aldosterone but not for plasma renin activity.
3. DRSP exhibits dose-linear pharmacokinetics within the dose range studies.

8.0 Clinical Study Report No. 8036

Human pharmacological comparative study (parameters of renin-angiotensin-aldosterone system and anti-ovulatory effect): Dihydrospirorenone (DRSP) versus Cyproterone Acetate

12 female volunteers age 20-28 years were studied for 3 cycles. After a control cycle they were given a daily dose of 2 mg DRSP or 1 mg cyproterone acetate (CPA), an anti-androgen drug approved for marketing in Europe, on cycle days 5 to 25 for one cycle, followed by a medication-free follow-up cycle. The following parameters were monitored: basal temperature, morning body weight, blood pressure, heart rate, plasma concentration of sodium, potassium, cortisol, aldosterone, renin activity, estradiol, progesterone, FSH, LH, prolactin, drug concentration, differential blood count, urinalysis, and 24-hour urinary sodium, potassium and aldosterone-18-glucuronide.

Headache, abdominal pain, nausea and vomiting occurred in a few cases. All symptoms were mild. Breast tension occurred with similar incidence and intensity in both groups. Ovulation was inhibited in all 6 DRSP subjects. 1 CPA subject ovulated.

Under DRSP, sodium and potassium excretion increased in the first half of the cycle and slightly declined in the 2nd half. Under CPA, there was an insignificant rise in sodium excretion in the first half of the cycle and no influence at all on potassium excretion. Under DRSP there was also a significant increase in the renin activity, a clear rise in plasma aldosterone, and in the excretion of aldosterone-18-glucuronide. These parameters were not influenced by CPA. There was no change in plasma cortisol with either medication. No significant effect was observed on routine laboratory parameters, blood count and differential, blood pressure, or heart rate with either medication. In the second half of the cycle a weight gain of 0.3 kg occurred with DRSP and 0.5 kg with CPA.

Conclusion
The sponsor concludes that these data show a clear aldosterone-antagonist effect of DRSP.

9.0 Clinical Study 89015 (Report No. 9370)

Placebo controlled single blind group comparison (N=6 per group) of systemic tolerability, the influence on hormonal regulation and of drug plasma levels after a single oral administration of 10, 25, 50, and 100 mg of drospirenone (aqueous microcrystalline suspension) to young healthy male volunteers

The trial was a single blind interindividual comparison with four increasing dosages of DRSP and placebo in 30 men ages 22 to 41. Four dosages of DRSP, 10, 25, 50, and 100 mg, were administered as a microcrystalline suspension in water. Clinical-chemical, hematological, and coagulation parameters, drug and hormone concentrations, EKG, blood pressure, and heart rate were monitored, and aldosterone metabolites were measured in 24-hour urine.

No clinically relevant effect was found in standard safety parameters. A slight decrease of the albumin fraction and simultaneous increase in the α_2 and β fractions was seen following administration of the 100 mg dose. A slight decrease in serum sodium was seen 8 hours after administration of the 50 and 100 mg doses. All values were within normal clinical limits.

With 100 mg DRSP, resting renin concentration in serum (and after active orthostasis) increased. 10 mg DRSP increased the resting aldosterone concentration in serum and after active orthostasis 23 hours after administration.

DRSP caused a dose-dependent inhibition of FSH, LH, and testosterone secretion.

The concentration of the active ingredient in the plasma increased approximately proportionally to the dose in the range of 25 to 100 mg DRSP.

Conclusions

1. Tolerability of DRSP in single doses up to 100 mg was good.
2. 100 mg DRSP led in the RAA system to a reactive increase in the serum renin concentration after a single administration. An increase in serum aldosterone concentration was observed only following a single administration of 10 mg DRSP.
3. DRSP inhibits the hormones FSH, LH, and testosterone dependent on dose.
4. Plasma levels of DRSP were dose-proportional in the dose range of 25 to 100 mg.

10.0 Clinical Study No. 89092 (Report No. 9371)

Investigation of the tolerability and influence on hormonal regulation during a 5-day s.i.d. treatment with 10 mg drospirenone in 6 healthy postmenopausal women

This trial was a randomized, single blind, interindividual group comparison of 10 mg micronized drospirenone compared to placebo administered in capsule form on 5 consecutive days to 12 healthy postmenopausal volunteers aged 49-73 years. The following parameters were monitored from 3 days before through 5 days after first substance intake: glucose tolerance, EKG, blood pressure, heart rate, clinical chemistry, hematological, and blood clotting parameters, FSH, LH, prolactin, TSH, testosterone, DHEAS, androstenedione, cortisol, aldosterone, renin, drospirenone concentration in plasma, and excretion of aldosterone metabolites in 24-hour urine.

No significant changes were observed in standard safety parameters. Resting plasma concentrations of aldosterone and renin after 5 days administration of 10 mg DRSP were only slightly higher than with placebo. Excretion of aldosterone metabolites increased somewhat more after DRSP than placebo. A slight decrease in LH concentrations in serum was seen. No other hormone or carbohydrate metabolism parameters were influenced.

Conclusions

- Treatment with 10 mg DRSP for 5 days was well tolerated.
- In terms of the RAA system, 10 mg DRSP for 5 days led to a slight increase in renin and aldosterone concentrations in plasma, and to a corresponding increase in aldosterone metabolites in urine.
- The glucose tolerance test was not influenced by DRSP.
- The antigonadotropic effect of DRSP was only slightly pronounced after administration of 10 mg DRSP for 5 days.

11.0 Clinical Study Report No. 5824

Sexual endocrinological effects of placebo, ZK 94 679, spironolactone and ZK 30 595 (DRSP) on the LH and testosterone level in healthy young males

28 healthy male volunteers were randomly assigned to one of the following treatments:

1. 1st day placebo, 2nd-4th day placebo
2. 1st day placebo, 2nd-4th day 80 mg ZK 94 679 (Metispirone)
3. 1st day placebo, 2nd-4th day 320 mg Spironolactone
4. 1st day placebo, 2nd-4th day 10 mg ZK 30 595 (Spiromethen/DRSP)

Changes of LH and Testosterone were monitored from the first to each of the next test days. All test subjects tolerated the treatments without side effects. The changes in LH and testosterone in the ZK 94 679 and spironolactone group did not differ from the placebo group. ZK 30 595/DRSP suppressed testosterone on day 3 and 4 and LH on day 4.

12.0 Clinical Study Report No. 8644 (Supplement to study 87 004)

The influence of ZK 30 595 (DRSP) on the renin-angiotensin-aldosterone system (supplement to study 87 004)

12 women volunteers aged 22 to 32 years were randomized to 2 mg DRSP and placebo. All were given a standardized amount of sodium and potassium in the diet for 10 days, the 3rd to 12th day of the cycle. Tablet ingestion was from the 6th to 11th day of the study. The following parameters were monitored: plasma concentrations of Na, K, osmolality, renin substrate, renin activity, aldosterone, vasopressin, and creatinine, urinary volume, Na, K, osmolality, aldosterone-18-glucuronide, creatinine clearance, body weight, blood pressure, and heart rate.

- Serum sodium decreased slightly in the DRSP group and increased slightly in the placebo group, but not significantly.
- There were no significant changes in serum potassium.
- Plasma osmolality fell significantly with DRSP and increased significantly with placebo.
- Plasma renin activity increased significantly in orthostasis in both groups, but to a greater extent with DRSP.
- Plasma aldosterone was temporarily higher with DRSP.
- Plasma vasopressin was temporarily increased in both groups, but to a greater extent with placebo.
- Urinary volume increased temporarily with DRSP and tended to fall with placebo.
- Sodium elimination increased by an average of 24% with DRSP and was not affected with placebo.
- Potassium elimination was lower than expected in both groups with no significant difference between groups.
- Urine osmolality was higher in the DRSP group.
- The aldosterone excretion rate was higher with DRSP.
- Creatinine clearance increased slightly with DRSP and fell slightly with placebo.
- DRSP subjects complained more often about tiredness. One DRSP subject had increased thirst and 2 had both increased thirst and appetite. There were no differences between groups with respect to headaches, nausea, or weight change. There were no significant changes in blood pressure or heart rate with DRSP.

13.0 Clinical Study Report No. 4417

Human pharmacological study of SK K 399 A-D (ZK 30 595), a new aldosterone antagonist, in healthy volunteers

The aldosterone antagonistic action of SH K 399 A-D (DRSP) was investigated in comparison with spironolactone following oral administration to 5 healthy male volunteers. A continuous IV infusion of aldosterone was carried out for 6 hours. The study preparation was given orally 2 hours before the beginning of the infusion. Urine was collected hourly during the infusion and 2 hours thereafter. Each volunteer took part in random order in 8 individual investigations at intervals of at least 1 week:

1. Baseline examination without any treatment
2. Baseline examination with aldosterone alone
3. to 5. Three examinations under treatment with aldosterone and a dose of spironolactone
6. to 8. Three further examinations under treatment with aldosterone and a dose of DRSP

The following doses were administered: 10, 40, and 160 mg DRSP, and 40, 160, and 640 mg spironolactone. Urine Na/K ratios served as the primary basis of evaluation.

Results:

1. With aldosterone alone, the urine Na concentrations and Na/K ratios decreased significantly, and the K concentrations increased.
2. Compared to aldosterone alone, Na concentrations and Na/K ratios increased both with spironolactone and DRSP, whereas the K concentrations decreased in the last 3-4 hours of the study only with the higher doses.

3. DRSP had an average potency 6.6 times higher than spironolactone.
4. The relative potency determined in humans was the same as that found in earlier studies on adrenalectomized rats, in comparison with spironolactone (mean 7.0).
5. The ED_{50} (50% inhibition of the action of exogenic aldosterone) for DRSP and spironolactone were 0.17 and 1.6 mg/kg body weight, respectively.

14.0 Clinical Study 89099 (Report No. 9693)

Investigation of hormonal and metabolic parameters following oral administration of ZK 30 595 in combination with ethinyl estradiol (EE)

This is an open-label, randomized trial with 52 female volunteers ages 20 to 35 years, taking DRSP 2 mg/EE 0.030 mg or DRSP 3 mg/EE 0.030 mg on cycle days 1-21, including 1 pretreatment cycle, 3 treatment cycles and a follow-up phase. The following parameters were monitored: LH, FSH, 17β-estradiol, progesterone, cervical score, spinnbarkeit, fern phenomenon, ultrasound for ovarian follicles, SHGB, CBG, prolactin, total testosterone, androstenedione, DHEA-S, glucose, triglycerides, cholesterol, HDL, LDL, blood pressure, heart rate, body weight, and cycle control.

Results
- LH and FSH were clearly suppressed with both trial preparations.
- Estradiol and progesterone were greatly decreased for all but 3 subjects in the 2 mg DRSP group.
- Follicular ripening occurred in several subjects in both groups. 3 ovulations were diagnosed with the 2 mg DRSP group, 1 described as equivocal and another as pill taking error. The difference in occurrence of ovulation during the treatment cycles is not statistically significant.
- Spinnbarkeit and ferning of the cervical mucus were greatly reduced in both groups.
- Prolactin increased minimally, and SHBG and CBG increased distinctly in both groups.
- Triglycerides and HDL increased in both groups, and LDL decreased. Total cholesterol was unchanged.
- Glucose tolerance was unchanged or slightly decreased.
- Testosterone, androstenedione and DHEA-S decreased minimally.
- In the follow-up phase, 19 of 23 subjects in the 2 mg DRSP group had ovulatory cycles, and 4 displayed a luteinized unruptured follicle (LUF) syndrome. 20 of 23 subjects in the 3 mg DRSP group had ovulatory cycles in the follow-up phase, 1 displayed follicular ripening, and 2 displayed LUF syndrome.

Conclusions
- The 2 trial preparations were tolerated equally well.
- No negative metabolic effects were observed. HDL increased
- These results confirm that 2 mg DRSP is the threshold for ovulation inhibition.
- Whereas the 3 mg DRSP preparation inhibited ovulation in all cases, it is expected that contraceptive reliability with the 3 mg preparation will be greater than that of the 2 mg preparation.

15.0 Clinical Study 90030 (Report 9970)

Study of the influence of SH T 470 F (Yasmin™), SH T 470 I, and SH T 470 K on parameters of the renin-angiotensin-aldosterone system (RAAS), electrolyte metabolism and lipid and carbohydrate metabolism

3 preparations of 3mg DRSP which differ in the dose of estrogen (30, 20, 15 µg EE) were studied in comparison to Microgynon® over 6 months in a total of 80 female volunteers of ages 18 to 34 years in a double blind randomized clinical study. The study included 1 pretreatment cycle, 6 treatment cycles and a follow-up of 28 days. The following parameters were monitored: plasma renin substrate, plasma renin activity, plasma aldosterone, Na, K, creatinine, ANF, triglycerides, cholesterol, HDL, LDL, and carbohydrate metabolism, tolerance, cycle control, body weight, and blood pressure.

Results

- Plasma renin substrate concentrations increased as an expression of estrogenic stimulation under all 4 preparations.
- Plasma renin activity and plasma aldosterone increased as an expression of the aldosterone-antagonistic effect with the DRSP preparations.
- Na, K and creatinine remained unchanged with all preparations.
- ANF increased with all preparations.
- Triglyceride and HDL levels increased significantly with the DRSP preparations in contrast to Microgynon®. Total cholesterol was largely unchanged in all treatment groups. LDL decreased slightly with the DRSP preparations but increased slightly with Microgynon®.
- Oral glucose tolerance remained unchanged or slightly decreased.
- Adverse events were observed more frequently with Microgynon® than with the DRSP preparations.
- Blood pressure and body weight remained constant or slightly decreased with the DRSP preparations but showed a slight increase with Microgynon®.
- Cycle control was good with all preparations but was best with 3 mg DRSP/30 µg EE.

Conclusions

- All DRSP preparations show a distinct aldosterone-antagonistic effect, with a greater increase in plasma aldosterone level than with Microgynon®.
- An effect on potassium and water balance is unlikely.
- Blood pressure and body weight remained constant or slightly decreased.
- No negative metabolic effects were observed except a slight increase in triglycerides. HDL was increased.
- All trial preparations were tolerated equally well, and adverse events were observed more often with Microgynon®.
- Cycle control was best with 3 mg DRSP/30 µg EE.

16.0 Clinical Study 89110 (Report No. 9692)

Clinical data, parameters of the renin-angiotensis-aldosterone system (RAAS), and electrolytes following oral administration of ZK 30 595 in combination with ethinyl estradiol (EE)

The study was an open-label, randomized trial of 4 months duration (1 pretreatment cycle, 3 treatment cycles) in a total of 70 female volunteers aged between 19 and 34 years taking either 2 mg DRSP/30 µg EE or 3 mg DRSP/30 µg EE. The following parameters were monitored: plasma renin substrate, plasma renin activity, plasma aldosterone, serum sodium, serum potassium, tolerance, body weight, blood pressure, and heart rate.

Results

- Plasma renin substrate concentration increased in both groups.
- Plasma renin activity and plasma aldosterone increased in both groups . However, a statistically significant difference was seen only in the first cycle and no longer in the 3rd cycle of treatment
- Serum sodium and potassium remained unchanged in both groups.
- Blood pressure, heart rate, and body weight remained constant in the majority of cases.
- Cycle control was good after the first cycle
- Clinically, there were no significant differences between the two groups.

Conclusion

- A distinct aldosterone-antagonistic effect was seen with both preparations. Plasma renin activity and plasma aldosterone were higher with 3mg DRSP than with 2 mg DRSP in the first cycle but no longer in the 3rd cycle.
- No influence in electrolytes was observed, indicating that an effect on water balance is unlikely.
- Both preparations were tolerated equally well.

17.0 Clinical Study 92038 (Report No. AE91): Phase 3, Hemostasis

Hemostasis, "Open-labeled, randomized study of the influence of the oral contraceptives SH T 470 FA (Yasmin™) and SH T 470 IA of hemostasis in comparison with Marvelon®"

The study was an open label randomized trial in 75 healthy women aged 18 to 35 years, taking 3 mg DRSP/30 µg EE (Yasmin™/SH T 470 FA) or 3 mg DRSP/ 20 µg EE (SH T 470 IA) or the commercially available comparator product Marvelon® (30 µg EE + 150 µg desogestrel) for 6 cycles. The subjects were monitored for contraceptive effectiveness, cycle control, blood pressure, body weight, adverse events, general clinico-chemical parameters, cervical cytology, and the following hemostatic parameters:

- Quick and PTT
- procoagulatory parameters
  fibrinogen = factor I
  factor VII activity
  thrombin-antithrombin III complex = TAT
- anticoagulatory parameters
  antithrombin III = AT III
  protein C antigen
  protein S antigen
  protein S activity
- fibrinolytic parameters
  tissue-type plasminogen activator t-PA antigen
  tissue-type plasminogen activator t-PA activity
- anti-fibrinolytic parameters
  plasminogen activator inhibitor PAI 1 antigen
  plasminogen activator inhibitor PAI 1 activity
- parameter of fibrin turnover
  DRSP-dimeric fibrin cleavage product

Results

No pregnancy occurred during the study. The bleeding pattern was best with Yasmin™. Intracyclic bleeding was reported most often with SH T 470 IA. There were no serious adverse events and no significant changes in clinico-chemical parameters. Adverse events were reported by 44% of Yasmin™ subjects, 48% of Marvelon® subjects, and 56% of SH T 470 IA subjects.

One subject in the SH T 470 IA group discontinued the study because of a severe allergic reaction over the whole body which the investigator considered unlikely to be related to the study preparation.

The changes in general hematological parameters, with few exceptions, were within the reference range. Individual values outside the reference range were measured sporadically and assessed by the investigator as of no clinical relevance. No negative trends were seen with regard to the changes.

- Hematocrit values fell slightly with all treatments and returned to baseline by the 3rd follow-up week. There were no differences between groups.
- Platelets increased under all treatments and close to baseline at the 3rd follow-up week. Differences between treatments were not significant.
- Quick (PT) fell slightly with all treatments and returned to baseline in the 1st follow-up week. Differences between treatment groups were not significant.
- PTT was unchanged with all treatments.

With regard to hemostasis there were no statistically significant differences between the treatments. The changes were minimal and did result in compensatory changes in the dynamic balance between coagulation and fibrinolysis.

- Fibrinogen values increased under all treatments and reached their maximum value in the 3rd cycle. These values did not return to baseline at the follow-up. At the end of treatment the median changes of

fibrinogen were + 31% in the SH T 470 IA group, + 50% in the Marvelon® group and + 40% in the Yasmin™ group.

- Factor VII activity increased with all treatments. The median relative change to the 6th cycle was + 68% with Yasmin™, + 59% with SH T 470 IA, and + 54% with Marvelon® .
- Thrombin-antithrombin III complex (TAT) increased in all groups, reached a maximum after the 3rd cycle, and returned quickly to baseline in the follow-up period. The median relative changes from baseline to the 6th cycle were + 41% with Yasmin™, + 0.2% with SH T 470 IA, and + 72% with Marvelon®. These changes were not statistically different between groups because of unexpectedly wide fluctuations during treatment and the relatively small number of subjects.
- Antithrombin III (AT III) values showed no remarkable changes, and the treatment groups were not significantly different.
- Protein C antigen increased with no significant difference between groups (+ 28% with Yasmin™, +17% with SH T 470 IA, and +16% with Marvelon®.)
- Protein S antigen decreased slightly in the first cycle and returned to baseline in the first follow-up week. Median changes were not significantly different between groups (- 27% with Yasmin™, - 16% with SH T 470 IA, and – 26% with Marvelon®).
- Protein S activity showed a stepwise decrease with all treatments. Compared to baseline, the median relative changes were – 35% with Yasmin™, - 25% with SH T 470 IA, and – 42% with Marvelon®. Abnormal values for Protein S antigen and Protein S activity were found in all 3 groups but were assessed as of no clinical relevance by the investigator.
- Tissue-type plasminogen activator (t-PA) decreased slightly in all groups and returned to baseline during follow-up with no significant difference between groups (- 16% with Yasmin™, - 23 % with SH T 470 IA, and – 31% with Marvelon®).
- Tissue-type plasminogen activator (t-PA) activity increased in all groups and returned close to baseline in the follow-up with no significant differences between groups (+ 81% with Yasmin™, +35% with SH T 470 IA, and + 57% with Marvelon®).
- Plasminogen activator inhibitor (PAI 1) antigen decreased in all groups. Only the SH T 470 IA group returned to baseline in the follow-up. The changes from baseline to the 6th cycle were not significantly different between groups. (- 71% with Yasmin™, - 73% with Marvelon® , and – 60% with SH T 470 IA).
- Plasminogen activator inhibitor (PAI 1) activity decreased in all groups and returned to baseline during follow-up. The median change from baseline to end of treatment was not significantly different between groups (- 9% with Yasmin™, -12% with SH T 470 IA, and – 19% with Marvelon®).
- DRSP-dimeric fibrin cleavage product increased in all groups and remained above baseline at the 3rd follow-up week. There were no significant differences between groups in changes from baseline to end of treatment (+ 168% with Yasmin™, + 89% with SH T 470 IA, and + 148% with Marvelon®).

Conclusions

The data describe a double-activation mechanism of both the coagulatory and the fibrinolytic activity with all 3 preparations. There was no disturbance of hemostatic balance. The changes were within the range expected for low dose oral contraceptives and of no clinical relevance in normal individuals. Fibrinogen was significantly more unfavorably changed with Marvelon® (+ 50%) compared to SH T 470 IA (+ 31%). Protein S was less impaired with SH T 470 IA (- 25%) than with Marvelon® (- 42%) or Yasmin™ (- 35%).

18.0 Clinical Study 92083 (Report No. AG44): Phase 3, Hemostasis and RAAS

Unicenter, open-labeled, randomized study on the influence of SH T 470 FA (Yasmin™)on parameters of the hemostatic system and on parameters of the renin-angiotensin-aldosterone system (RAAS) in comparison with Marvelon® in 60 healthy women over 13 cycles.

The study was conducted at one center as an open, randomized study. Two independent groups of 30 volunteers were recruited from healthy women seeking contraception. The study consisted of one medication-free pre-cycle after a washout phase of one cycle, 13 treatment cycles, and a follow-up phase of

28 days without medication. Volunteers were randomly assigned to receive either SH T 470 FA (Yasmin™) or Marvelon® . Both were taken for 21 days followed by a 7-day tablet-free period for 13 cycles.

All subjects were monitored for contraceptive effectiveness, cycle control, and safety parameters, including general hematological (hematocrit and platelets) and general (PT/Quick, and aPTT) and special hemostatic parameters (fibrinogen/factor I, factor VII activity, thrombin-antithrombin III complex/TAT, antithrombin III/ AT III, Protein C, Protein S antigen and activity, tissue-type plasminogen activator/t-PA antigen and activity, plasminogen activator inhibitor/PAI 1 antigen and activity, and DRSP-dimeric fibrin cleavage product) and RAAS parameters (plasma renin substrate, plasma renin activity, and plasma aldosterone). β-HCG testing was done before the first tablet intake and then only with absence of monthly withdrawal bleeding and was not required at the final visit.

Results

3(13%) Yasmin™ users and 2 (7%) Marvelon® users discontinued the study prematurely.

One pregnancy was reported (9) in a Marvelon® user. This 22 year old white woman 170 cm tall and weighing 75 kg started taking the study medication on June 12, 1993. In the 7th cycle, she experienced vomiting from November 25 to December 5. She did not have withdrawal at the end of the cycle and pregnancy was diagnosed on January 3. Her EDC was August 26, and she delivered a healthy baby girl on August 22.

One Yasmin™ user(35) missed her menstrual period and started the pills blindly on July 22, 1993. After taking several pills she was found to be pregnant on August 12, 1993. Her last menses was June 3, and conception was believed to have occurred on July 15. She had an abortion on September 9.

In cycles 2-6, 38% of Yasmin™ users and 40% of Marvelon® users reported intracyclic bleeding. In cycles 2-13, 55% of Yasmin™ and 53% of Marvelon® users reported intracyclic bleeding. Most bleeding with both treatments was scanty, and only in single cases was it normal/excessive.

Adverse events were reported at least once during the study by 19 Yasmin™ users and 12 Marvelon® users. Only 1 serious adverse event was reported, an epileptic seizure in cycle 9 in a Marvelon® user.

In both groups, the changes in general hematological and hemostatic parameters were within the reference range. The sporadic measurements outside the reference range were assessed by the investigator as of no clinical relevance.

- Hematocrit values decreased in both groups, more under Marvelon®. Relative changes at cycles 3, 6, and 13: with Yasmin™ -0.52, -0.54, -1.7%, with Marvelon® -3.9, -4.5, -5.9%
- Platelet counts increased in both groups, with no significant difference in the median changes. Median relative changes in cycles 3, 9, and 13: with Yasmin™ +1.2, +3.6, +5.3%, and with Marvelon® +2.1, +0.7, -4.0%. The upper normal range was not reached in any case.
- Quick (PT) decreased in both groups, more with Marvelon® , and returned close to baseline in follow-up. Median relative changes in cycles 3, 6, and 13: With Yasmin™ - 0.4, -4.0, -2.4%, and with Marvelon® -3.6, -5.0, -3.5%. These fluctuations can be regarded as physiological. Only one subject had an abnormally low value (9.5 sec) in the pre-cycle.
- PTT increased in both groups. Median relative changes in cycles 3, 9, and 13: with Yasmin™ -2.0, +13.7, +14.9%, and with Marvelon® -2.8, +12.2, +12.4%. It is unclear whether these changes are of clinical relevance.

Changes in the special hemostatic parameters, with few exceptions, were within the reference range. Individual values outside the reference range were of no clinical relevance. No negative trends were demonstrable with regard to hemostatic balance. For both preparations a slight increase of protein C antigen and a more pronounced decrease of AT III and protein S was found, a pattern also seen with other OCs.

A distinct aldosterone-antagonistic effect for Yasmin™ was observed as expected. This effect was not seen for Marvelon®.

- Median plasma renin substrate (PRS) levels increased distinctly in both groups as expected with estrogen stimulation, although more with Marvelon® . The median absolute and relative changes were statistically different between treatments in cycles 3 and 9 but in cycle 13 only the median relative changes were statistically different. Relative changes in PRS in cycles 3, 9, and 13: with Yasmin™ +280%, +264%, and +231%, with Marvelon® , +338%, +351%, and +314%.
- Plasma renin activity increased distinctly with Yasmin™ and slightly increased with Marvelon® . In both groups the values returned close to baseline. The median absolute and relative changes were statistically different only in cycle 3. Relative changes of plasma renin activity in cycles 3, 9, and 13: with Yasmin™ , +155%, +80%, and +86%, with Marvelon® . +17%, +39%, and +42%.
- Plasma aldosterone levels increased distinctly with Yasmin™ and reached their maximum in cycle 3, while with Marvelon® no remarkable increase was seen. The median absolute and relative changes were statistically different between groups in all cycles. Median relative changes to cycles 3, 9, and 13: With Yasmin™ +184%, +89% and +114%, and with Marvelon®, +19%, +10%, and +1.5%.
- Serum sodium and potassium levels remained unchanged.

Conclusions

1. The data on hemostatic parameters show a double-activation mechanism of both the coagulatory and fibrinolytic activity with both preparations. No disturbance of hemostatic balance was found. The magnitude of changes was within the range expected for low dose OCs and of no clinical relevance in normal individuals.
2. A distinct aldosterone-antagonistic effect was seen with Yasmin™ .
3. With regard to cycle control and tolerance, the differences between preparations were small.

19.0 Clinical Study 93050 (Report No. AL84): Phase 3, Lipid and Carbohydrate Study

Single-center, open, randomized study on the influence of SH T 470 FA on lipid and carbohydrate metabolism in comparison to Marvelon® in 60 healthy women under 13 cycles of contraceptive use

A total of 60 healthy women between 18 and 35 years old were randomized, 30 per treatment, to receive either SH T 470 FA (Yasmin™) or Marvelon® for 21 days, followed by a 7-day tablet-free interval for 13 cycles of use following a 2-month washout period with no sex hormones.

25 subjects were valid for efficacy in each group. The subjects were monitored for contraceptive effectiveness, cycle control, and safety parameters, including general clinico-chemical and hematological parameters, parameters of lipid and carbohydrate metabolism, cervical cytology, adverse events, blood pressure, heart rate, and general and gynecological examination.

Primary target variables were HDL-, HDL_2-, HDL_3-, LDL-cholesterol and the areas under the curve (AUC) for glucose and insulin in the oral glucose tolerance test (oGTT) and intravenous glucose tolerance test (ivGTT). [The ivGTT was performed in a subset of 8 subjects from each group.] Secondary objectives were total cholesterol, total triglycerides, total phospholipids, HDL-cholesterol, HDL-triglycerides, HDL-phospholipids, HDL_2-cholesterol, HDL_2-triglycerides, HDL_2-phospholipids, HDL_3-cholesterol, HDL_3-triglycerides, HDL_3-phospholipids, LDL-cholesterol, LDL-triglycerides, LDL-phospholipids, VLDL-cholesterol, VLDL-triglycerides, VLDL-phospholipids, apolipoprotein AI (ApoAI), apolipoprotein AII (ApoAII), apolipoprotein B (ApoB), apolipoprotein E (ApoE), lipoprotein A (Lp(a)).

Results

1. No pregnancy occurred in either group. Only 1 Marvelon® subject used condoms for AIDS prophylaxis.
2. Both preparations were found to be effective for cycle control.
3. Amenorrhea and dysmenorrhea were somewhat less with Yasmin™ than with Marvelon® .

4. There were no statistically significant differences between groups with regard to the primary target variables. However, an increase in mean HDL-, HDL_2-, and HDL_3-cholesterol was seen in both groups.
5. There was little effect on carbohydrate metabolism with either preparation.
6. One serious adverse event occurred in each group, both appendectomy, unrelated to the study drug.
7. One Yasmin™ subject withdrew from the study due to an adverse event (mastodynia). Breast pain was the only event seen conspicuously more frequently in the Yasmin™ group (5 subjects vs. 1 in the Marvelon® group).
8. Mean body weight was slightly decreased in most Yasmin™ cycles and slightly increased in every Marvelon® cycle.
9. No significant changes were seen in blood pressure or clinical chemistry or hematology parameters.

Lipid Profiles

Parameter (Reference range in mg/dl)	**Yasmin™** Median values in mg/dl				**Marvelon®** Median values in mg/dl (n)			
	Cycle 0 N=25	Cycle 3 N=24	Cycle 6 N=23	Cycle 13 N=25	Cycle 0 N=25	Cycle 3 N=25	Cycle 6 N=25	Cycle 13 N=25
Total cholesterol (150-250)	169.0	194.0	178.0	181.0	157.0	178.0	167.0	173.0
HDL-cholesterol (>45)	57.0	66.0	66.0	61.0	53.0	59.0	54.0	55.0
HDL_2-cholesterol (>12)	25.6	27.3	27.1	24.7	23.2	24.2	22.8	20.7
HDL_3-cholesterol (>20)	25.5	30.0	29.4	28.7	22.3	26.5	26.1	25.6
LDL-cholesterol (<160)	69.7	71.7	70.6	75.2	70.9	77.0	77.8	77.4
VLDL-cholesterol (<75)	22.1	25.0	22.1	30.7	20.4	22.1	25.8	23.9
Total triglycerides (≤160)	63.0	96.5	103.0	113.0	56.0	97.0	84.0	85.0
HDL-triglycerides (<35)	17.0	25.5	24.0	25.0	17.0	27.0	22.0	20.0
HDL_2-triglycerides (<12)	4.5	7.8	7.6	6.6	4.9	7.2	7.0	6.1
HDL_3-triglycerides (<24)	6.6	9.9	9.8	10.3	5.9	9.2	9.2	9.9
LDL-triglycerides (<30)	9.5	15.1	17.8	16.3	10.3	15.4	14.9	16.6
VLDL-triglycerides (<100)	32.1	49.9	52.1	57.6	23.3	47.3	38.4	44.3
Total phospholipids (140-300)	197.0	235.5	222.0	226.0	184.0	216.0	207.0	202.0
HDL-phospholipids (<170)	111.0	132.0	137.0	126.0	96.0	126.0	117.0	122.0
HDL_2-phospholipids (<100)	38.9	46.2	46.0	41.2	37.2	41.3	41.3	38.6
HDL_3-phospholipids (<100)	38.9	58.4	58.4	55.5	39.9	52.3	51.7	51.8
LDL-phospholipids (<60)	49.7	53.2	51.6	50.9	49.9	56.9	50.5	54.3
VLDL-phospholipids (<30)	20.3	23.7	24.9	31.2	17.1	23.5	24.4	22.4

Apolipoprotein AI (100-210)	170.0	231.5	236.0	232.0	158.0	214.0	205.0	214.0
Apolipoprotein AII (35-55)	37.0	53.5	52.0	53.0	35.0	48.0	43.0	49.0
Apolipoprotein B (55-120)	94.0	126.0	118.0	113.0	95.0	114.0	116.0	109.0
Apolipoprotein E (1.8-6.7)	3.4	3.0	2.8	2.8	3.3	2.6	2.6	2.8
Lipoprotein (a) (<30)	17.5	13.8	19.9	9.2	8.6	8.1	6.3	8.4

Oral Glucose Tolerance Test
(mean values)

Parameter	Treatment group	Cycle	Time to reach Maximum	Highest mean value recorded	Clinical Reference Range	Time to return to baseline
Glucose	Yasmin™	0	30 min	114.2 mg/dl	80-150 mg/dl	150-180 min
		6	30 min	132.4 mg/dl	80-150 mg/dl	180 min
		13	30 min	135.9 mg/dl	80-150 mg/dl	180 min
	Marvelon®	0	30 min	125.1 mg/dl	80-150 mg/dl	>180 min
		6	60 min	121.3 mg/dl	55-150 mg/dl	>180 min
		13	30 min	127.4 mg/dl	80-150 mg/dl	>180 min
Insulin	Yasmin™	0	60 min	53.9 µU/ml	15-100 µU/ml	>180 min
		6	30 min	69.2 µU/ml	15-90 µU/ml	>180 min
		13	30 min	58.2 µU/ml	15-90 µU/ml	>180 min
	Marvelon®	0	30 min	54.2 µU/ml	15-90 µU/ml	>180 min
		6	60 min	70.6 µU/ml	15-100 µU/ml	>180 min
		13	60 min	55.6 µU/ml	15-100 µU/ml	>180 min
C-Peptide	Yasmin™	0	60 min	2492.1 pmol/ml	1600-3300 pmol/ml	>180 min
		6	60 min	2665.1 pmol/ml	1600-3300 pmol/ml	>180 min
		13	90 min	2400.4 pmol/ml	1450-3150 pmol/ml	>180 min
	Marvelon®	0	60 min	2478.3 pmol/ml	1600-3300 pmol/ml	>180 min
		6	60 min	2647.8 pmol/ml	1600-3300 pmol/ml	>180 min
		13	60 min	2391.7 pmol/ml	1600-3300 pmol/ml	>180 min
Free Fatty Acids	Yasmin™	0	120 min	84.4 µEq/l	10-210 µEq/l	>180 min
		6	150 min	95.8 µEq/l	10-200 µEq/l	>180 min
		13	150 min	86.9 µEq/l	10-200 µEq/l	>180 min
	Marvelon®	0	120 min	85.1 µEq/l	10-210 µEq/l	>180 min
		6	150 min	99.8 µEq/l	10-200 µEq/l	>180 min
		13	150 min	79.2 µEq/l	10-200 µEq/l	>180 min

The ivGTT confirmed the general result of the oGTT: no pronounced difference between the two treatment groups could be found. All changes of mean plasma glucose, insulin and C-peptide levels lay within normal range except for a few individual outliers.

Conclusions

There were no statistically significant differences between the two treatment groups with regard to the primary target variables HDL-, HDL_2-, and LDL-cholesterol. An increase of HDL-, HDL_2 and HDL_3-cholesterol was seen with both preparations. Both preparations had little effect on carbohydrate metabolism as assessed by oGTT and ivGTT. The changes observed were small and well compensated and the minor effects of both treatments on carbohydrate metabolism are not considered clinically important.

Reviewer's comments

1. **4 Yasmin™ subjects (and 1 Marvelon® subject) reported breast pain as an adverse event (3 as premenstrual breast tension). One discontinued the study prematurely because of breast pain.**
2. **2 Yasmin™ subjects (and no Marvelon® subject) reported depression as an adverse event**
3. **2 Yasmin™ subjects (and 1 Marvelon® subject) reported acne as an adverse event. One of them had acne prior to the study**
4. **An 18 year old Yasmin™ subject had normal liver parameters at baseline with ASAT/GOT of 18 (normal range 0-30 U/L) and ALAT/GPT 12 (normal range 0-30 U/L). At cycle 3, ASAT/GOT was elevated to >3x ULN at 121 U/L and ALAT/GPT was mildly elevated at 45 U/L. Both values returned to normal by cycle 13, with ASAT/GOT 13 U/L and ALAT/GPT 9 U/L. All bilirubin values were normal. LDH was also elevated at cycle 3, with a value of 720 U/L (normal range 200-380 U/L), and was normal at baseline and at cycle 13. Her only adverse event was severe breast pain.**
5. **A 19 year old Yasmin™ subject had normal transaminases at baseline with ASAT/GOT 24 U/L and ALAT/GPT 27 U/L. At cycle 3 both values were elevated >3xULN with ASAT/GOT 165 U/L and ALAT/GPT 113 U/L. Both values had returned to normal by cycle 13, with ASAT/GOT 20 U/L and ALAT/GPT 14 U/L. All bilirubin values were normal. LDH was also elevated only at cycle 3 (641 U/L). Her only adverse events were moderate acne and severe breast pain.**
6. **3 Yasmin™ subjects had Potassium levels above the upper normal limit (normal range 3.8-5.2 mmol/l). The maximum value was 5.7 mmol/l. 2 Marvelon® subjects had potassium levels above the upper normal limit with a maximum value of 6.5 mm/l.**

20.0 Clinical Study 94151 (Report No. AM90): Phase 3 Safety Study on the Endometrium

Open, randomized, multicenter study on endometrial morphology in healthy women requiring or agreeing to contraceptive protection under SH T 470 FA over 13 treatment cycles in comparison to the pretreatment value.

The purpose of the study was to provide an in-depth assessment of the effects of the oral contraceptive, SH T 470 FA (Yasmin™) on the endometrium by means of endometrial morphometry in comparison to an untreated cycle. A washout period of 3 months with no sex hormone therapy was required. In order to evaluate a possible impact of the duration of treatment, the effect of Yasmin™ on the endometrium was examined in an untreated precycle at baseline and after 3, 6, and 13 treatment cycles. This long observation period and the narrow biopsy intervals were planned to give information on the dynamics of endometrial changes with Yasmin™ treatment. Additionally, more data was gained with regard to contraceptive reliability and cycle control.

40 healthy women ages 18 to 35 years were randomized into two groups. Group A consisted of 19 subjects to have an intermediate biopsy at cycle 3, and group B consisted of 21 subjects to have an intermediate biopsy at cycle 6. Both groups had endometrial biopsies at baseline and at cycle 13. Two subjects from group A were erroneously switched to group B before the intermediate biopsy. 32 subjects completed the medication phase. A total of 26 subjects were valid for VCA, 13 in each group.

In the untreated precycle, all subjects used a home monitoring kit to detect the LH peak. They returned 5-6 days after the LH peak for ultrasonography and endometrial biopsy. The treatment phase began on the first day of menstrual bleeding after the precycle. Subsequent biopsies were taken on days 18-20 of cycles 3 or 6 and 13.

Morphometric parameters acknowledged in the literature are the primary endpoints of the study (glandular diameter, glandular epithelial height and number of vacuolated cells per 1000 cells in the endometrial tissue). Secondary endpoints were ultrasonography, adverse events, general clinico-chemical and hematological parameters, cervical cytology, blood pressure, general and gynecological examination.

Efficacy endpoints were contraceptive reliability and cycle control.

Results

1. No pregnancies occurred in the course of the study.
2. Cycle control was good.
3. Endometrial biopsies and ultrasonography showed strong suppression of the endometrium. No cancers or endometrial polyps were found throughout the study. Endometrium tended to be atrophied with diminished glandular diameter and number of glands. Endometrial thickness as measured by ultrasonography was reduced. Reliable suppression was seen in all subjects
4. No increased safety risk was identified.
5. 4 subjects discontinued the study prematurely due to adverse events (one with acne, two with headache, one with obesity)
6. One serious adverse event, a bicycle accident, was unrelated to the study drug.
7. One case of superficial phlebitis of a leg was reported as an adverse event during cycle 3 (end of study medication) by a 37 year old nonsmoking Caucasian subject weighing 57 kg. This AE resolved in 16 days without treatment and was not considered serious. This subject was discontinued from the study prematurely due to a protocol violation (age > 35 years).

Endometrial histology at baseline and under treatment (VCA)						
	Slightly suppressed	Moderately suppressed	Highly suppressed	Atrophic	Other proliferative	n
Baseline (all)	0	0	0	0	26 (100%)	26
Cycle 3 (Group A)	1 (8%)	4 (31%)	2 (15%)	6 (46%)	0	13
Cycle 6 (Group B)	0	1 (8%)	5 (42%)	5 (42%)	1 (8%)	12
Cycle 13 (all, EOSM*)	0	3 (12%)	7 (27%)	16 (62%)	0	26

*EOSM = end of study medication

Categories of endometrial histology defined by Johannisson

There were no notable differences in histologic assessment between ITT and VCA populations.

Conclusions

1. Yasmin™ appears to be safe concerning the effect on the endometrium.
2. No signs of proliferation were seen in the course of the study. These results are consistent with the transformation into a suppressed to atrophic endometrium after 13 cycles of treatment. It can be concluded that Yasmin™ has an effect of endometrial suppression on the endometrium similar to that of other oral contraceptives.

Number of Pages Redacted 10

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Confidential,
Commercial Information

27.0 FINAL CONCLUSIONS AND RECOMMENDATIONS

The studies presented in this NDA reveal Yasmin™ to be a safe and effective oral contraceptive with a safety profile similar to that of other approved oral hormonal contraceptives when taken by healthy women with no renal impairment. However, the antimineralocorticoid properties of the new molecular entity drospirenone, which are similar to those of spironolactone, suggest potential safety risks for women with renal impairment, hyperkalemia, and possibly those taking angiotensin converting enzyme (ACE) inhibitors.

For the application to be approved at this time with the available study results, labeling must include all of the contraindications, warnings, and precautions currently included in the labeling for spironolactone.

28.0 LABELING

Proposed labeling was presented by the sponsor and reviewed by the Division. Recommended changes were discussed with the sponsor. Final labeling is pending with the understanding that the study in subjects with renal impairment may alter warnings, precautions, etc. regarding the antimineralocorticoid effects of the drug and its safety profile. Depending on results from the ACE inhibitor/DRSP interaction study for HRT patients, it may be necessary to include a statement about the possibility of unknown drug/drug interactions with Yasmin™ in patients taking ACE inhibitors.

/S/

Dena R. Hixon, M.D., FACOG
Medical Officer, DRUDP

/S/

Marianne Mann, M.D.
Deputy Director, DRUDP

Cc: NDA 21-098, HFD-580, S. Allen, M. Mann, D. Hixon

JUN 2 9 1999

Filing Memorandum
Division of Reproductive and Urologic Drug Products

NDA 21-098

Trade Name:	Yasmin™
Generic Names:	Drospirenone and Ethinyl Estradiol
Sponsor:	Berlex Laboratories, Inc.
Submission Date:	May 14, 1999
Date Received:	May 17, 1999
Indication:	Combined oral contraception
Dose:	3 mg Drospirenone and 0.030 mg Ethinyl Estradiol
Dose Regimen:	Daily oral tablet Yasmin 21 contains 21 active tablets Yasmin 28 contains 21 active tablets and 7 inert tablets
User Fee Goal Date:	March 17, 2000
Division Goal Date:	February 4, 2000
Date of Filing Meeting:	June 18, 1999
Reviewed by:	Dena Hixon, M.D., Medical Officer Theresa H. van der Vlugt, M.D., M.P.H., Medical Officer

/S/
6/25/99

Background

Drospirenone (DRSP), a new molecular entity, is a derivative from 17α-spironolactone with progestational, antimineralocorticoid (aldosterone-antagonistic), and antiandrogenic properties but devoid of any androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. Ethinyl estradiol (EE) belongs to the class of estrogens and is a frequently uses estrogen in oral contraceptive products.

Significant antimineralocorticoid activity (6-8 times higher than that of spironolactone) was observed with DRSP following single oral dose or single or repeated subcutaneous doses administered to rats characterized by increased sodium excretion and an increase in the urinary Na^+/K^+ ratio. Pharmacodynamic studies support the hypothesis that DRSP activated the Renin-Angiotensin-Aldosterone System (RAAS) by acting as an antagonist at the kidney. Renin activity in plasma and aldosterone concentrations in plasma increased but serum Na^+, K^+, and creatinine levels remained unchanged.

Drospirenone (DRSP) 3 mg and ethinyl estradiol (EE) 30 μg has not been marketed anywhere in the world.

At a Phase III meeting held on February 12, 1997, it was determined that the completed European Phase III clinical trial (Study 92052/Report A151) appeared adequate in terms of reported observed cycles and available safety data to support the filing of an NDA. Because this study population was approximately 96% Caucasian, a second US trial (Study 96049/Report 98180 conducted under , was recommended to include a more varied ethnic mix.

At a pre-NDA meeting held on January 28, 1999, it was determined that the overall proposal for the NDA application appeared acceptable, that additional biopharmaceutics special population and drug interaction studies should be considered, and that should additional toxicology studies be required they will be requested as a Phase IV commitment.

Submission Resume

Two pivotal efficacy and safety studies and 33 supportive clinical trials support this NDA for the prevention of pregnancy in women who elect to use a combined oral contraceptive method. Overall, a total of 3,317 female subjects were exposed to treatment with any dose DRSP (2940 subjects were exposed to 3 mg DRSP/30 μg EE). Forty-nine percent (n=1623 of 3317) of subjects completed 13 cycles of use.

European Study 92052 (Pivotal Report A151) was a multi-center, open-label, parallel group, Phase III study in which 887 reproductive aged women (mean age of 26.2 years) were randomized to receive either 3 mg DRSP/30 ug EE (n=442) or 0.15 mg Desogestrel/30 ug EE (Marvelon/Desogen) (n=445) for 26 cycles. 310 women completed 26 cycles of DRSP30/EE0.03. 73 % of participants were on oral contraceptives at baseline. 98% of participants were Caucasian. There were 3 pregnancies in the DRSP/EE group and 3 in the Marvelon group, giving a corrected Pearl Index of 0.41 for both groups and a Pregnancy Ratio of 1.12% for DRSP30/EE0.03 and 1.18% for Marvelon. All of the pregnancies were considered user failures. One pregnancy resulted in a healthy baby boy, one had an induced abortion, and the other was lost to follow-up.

US Study 96049 (Pivotal Report 98180) was a six center, open-label, non-randomized, single-group, Phase III study in which 326 reproductive aged women (mean age of 26.4 years) received 3 mg DRSP/30 ug EE for up to 13 cycles. 222 subjects completed 13 cycles. 54% of subjects were on oral contraceptives at baseline. 87% of subjects were Caucasian. There was one pregnancy in the third cycle of use, giving a corrected Pearl Index of 0.407 and pregnancy ratio of 0.455. The subject had missed her pill on cycle day 5 and took 2 pills the following day. She elected to terminate the pregnancy.

Supportive European Study 93044 was a multi-center, open-label, parallel group, Phase III study in which 2069 reproductive aged women (mean age of 25.2) were randomized to receive 3 mg DRSP/30 ug EE (n=1657) or Marvelon/Desogen (n=412) for 13 cycles.

The most common reason for discontinuation from study medication was adverse events (8% [n=265] for any DRSP dose and 9% [n=252] for 3/30 DRSP). A similar proportion of subjects prematurely discontinued due to "other" reasons (7% [n=246] for any DRSP dose and 8% [n=243] for 3/30 DRSP).

There was one death reported in all studies. Subject 228 (supportive Study 93044), a 28 year old who had taken DRSP 3/30 for five months, died suddenly of cardiac arrest from a severe post-streptococcal myocarditis with extensive inflammatory infiltrates. Serious adverse events, including 1 pulmonary embolism (Subject 384/Study 92052) were reported for 2% (n=54/3317) for all DRSP treated subjects. Two percent (n=26/1123) of subjects treated with active controls experienced serious adverse events. The adverse event that occurred most often among DRSP treated subjects in all studies was headache.

Review Issues

73% of subjects in the pivotal European study and 54% of subjects in the US study were taking oral contraceptives at baseline. This could affect safety laboratory analysis, especially regarding lipid evaluations.

Having 54% of subjects in the US study on oral contraceptives at baseline and only 222 subjects completing 13 cycles makes this study inadequate for efficacy analysis. Those subjects on OCs at baseline without a 2 month washout period should have completed 15 cycles.

98% of subjects in the pivotal European study and 87% in the US study were Caucasian. There is no subset analysis of bleeding patterns or other safety/efficacy data presented based on race or ethnicity.

At the Pre-NDA meeting, the sponsor was asked to provide a separate listing of study subjects who enrolled in this study after having used other contraceptive products along with the dates of discontinuation of other hormonal contraceptives. Analysis of efficacy rates was also requested for subjects who did not use another birth control method and who did not use oral contraceptives within 2 months of enrollment or injectable hormonal products within 10 months of enrollment.

As stated at the pre-NDA meeting, mineralocorticoid effects of this drug could be a safety issue, and warnings and contraindications currently in the spironolactone label may become part of this oral contraceptive label if the issues are not adequately addressed.

The sponsor's proposed labeling is consistent with standard oral contraceptive labeling. The label will need a CLINICAL STUDIES section including further data from the current studies. Some of the warnings and contraindications from the spironolactone label might be included.

Recommendations

The provided information is appropriate to support the filing of NDA 21-098.

The following sites for Report Number 98180/ Protocol Number 96049 (the US pivotal trial) are recommended for DSI audit:

1. Center number 4905
   Investigator Dan C. Henry, MD
   2295 Foothill Drive
   Salt Lake City, UT 84109
   This center had the largest number of subjects enrolled (64) and also the largest number of dropouts (27) including 11 protocol deviations and 10 lost to follow-up.

2. Center number 4901
   Investigator Jeff Adelglass, MD
   Research Across America
   9 Medical Pkwy., Plaza 4, Suite 202
   Dallas, TX 75234
   This center had 50 subjects enrolled, 22 dropouts; 12 withdrew consent, 4 protocol deviations, and 3 lost to follow-up.

3. Center number 4903
   Investigator Steven Bowman, MD
   Tampa Bay Med. Research, Inc.
   3253 McMullen-Booth Rd., Ste 200
   Clearwater, FL 34621-2010
   This center had 51 subjects enrolled, 24 dropouts; 14 lost to follow-up, and 1 pregnancy.

Of the above list, #1 is strongly recommended for audit, and #2 or #3 are suggested for a second site at the discretion of DSI.

Attachment: 45 Day Filing Meeting Checklist
cc: NDA 21-098 Division File
HFD-580/JMercier/SAllen/DHixon/TvanderVlugt

NDA 21-098
Yasmin® 28 Tablets (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

Safety Update Review is located in the Medical Officer's Review of April 13, 2001, Pg. 31.

/S/
5/1/01

APPEARS THIS WAY
ON ORIGINAL

NDA 21-098
Yasmin® 28 Tablets (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

Safety Update Review is located in the Medical Officer's Review of June 21, 2000, page 12.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-098
Yasmin® 28 Tablets (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

Safety Update Review is located in the Medical Officer's Review of February 23, 2000, page 70.

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	021098	**Trade Name:**	YASMIN(DROSPIRENONE 3MG/ETHINYL ESTRADIO
Supplement Number:	000	**Generic Name:**	DROSPIRENONE 3MG/ETHINYL ESTRADIOL .30MG
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	AE-AP	**COMIS Indication:**	ORAL CONTRACEPTIVE
Action Date:	3/17/00		

Indication # 1 Oral Contraception
Label Adequacy: Does Not Apply
Formulation Needed: NO NEW FORMULATION is needed
Comments (if any): Approval Date is May 11, 2001

Ranges for This Indication

Lower Range	Upper Range	Status	Date
Adult	Adult	Waived	5/11/01

Comments: This product is for postmenarchal females.

This page was last edited on 5/11/01

/S/ 5/11/01

Signature Date

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21098	**Trade Name:**	YASMIN(DROSPIRENONE 3MG/ETHINYL ESTRADIO
Supplement Number:		**Generic Name:**	DROSPIRENONE 3MG/ETHINYL ESTRADIOL .030M
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	AE	**Proposed Indication:**	Oral Contraception

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Oral Contraceptive Class Labeling addresses use in young females that have achieved menarche.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JEANINE BEST

/S/ 7/10/00

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21098	**Trade Name:**	YASMIN(DROSPIRENONE 3MG/ETHINYL ESTRADIO
Supplement Number:		**Generic Name:**	DROSPIRENONE 3MG/ETHINYL ESTRADIOL .030M
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	AE	**Proposed Indication:**	Oral Contracption

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/S/ 3/3/00

Signature Date